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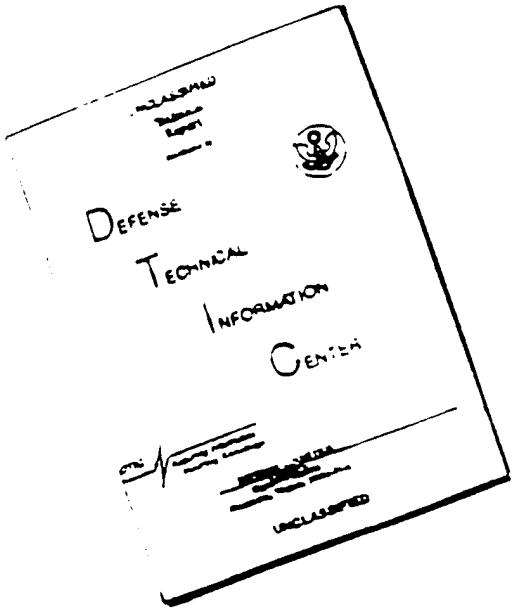
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PREFACE

It is a pleasure to introduce this special issue of *Phosphorus, Sulfur, and Silicon* which consists of the Proceedings of the XIIIth International Conference on Phosphorus Chemistry, held on July 16–21 in Jerusalem, Israel. The Conference attracted 366 participants and 54 accompanying persons from 32 countries, among these 86 from Eastern European, formerly communist, countries. The largest delegations were: France (25), Germany (74) Israel (77), Poland (22), Russia (38) UK (40) and the USA (56).

The Conference was held in the Holiday Inn Crowne Plaza Hotel, where about a third of the participants stayed. Most of the other participants stayed in hotels within walking distance from the Conference venue. The Holiday Inn Crowne Plaza has pleasant ambiance, excellent facilities and a great deal of experience in hosting successful scientific meetings. It proved to be an excellent choice.

The structure of the scientific program was similar to previous ICPC's in the series, insofar as not having plenary sessions except for the opening one. The scientific program started with a lecture given by Professor Robert R. Holmes entitled "HORIZONS IN PHOSPHORUS CHEMISTRY" which was the only plenary in the Conference. Following this, the 175 oral presentations were split to five parallel sessions to accommodate the many faces and multidisciplinary implications of phosphorus chemistry. In addition, there were 274 posters presented in two sessions.

In order to reflect recent advances in life sciences, our goal was to have in this meeting a strong representation of the bioorganic and biomedical aspects of phosphorus chemistry, in addition to all the traditional aspects which were represented in the previous ICPC's. We considered that exposing the phosphorus chemists' community to these new frontiers and opportunities for development, will widen horizons and stimulate the conception of new ideas. To achieve this, there was a need to attract scientists who normally do not participate in such a Conference. Thus, we contacted several pharmaceutical companies, medicinal chemists, biochemists and biologists. We succeeded at least partially in this goal, as it is apparent from the various special minisymposia:

* Biologically active bisphosphonates (7 lectures)
* Phosphorus related abzymes (8 lectures)
* Nucleotides (8 lectures)
* Phospholipids (7 lectures)
* Biological applications of P-31 NMR spectroscopy (4 lectures)
* Phosphorus containing NMDA antagonists (6 lectures)
* Inositol phosphates (7 lectures)
* Phosphorus containing agrochemicals (6 lectures)

In addition to these, there was a general bioorganic-medicinal session (9 lectures) as well as sessions devoted to computational phosphorus chemistry (4 lectures), inorganic phosphorus chemistry (9 lectures), coordination chemistry (26 lectures) and to flame retardants (4 lectures). Still, as in previous ICPC's the major portion of the Conference consisted of contributed presentations in various aspects (synthetic, structural and mechanistic) of organophosphorus chemistry (70 lectures).

One of the risks one takes when organizing a Conference in a place like Jerusalem (*there is no place like Jerusalem – so central in the history of three major religions: Judaism, Christianity and Islam*), is that many of the participants may find touring the city more attractive than attending the Conference. I think we overcame this difficulty successfully, as both the lectures and the poster sessions were all very well attended. The Conference participants were rewarded with a social program which included a sound and light show at the Tower of David Citadel along the wall of the Old City, a reception and a visit in the

Israel Museum (containing among other unique exhibits, the famous "Dead-Sea Scrolls") hosted by the Municipality of Jerusalem, as well as a half day tour of selected sites and sights of the city. The conference ended with a farewell dinner.

We wish to acknowledge the donations received from the numerous institutions and companies (their list appears at the page preceding this preface) which enabled us to extend financial support to needy participants especially from the Former Soviet Union and other Eastern European Countries.

Finally the Chairman wishes to thank all the members of the National and International Committees, and last but not least, all the participants, without whom this Conference could not have succeeded. We look forward to meeting again in Cincinnati in 1998.

Eli Breuer
(Chairman, XIIIth ICPC)

PLENARY LECTURE

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HORIZONS IN PHOSPHORUS CHEMISTRY

ROBERT R. HOLMES
Department of Chemistry, Box 34510, University of Massachusetts, Amherst, MA 01003-4510 USA

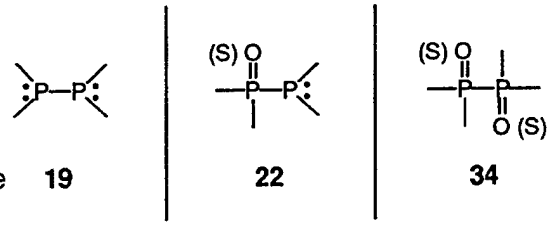
Abstract Where has phosphorus chemistry been and where is it going? To answer this question, we must explore current areas of activity, the concentration of research in these areas, and what appears to be trends and emerging areas that might suggest what the future may hold. For this purpose, we shall examine several sources of current research information. These comprise current literature, reviews and overviews, recent symposia and correlative articles. This should place us in a position to learn in which directions phosphorus chemistry may be headed in the 21st century. We must keep in mind that some of the best discoveries leading to new areas of importance result from so called "accidental" discoveries. However, a perceptive mind stimulated by research at the forefront of knowledge is best tuned to seize these opportunities. It is hoped that this discussion will provide insight into our own research and perhaps suggest new and untried approaches. One approach is to examine related chemistries to learn their similarities and differences. This often leads to new ways of looking at a research area which makes one think more broadly in the design of experiments that could lead to new horizons.

The first phosphorus meeting in this series took place in Heidelberg, Germany in 1964. An article in *Chem. Revs.* by Alan Cowley [1a] appeared in 1965 and described three known types of compounds containing phosphorus–phosphorus bonds, Chart 1. In 1978, a review by Lutsenko and Proskurnina [1b] reported only increasing numbers of examples of these same three kinds of compounds.

In the last 15 years, the situation has changed completely. Phosphorus chemistry has greatly expanded in the scope of chemical types that are now known and in the exploration of the subsequent chemistry. Since 1965, it is estimated that about 100,000 papers on phosphorus chemistry have appeared in the literature.

What I wish to present today is some of the phosphorus chemistry that has resulted during this time with a view to what might come about in the future. The material to be presented is not by any means comprehensive. Also it would be presumptuous of me to assign importance to one area over another. Thus, what is presented may be thought of as an excursion through the vast field of phosphorus chemistry with an object of awakening constructive thoughts that might prove valuable in furthering our own research areas. For this purpose, part of the presentation will be based on a description of possible phosphorus–phosphorus bonds, known and unknown, as summarized in an article by Lydia Lamandé,

CHART 1 Known P–P bonds in 1965.



Mode	19	22	34

Cowley, *Chem. Revs.* [1a]

By 1978, only the same three types were known.

Lutsenko & Proskurnina, *Usp. Khim.* [1b]

Present Number	hundreds	~ 180	~ 250

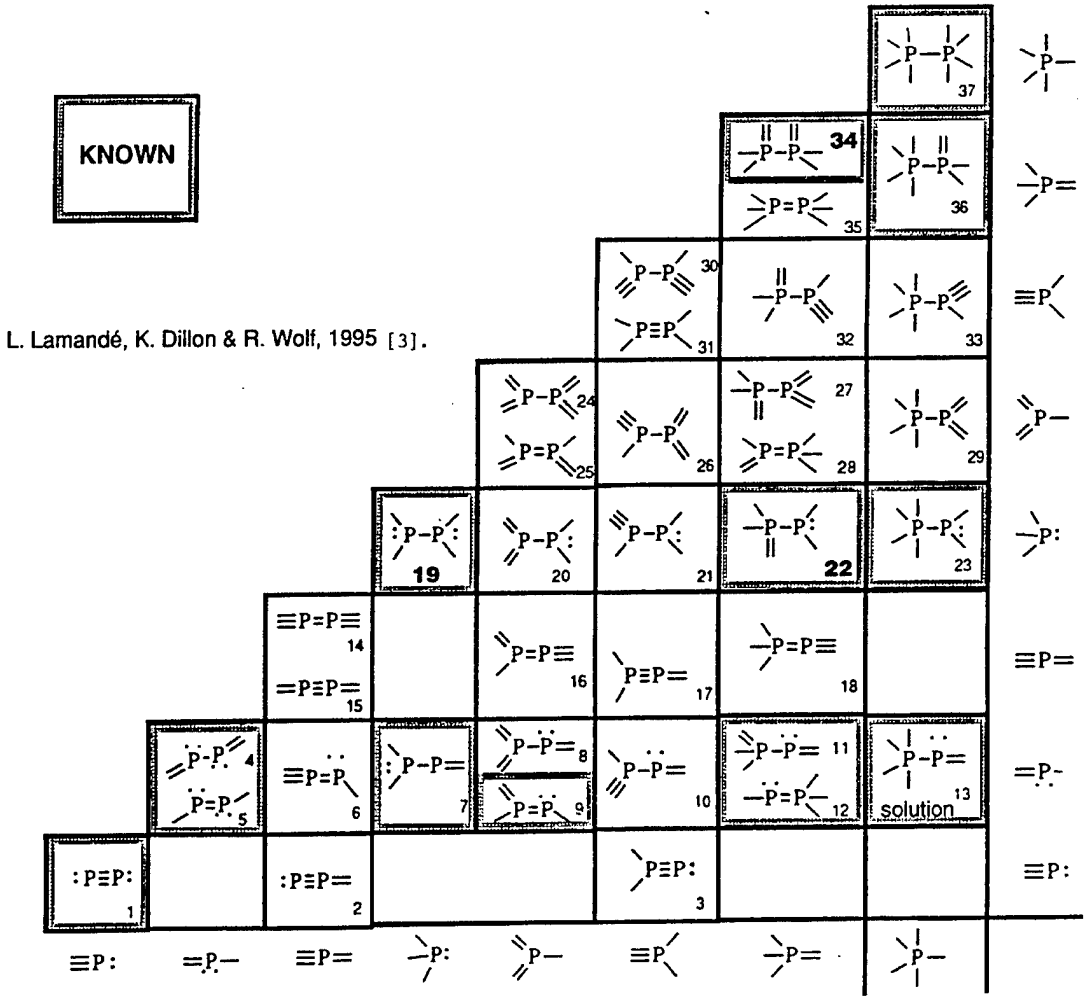
Keith Dillon, and Robert Wolf [3]. As far as ascertaining future directions in phosphorus chemistry, each one of us is in a slightly different position based on our own special expertise and area of concentration. Consequently, insight into the future will depend on this varying perspective and, in addition, on unforeseen events that frequently are encountered in the course of research.

If we assume the eight possible hybridization types shown in Table 1 for a neutral phosphorus atom, we are able to couple them in pairs to obtain 37 modes of formation of phosphorus–phosphorus bonds, Table 2 [3]. The boxes that are shaded indicate compositions that are known in the condensed phase, either in solid or solution form, other than diatomic phosphorus which is detected in the gas phase from the pyrolysis of white phosphorus above 800°C [4].

TABLE 1 Eight hybridization types of neutral phosphorus atoms utilizing coordination numbers 1 to 5.

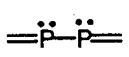
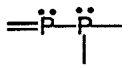
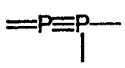
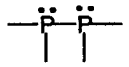
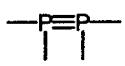
≡P:	rare	=P=	~ 100
=P:	~ 2000 (*e.g.*, –P=N–)	–P≡	very rare
≡P=	rare	–P=	tens of thousands (ylides & phosphates)
–P–	thousands	P	~ 6000

TABLE 2 Neutral phosphorus–phosphorus bonds.



One reason for the absence of certain modes of P–P bonding is that structures with localized electron pairs are frequently the more stable forms. Thus Modes **4**, **7**, and **19** in Table 2 having phosphorus–phosphorus single bonds represent stable forms in contrast to the respective Modes, **15**, **17**, and **31**, which are unknown isologs and have phosphorus–phosphorus triple bonds. These modes are compared in Table 3 [3].

TABLE 3 Structures with localized lone pairs are frequently the stable forms.

Stable form	Mode	Unknown Isolog	Mode
	(4)		(15)
	(7)		(17)
	(19)		(31)

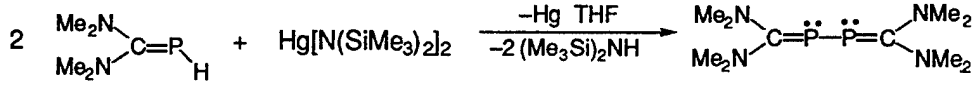
Let us examine the method of synthesis used to obtain the first examples of some of stable modes of phosphorus–phosphorus bonds. With reference to Table 2, Schemes 1–7 illustrate the syntheses of compounds corresponding to Modes **4**, **5** and **9**, **7**, **11** and **12**, **23**, **36**, and **37**, respectively. In these schemes, an estimate of the number of known derivatives of each type is shown in parentheses.

In the synthesis of the =P̈–P̈= unit in Scheme 1, Romanenko and coworkers [5] caused the cleavage of P–H bonds in a condensation reaction where the liberated hydrogen atoms were taken up by the nitrogen atom of hexamethyldisilazide moieties.

Yoshifuji and coworkers [6] obtained the first isolated diphosphene with a localized P=P bond, Scheme 2, corresponding to Mode **5** by the reaction of magnesium metal with the sterically encumbered molecule, (2,4,6–tri–*t*–butylphenyl)phosphonous dichloride in THF solution. The diphosphene is stable in air. Its reaction with elemental sulfur in Et_3N at room temperature resulted in a Mode **9** formulation [7]. The X-ray structures of the diphosphene and its monosulfur derivative show little difference in the lengths of the P=P double bond.

SCHEME 1

Mode **4** $=\ddot{P}-\ddot{P}=$ (a few)



^{31}P, 33.9 [a]

Romanenko & coworkers, 1985 [5].

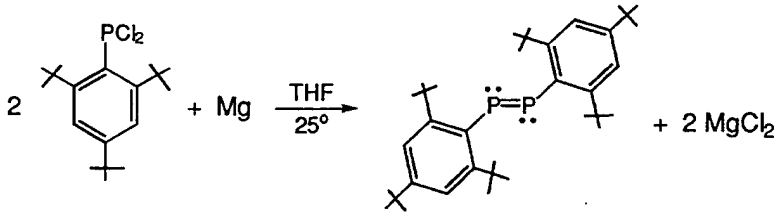
[a] All ^{31}P NMR chemical shifts here and to follow are in ppm.

SCHEME 2

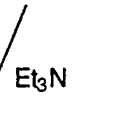
Mode **5** $-\ddot{P}=\ddot{P}-$ (~100)

First Diphosphene

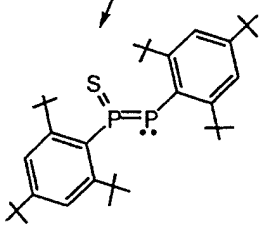
Yoshifuji & coworkers, 1981 [6]



^{31}P, –59; P–P = 2.034Å



Mode **9** $-\overset{\|}{P}=\ddot{P}-$ (some)

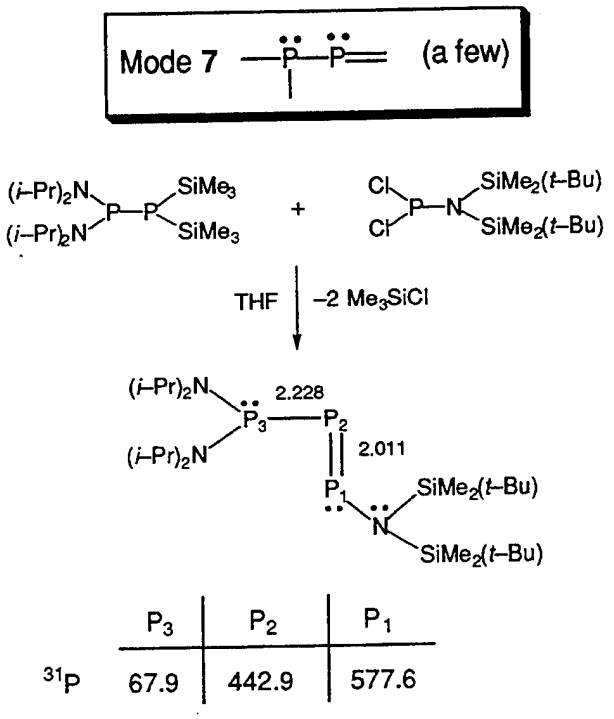


^{31}P, 255.8, 247.8; P–P = 2.054Å

Yoshifuji & coworkers, 1983 [7]

A few examples of diphosphenes corresponding to Mode **7** are known, one of which was prepared by Schoeller, Niecke, and coworkers [8] (Scheme 3) by treating a diphosphane in a condensation reaction with an aminophosphonous dichloride in THF. Each phosphorus and nitrogen atom apparently retains a lone pair of electrons which might allow an extensive reaction chemistry.

SCHEME 3



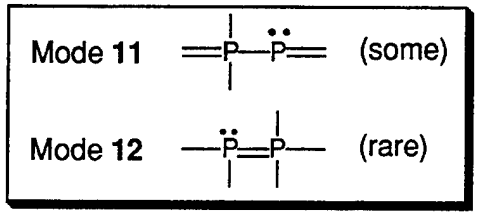
	P_3	P_2	P_1
^{31}P	67.9	442.9	577.6

Schoeller, Niecke & coworkers, 1989 [8].

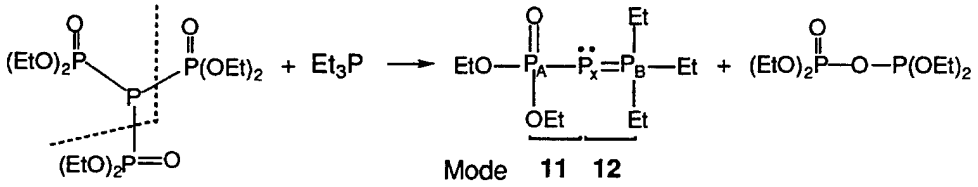
In Scheme 4, a rare combination of Modes **11** and **12** was found by Weber and Fluck [9] by treating triethylphosphine with $[(Et_2O)_2PO]_3P$ which underwent an elimination reaction to yield the triethylphosphine–diethyloxyphosphoryl–phosphinidene product.

The previous schemes, 1–4, illustrated examples of modes containing low coordinate phosphorus. Modes **23**, **36**, and **37**, shown in Schemes 5–7, respectively, relate to bonding with five–coordinate phosphorus.

SCHEME 4



Mode **11–12** Combination



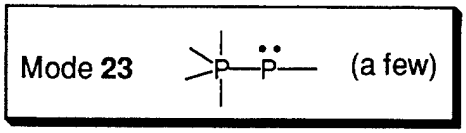
Mode **11** **12**

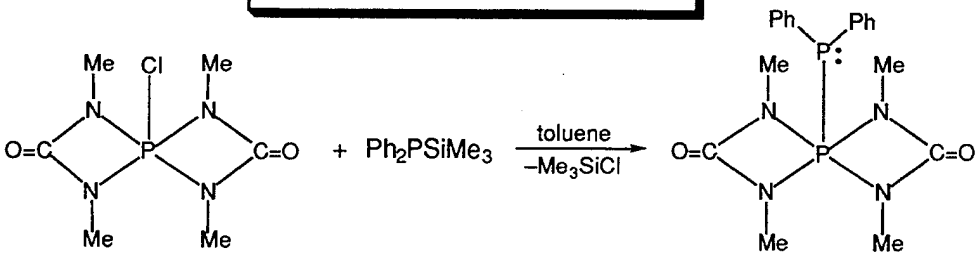
	P_A	P_x	P_B
^{31}P	–57.3	217.8	–44.2

Weber and Fluck, 1976 [9].

The first example of a Mode **23** compound was described by Schmutzler; Schomburg, and coworkers [10], Scheme 5. They reacted a chlorophosphorane with Ph_2PSiMe_3 in toluene solution. This caused a direct introduction of a Ph_2P group at a five–coordinate phosphorus center. The X-ray structure revealed a P–P bond length of 2.214Å, in the single bond range.

SCHEME 5



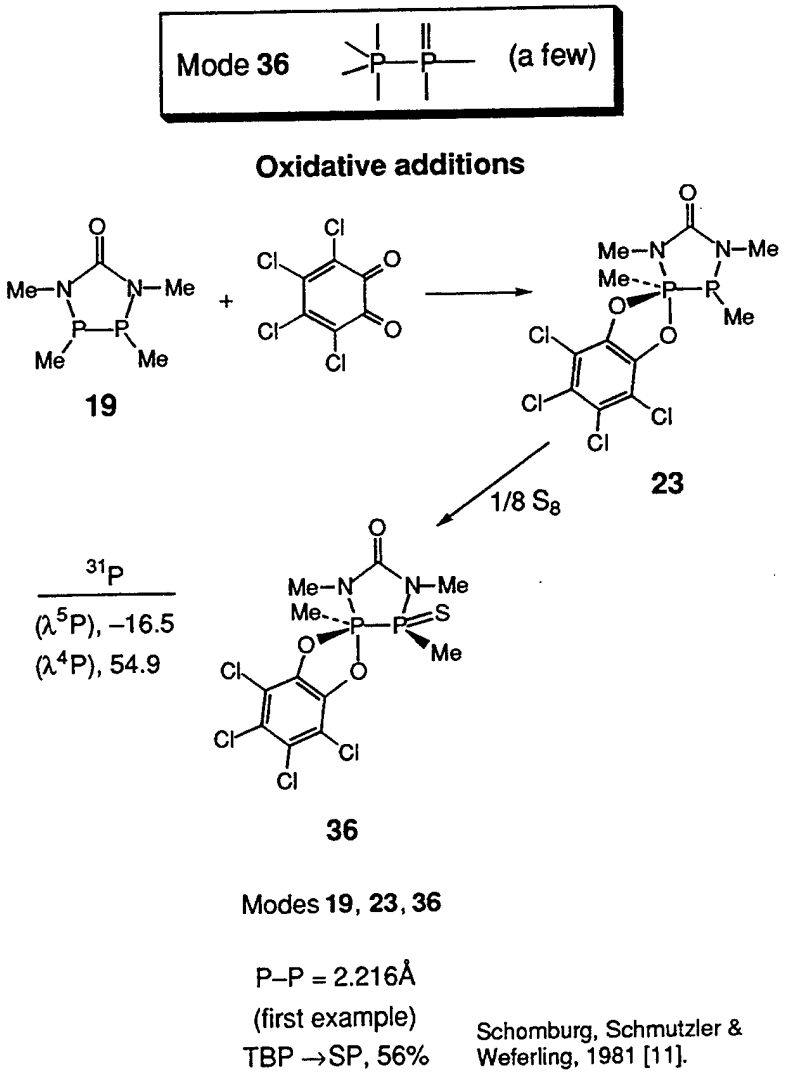


$^{31}P(\lambda^5P)$, –65.8; (λ^3P), –10.6 P–P = 2.214Å (first example)

Schmutzler, Schomburg & coworkers, 1983 [10]

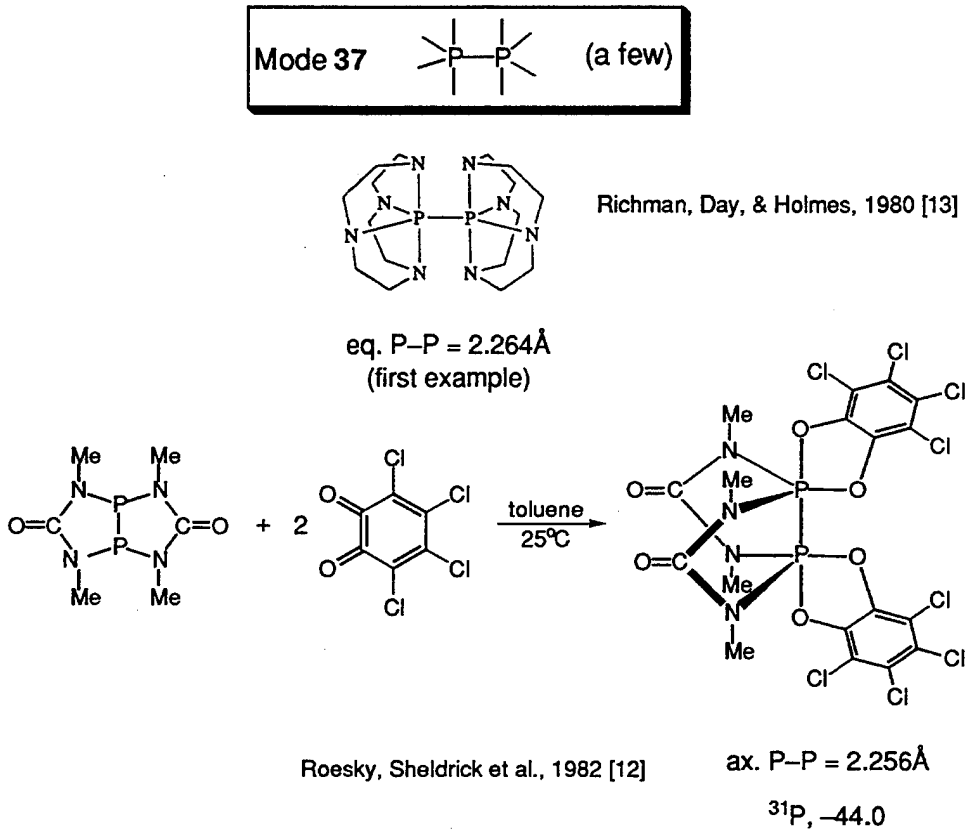
This same group [11] also reported the first synthesis of λ^5P–λ^4P diphosphorus compound, represented by Mode **36** in Scheme 6. This was accomplished by an oxidative addition of tetrachloro–*o*–benzoquinone to an N,N′–dimethylurea–bridged diphosphine (Mode **19**) to obtain a λ^5P–λ^3P Mode **23** derivative. Treatment of the latter with elemental sulfur gave the new diphosphorus compound with the phosphorus bound methyl groups in a *trans* orientation as shown by an X-ray study. The geometry at the pentacoordinate phosphorus atom is displaced about 56% from a trigonal bipyramidal toward a square pyramid.

SCHEME 6



Using this same type of oxidative addition with tetrachloro–*o*–benzoquinone as just described, Roesky, Amirzadeh–Asl, and Sheldrick [12] obtained a λ^5P–λ^5P compound (Mode **37**) depicted in Scheme 7. An X-ray study shows TBP geometries at each phosphorus atom where the P–P bond is in an axial position. This compares with the first example of a Mode **37** compound, the cyclam structure reported by Richman, Day, and Holmes [13] which has the P–P bond in an equatorial position.

SCHEME 7

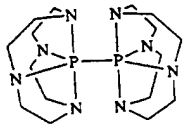
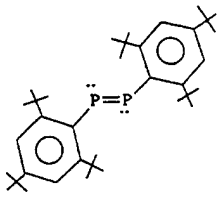
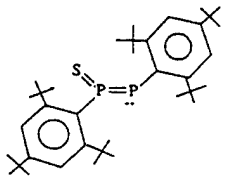


However, in this molecule the geometry is displaced one-third the way from a TBP toward a square pyramid. This may account partially for the equality in the two P–P bond lengths.

A listing of some P–P bond lengths varying in multiple bond character is given in Table 4 to compare with other examples discussed in this article.

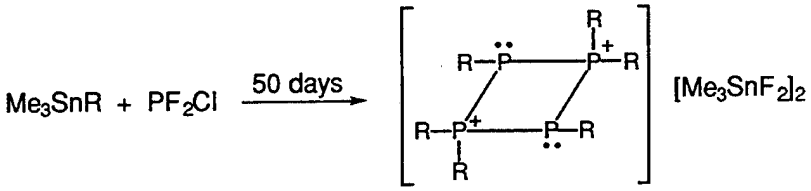
In addition to neutral compounds containing phosphorus–phosphorus bonds, it is instructive to consider both cationic and anionic derivatives. According to the procedure of Wolf and coworkers [3], they list 39 possibilities for cationic species comprised of phosphorus–phosphorus bonding and 94 kinds of anionic species. The number of known compounds that are cationic are few, whereas a considerable number of anionic derivatives

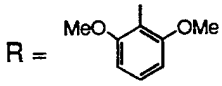
TABLE 4 P–P bond lengths

Mode	Examples	P–P, Å	
37		2.264(2)	Richman, Day & Holmes, 1980 [13]
5		2.034(2)	Yoshifuji et al., 1981 [6]
9		2.054(2)	Yoshifuji et al., 1983 [7]
1 $P_4 \xrightarrow{\Delta}$:P≡P:		1.895	Bock & Müller, 1984 [4]

have been reported [3]. Schemes 8 [14] and 9 [15] illustrate the synthesis of an example of each. There are also compounds containing adjacent cationic [16] or anionic [17] phosphorus centers. Synthesis of these are shown in Scheme 10.

SCHEME 8 A cationic compound

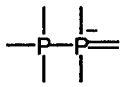


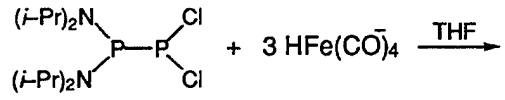


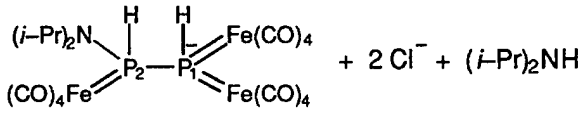
P–P = 2.231 and 2.232Å

Huer, Ernst, Schmutzler, Schomburg, 1989 [14]

SCHEME 9 An anionic compound





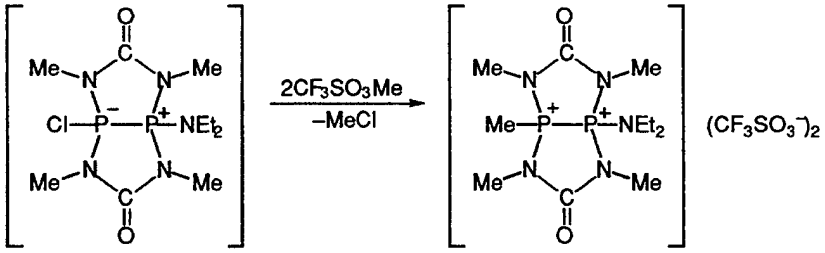


$^{31}P_1$, 77.8; $^{31}P_2$, 1.91 P–P = 2.283Å

Niecke, Majoral & coworkers, 1989 [15]

SCHEME 10 Other possibilities

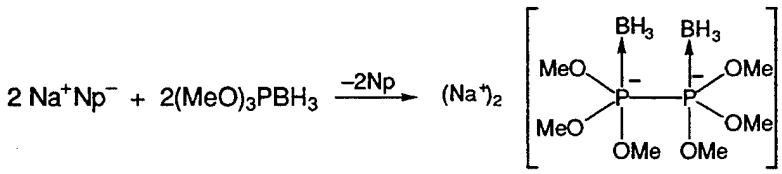
2 adjacent cationic phosphorus atoms



^{31}P, 42.7P–P = 2.189Å

Schomberg, Bettermann, Ernst, Schmutzler, 1985 [16]

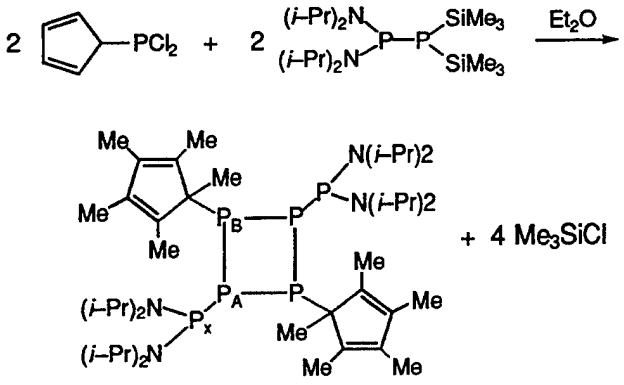
2 adjacent anionic phosphorus atoms



Peacock & Geanangel, 1976 [17]

The use of cyclopentadienyl introduces a range of other possibilities. The formation of a tetraphosphetane in Scheme 11 illustrates a member of this class [18].

SCHEME 11 Cp–P attachment



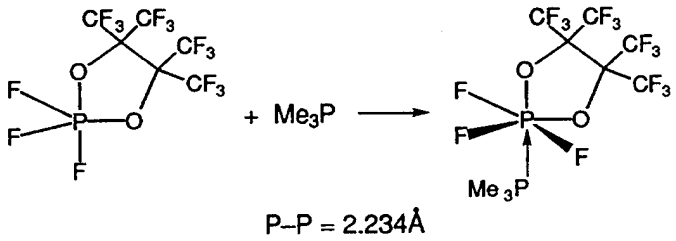
	A	B	X
^{31}P	–60.1	23.7	101.7

Ave. P–P (ring) = 2.234Å

Westermann & Nieger, 1991 [18]

There are a number of other types of compounds that contain phosphorus–phosphorus bonding. Among these are those that are radicals, those that are molecular adducts, formed as a result of Lewis acid–base interaction, *e.g.* that shown in Scheme 12 [19], and the

SCHEME 12 Hexacoordinated adduct via P–P bonding

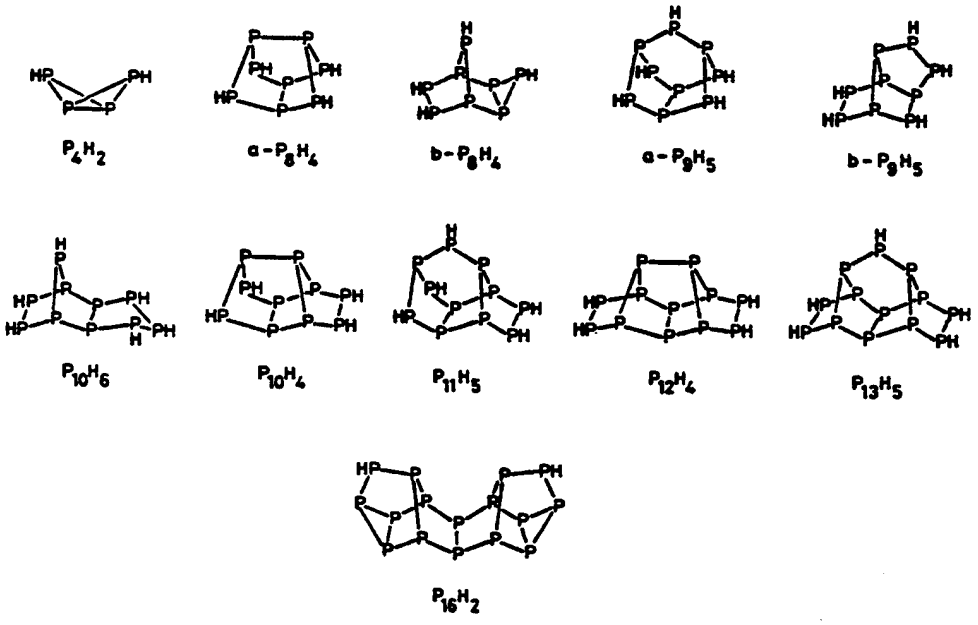


P–P = 2.234Å

Sheldrick & Röschenthaler, 1978 [19]

extensive array of polyphosphorus compounds both open chain [20] and cyclic [21] derivatives whose chemistry has been elucidated largely by Marianne Baudler and her coworkers. Structures of polycyclic phosphorus hydrides [21] in Scheme 13 indicate the range assigned to this class.

SCHEME 13 Structures of polycyclic phosphorus hydrides

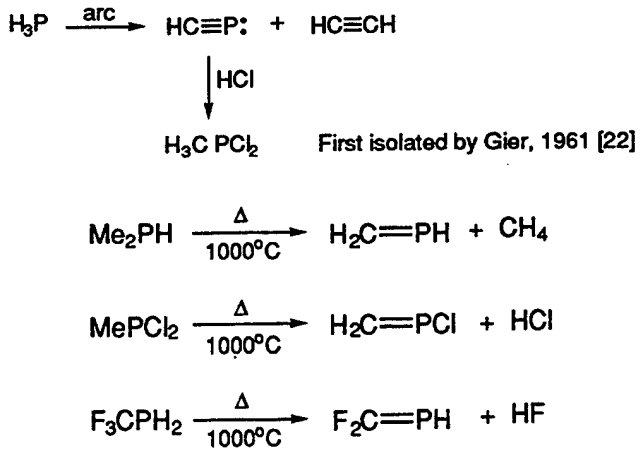


Baudler, 1987 [21]

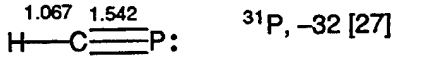
We have reviewed samplings concerning the vast literature devoted to compounds containing phosphorus–phosphorus bonds that varied from monocoordinate to hexacoordinate in composition. Let us now examine some of the recent areas of phosphorus chemistry that involve connectivities to other atoms, usually C, N, O, S, F, Cl, Br, H, and metal atoms. Again the whole range of coordinate forms will be considered. In doing so, we may gain an appreciation of the growth that has occurred in phosphorus chemistry in recent times, and it is hoped that some projection into future work may be visualized. Much of the material in what is to follow is based on articles in a thematic issue of *Chemical Reviews* devoted to phosphorus chemistry that appeared in August, 1994.

The syntheses of several types of unstable P–C multiple bonds in Scheme 14 are all performed at high temperature from the thermal decomposition of phosphines [22, 23]. Microwave structures are included in Scheme 15 [24–26] along with ^{31}P chemical shifts [27, 28]. As an indication of instability, for example, HC≡P is a colorless gas which is spontaneously inflammable in air and polymerizes above –130°C [22]. Stabilization can be achieved with the use of a *t*–butyl group, Scheme 16.

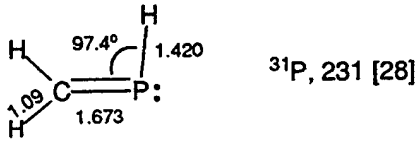
SCHEME 14 Unstable compounds with phosphorus carbon multiple bonds



SCHEME 15 Microwave structures

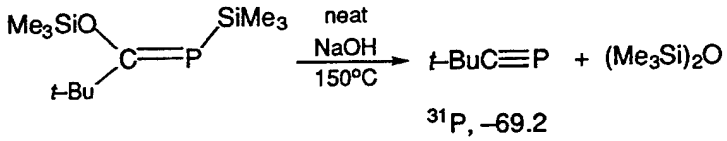


Tyler, 1964 [24]. Frost, Lee, McDowell, 1973 [25].



Kroto, Nixon & Ohno, 1981 [26]

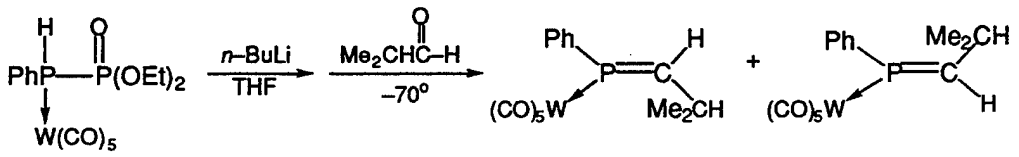
SCHEME 16 Stable phosphaalkynes

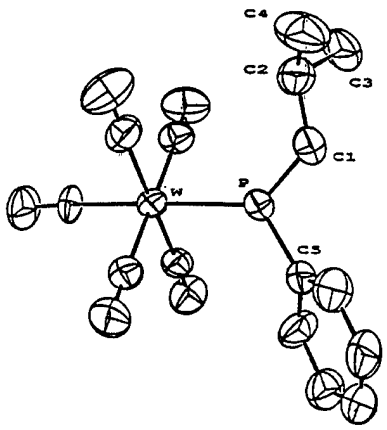


Becker, Gresser, Uhl, 1981 [29]

This class of low–coordinate compounds has proven useful in synthesis in organophosphorus and organometallic chemistry. Schemes 17 and 18 illustrate these applications.

SCHEME 17 Phospha–Wittig reactions yielding phosphorus–carbon double bonds

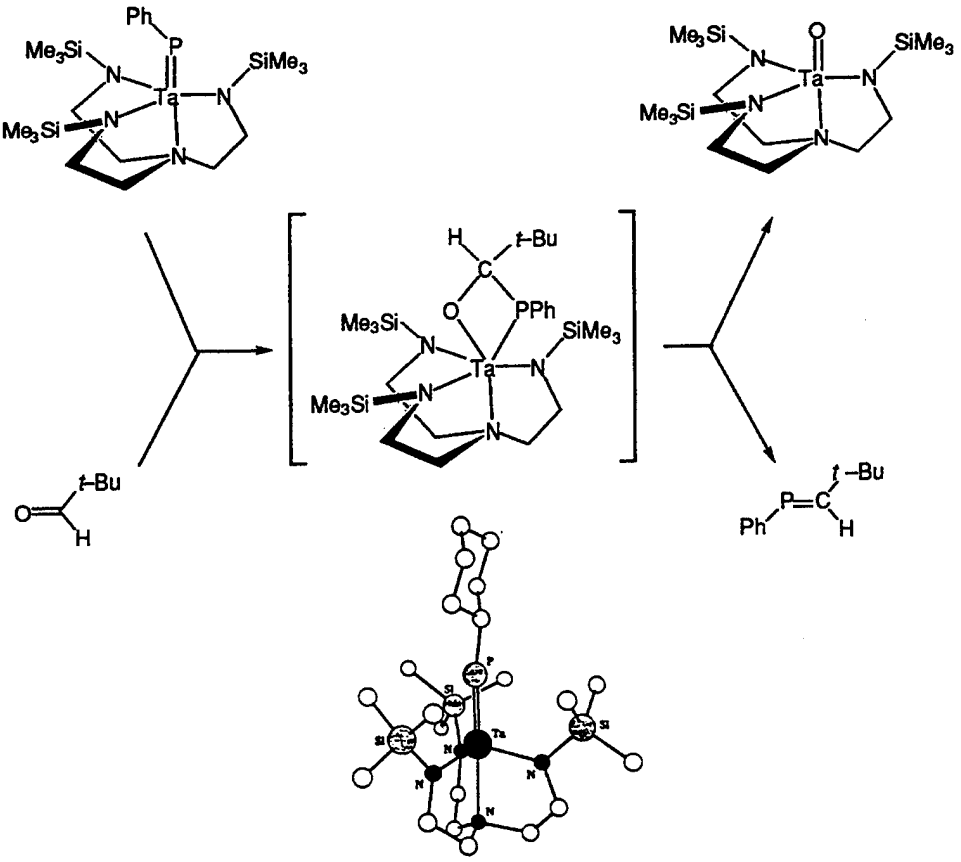




ORTEP of (Z)ISOMER

Mathey and coworkers, 1990 [30]

SCHEME 18 First stable phosphinidine tantalum complexes as phospha–Wittig reagents



Cummins, Schrock, Davis, 1993 [31]

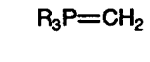
Another related area dealing with unsaturation in phosphorus bonds concerns the class of phosphonium ylides, Table 5, where metalated and main group element attachments have proven useful as reagents in organic synthesis [32–39].

Discussions of the mode of bonding in phosphonium ylides center on a resonance hybrid between a dipolar form and a double bond form [40].

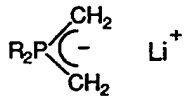
$$R_3\overset{+}{P}-\overset{-}{C}R_2 \longleftrightarrow R_3P{=}CR_2$$

On the basis of chemical reactivity, the dipolar form is considered more important [40–42]. This is in agreement with data from physical measurements indicating a build-up of charge at carbon [40, 43]. Theoretical treatments are in agreement with the results of physical measurements [40]. One model [40, 43–45] (Scheme 19) that has considerable support describes the phosphorus carbon bond comprising two electron pairs with the electron density strongly skewed toward carbon. The bond is viewed as a composite of a σ bond to

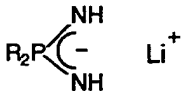
TABLE 5 A sampling of parent phosphonium ylides
(from a review by Cristau, 1994)



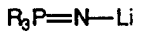
Staudinger, 1919 [33]
Wittig, 1949 [34]



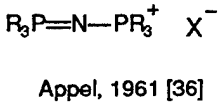
Wittig, 1949 [34]



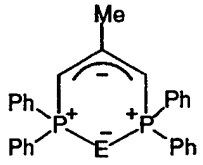
Scherer, 1969 [35]



Schmidbaur, 1967 [37]



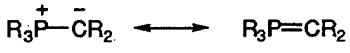
Appel, 1961 [36]



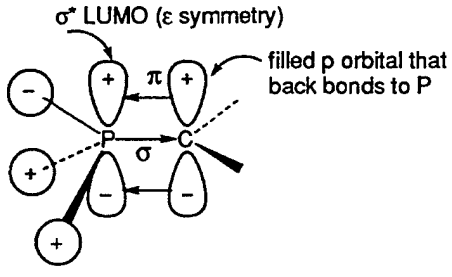
E = CH, N, BH_2, P, As

Schmidbaur & coworkers, 1991–1993 [38–39]

SCHEME 19 Bonding model for phosphonium ylides



Bonding Model



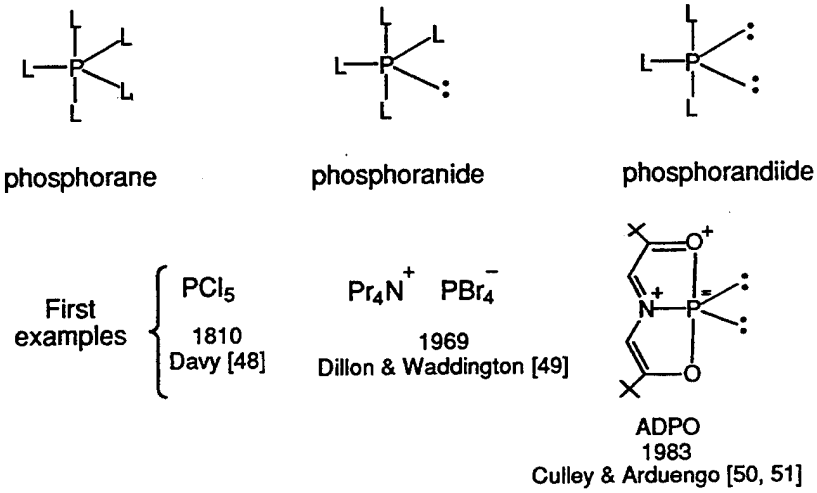
perpendicular form

Review by Gilheany, 1994 [40]

carbon from the lone pair of electrons from phosphorus and a π back–bond from a filled p orbital on the anionic–like carbon to one of two possible acceptor orbitals on phosphorus which are antibonding in character with respect to the other ligands on phosphorus. Since the back bonding is to antibonding phosphorus orbitals in both perpendicular and parallel conformations of the phosphonium ylide, this would rationalize the low barrier to rotation about the phosphorus–carbon bond, in the range of 4–5 kJ/mol [45–47].

Next we will look at phosphoranides, phosphorandiides, and their metal complexes. Scheme 20 shows these formulations and their relationship to phosphoranes, the latter of

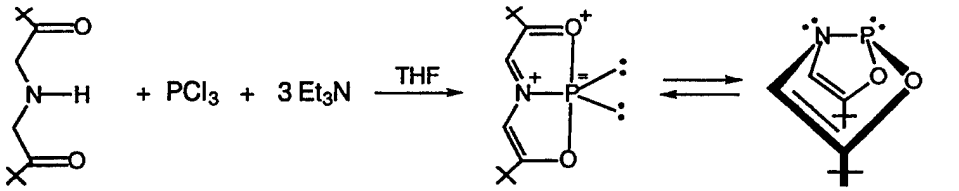
SCHEME 20



ADPO = 5 aza–2,8–dioxa–1–phosphabicyclo[3.3.0]octa–2,4,6–triene

which have been known for an extremely long time [48] compared to the phosphoranides [49] and diides [50, 51]. Phosphoranides play a role as models for reactive intermediates in nucleophilic substitution reactions at phosphorus(III) centers [52]. The formations of members of these two classes follow relatively simple syntheses, Schemes 21 [51] and 22 [49]. However, the availability of suitable starting ligands and ease of hydrolysis, *e.g.* ADPO rapidly hydrolyzes in moist CH_2Cl_2 in minutes at room temperature [53], no doubt enters into the late arrival of the phosphorandiides. In the case of phosphoranides, stability may be increased by forming cyclic organophosphoranides (Scheme 23 [55]) and by incorporating strongly electron withdrawing ligands such as CN, CF_3, or C_6F_5 [52]. As yet, no transition metal complexes have been formed with acyclic phosphoranides [52], although such possibilities exist.

SCHEME 21 Synthesis of the first phosphoranidiide



^{31}P, 187 electromorphism

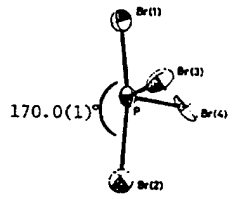
Culley & Arduengo, 1984 [51]

SCHEME 22 First phosphoranide
(Dillon and Waddington, 1969 [49])

$$n\text{-}Pr_4N^+Br^- + PBr_3 \xrightarrow{ClCH_2CH_2Cl} [n\text{-}Pr_4N]^+[PBr_4]^-$$

^{31}P, –229 ppm ^{31}P, –150 ppm

Fumes readily in air



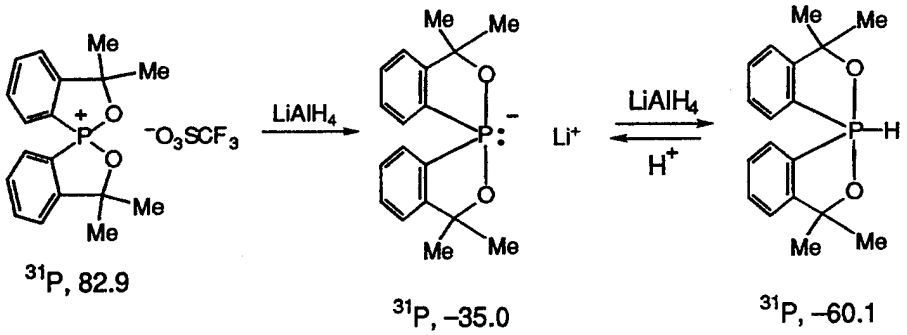
Sheldrick et al., 1981 [54]

ORTEP plot of PBr_4^- in $[Pr_4N]^+[PBr_4]^-$.

$P–Br_{ax}$ = 2.527(4)Å, 2.620(4)Å

$P–Br_{eq}$ = 2.221(3), 2.255(3)Å

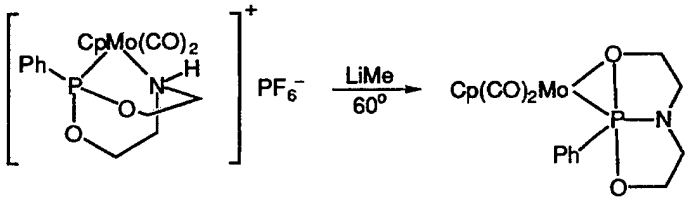
SCHEME 23 First cyclic organophosphoranide



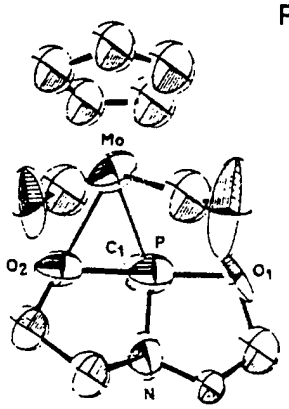
Granoth & Martin, 1978 [55]

The first phosphoranide metal complex was obtained by Riess and coworkers [56] and is shown in Scheme 24. With platinum, the formation of both (cyclen P)PtCl(PPh$_3$) [57] and

SCHEME 24 First phosphoranide metal derivative



P–N$_{eq}$ = 1.69Å ^{31}P, 23.8

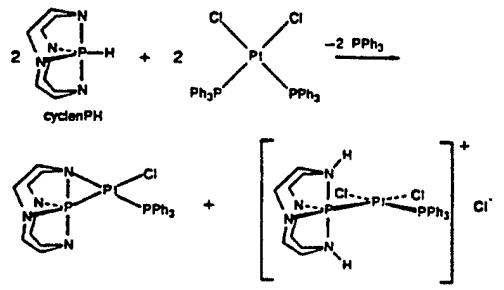


Molecular structure of the Mo complex; only the C–1 atom of the phenyl group bonded to phosphorus is included, for clarity.

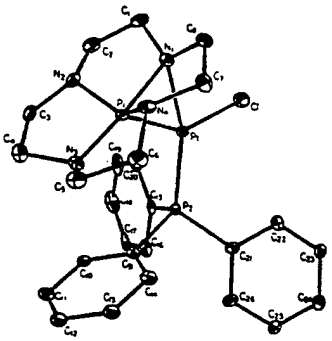
Riess & coworkers, 1981 [56]

[(*cis*–H_2 cyclen P)$PtCl_2(PPh_3)$]$^+Cl^-$ [58] occurred from the reaction of *cis*–$Cl_2Pt(PPh_3)_2$ with cyclen PH in THF, Scheme 25 [59].

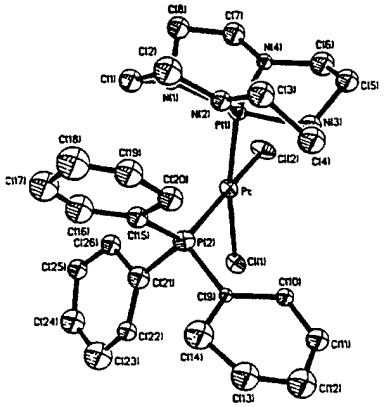
SCHEME 25 Phosphoranide metal complexes



^{31}P, –55 ^{31}P, –59



ORTEP view of (cyclen P)PtCl(PPh_3) [57]

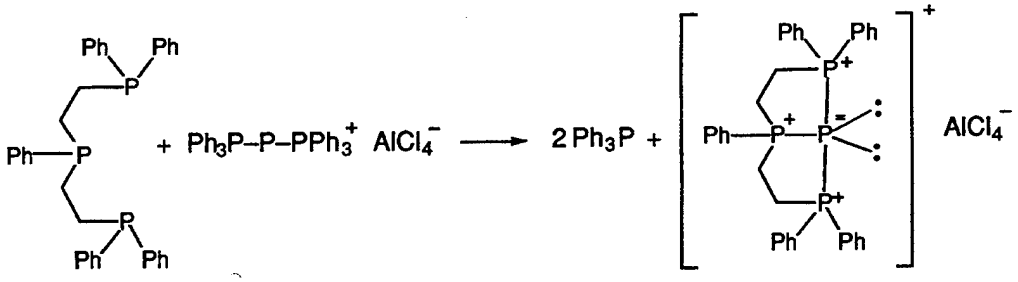


ORTEP drawing of the cation [(*cis*–H_2cyclen P)$PtCl_2PPh_3]^+Cl^-$ [58]

Lattman and coworkers, 1987 [57–59]

An all phosphorus phosphorandiide was synthesized by Schmidpeter and Lochschmidt [60] in 1985 (Scheme 26), shortly after the report of Culley and Arduengo on ADPO [50, 51].

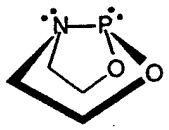
SCHEME 26 All phosphorus phosphorandiide



^{31}P, 65.1

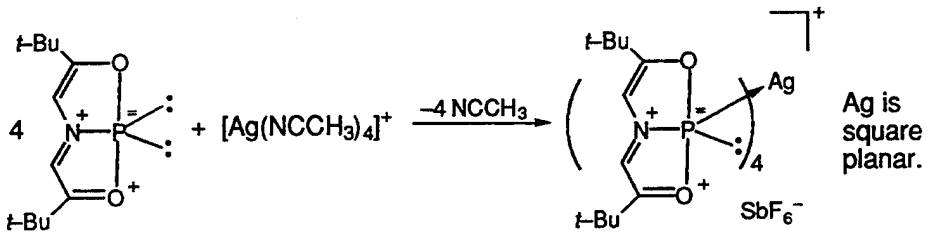
Schmidpeter & Lochschmidt, 1985 [60]

Due to the electromorphism associated with phosphorandiides like ADPO in Scheme 21, metal complexation can take place via the planar or folded geometries, both of which are considered potential ground state structures where the more classical folded arrangement is calculated to be about 14 kcal/mol above the planar form [61]. Wolf and coworkers [62–65] have found many related structures in the folded form for saturated bicyclic compounds.



For ADPO derivatives, only when the metal interaction with phosphorus is sufficiently weak as with Ag^+ is the planar form observed, Scheme 27 [66]. For most transition metals, the bond to phosphorus exceeds the 14 kcal/mole barrier and the folded geometry prevails. By contrast, antimony or arsenic in place of phosphorus in ADPO type compounds have higher barriers from the planar geometry to the less stable folded form such that the planar form on metal coordination is the preferred geometry [61], Scheme 27 [67].

SCHEME 27 Phosphorandiide metal complexes



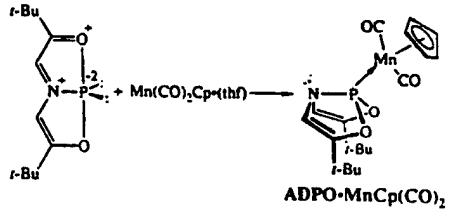
ADPO

^{31}P, 187

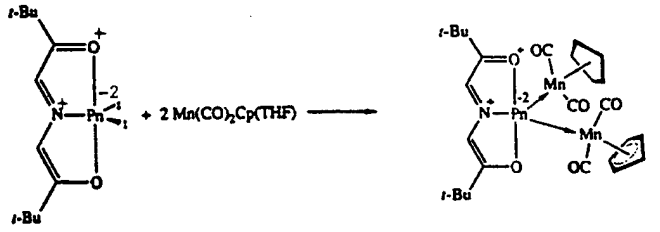
$[(ADPO)_4Ag]+SbF_6^-$

^{31}P, 166

Arduengo, Dias & Calabrese, 1991 [66]



^{31}P, 256



Pn = Sb, As

Arduengo et al., 1991 [67]

We turn now to metal complexes of the phosphazenes and phosphazanes. A large variety of materials are possible due to the different electron donor abilities of phosphorus and nitrogen [68]. Nitrogen, which is a hard base, has the ability of stabilizing metals in their higher oxidation states. In contrast, phosphorus, which acts as a soft base, is more prone to stabilize metals in lower oxidation states. The first metal phosphorus–nitrogen compounds date back to those of Payne and coworkers in 1962 [69], Scheme 28.

SCHEME 28 Metal coordinated phosphazenes and phosphazanes

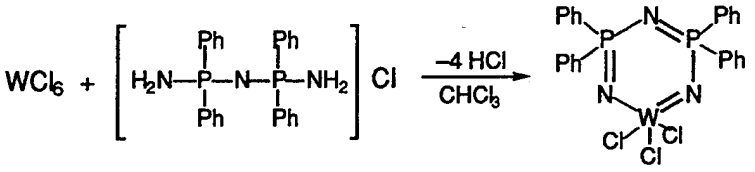
First Metal P–N Compounds

$Ph_2PNEt_2{\cdot}HgI_2$

$[Ph_2PNEt_2CuI]_4$

Payne et al., 1962 [69]

First Cyclic Phosphazene with a Metal Atom in the Ring



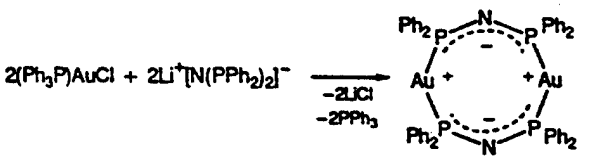
Roesky et al., 1986 [70]

The first cyclic phosphazene with a metal atom in the ring was synthesized more recently by Roesky et al. [70] in 1986, Scheme 28. Depending on the hardness of the metal, bonding to phosphorus or nitrogen is established to some degree. With softer metals like Au^+ [71] or R_2Ga^- [72], bonding takes place preferentially with the softer phosphorus atom, Scheme 29. With Me_2Al^- [72] and Ni^{2+} [73], bonding to both phosphorus and nitrogen occurs, Scheme 30, whereas with the use of Na^+, which is a hard acid, bonding with the harder nitrogen atom is found, Scheme 31 [74]. K^+ and Ca^{++} also bond to nitrogen atom similarly to Na^+ in terms of the local framework of the phosphazene [74]. This area has given rise to a great variety of cyclic main group and transition metal phosphazanes and phosphazenes, some of which have had applications as catalysts and precursors for new materials [68].

SCHEME 29 Metals bonded to phosphorus

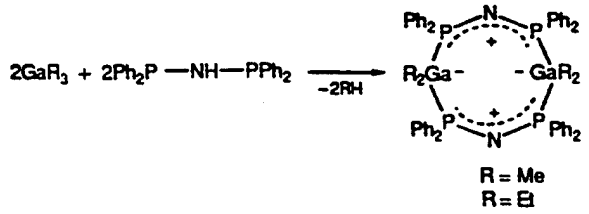
Soft P–Soft Metals

Negative charge over P–N–P skeleton



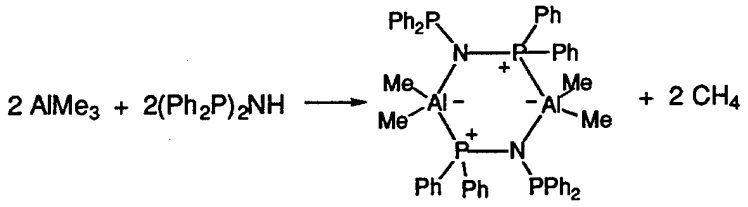
Uson et al., 1986 [71]

Positive charge over P–N–P skeleton

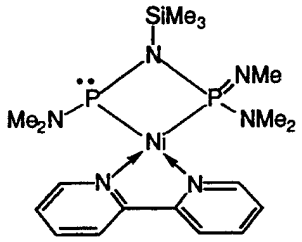


Schmidbaur & coworkers, 1983 [72]

SCHEME 30 Metals bonded to phosphorus and nitrogen



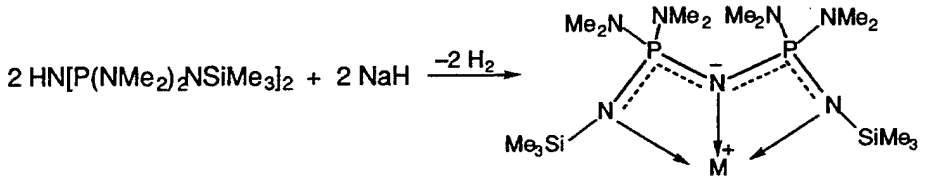
Schmidbaur et al., 1983 [72]



Scherer et al., 1985 [73]

SCHEME 31 Metals bonded to nitrogen

Hard N–Hard Metals



Roesky et al., 1993 [74]

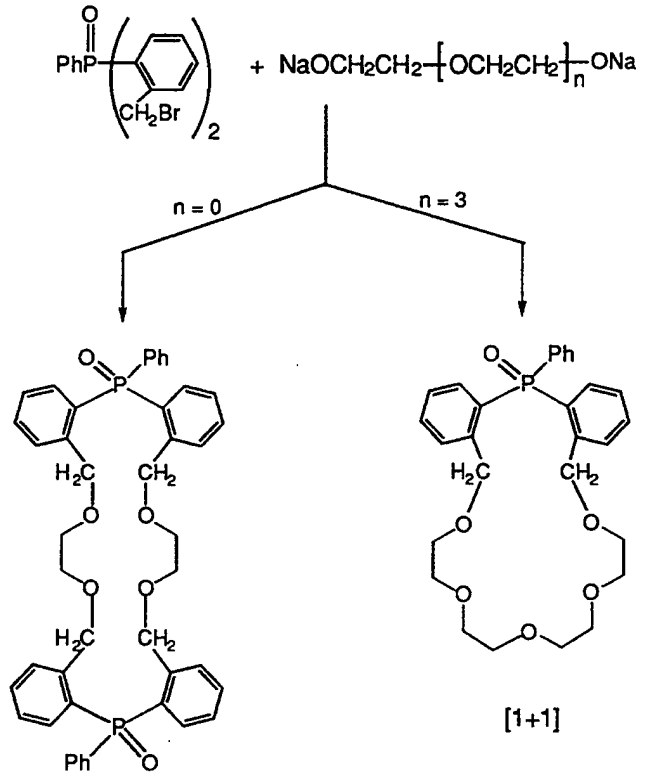
$M^+ = Na^+, K^+, Ca^{2+}$

By incorporating phosphorus in macrocycle environments, advantage may be taken of its high complex fomring ability and its softness in stabilizing transition metals in low oxidation states [75]. Some of these phosphorus containing macrocycles have been found to transport transition metals through liquid membranes. Potential applications in homogeneous catalysis and phase–transfer catalysis are also visualized [75]. Members of

this class are obtained by cyclocondensation reactions, the most common method. Several examples are depicted in Schemes 32 [76] and 33 [77–89].

SCHEME 32 Phosphorus macrocycles

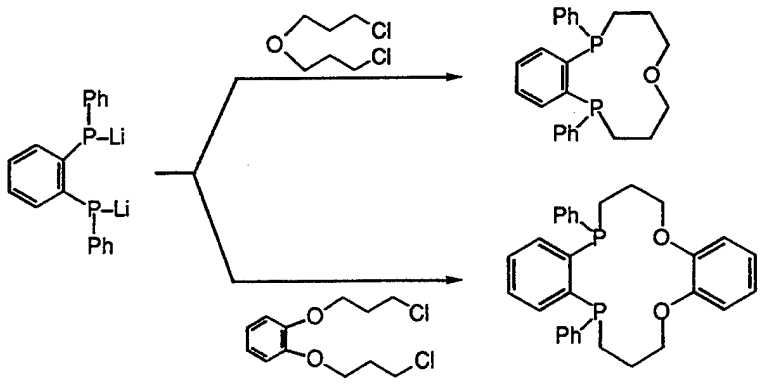
Synthesis by cyclocondensation



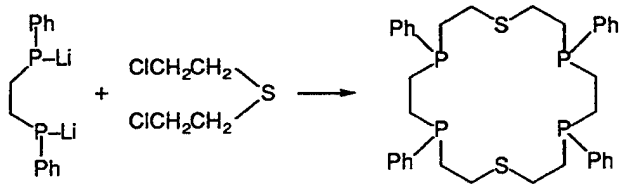
Kaplan, Weisman & Cram, 1979 [76]

This method was developed by Kyba and coworkers [75, 77–80] from 1977 to 1985, and further explored by Ciampolini and coworkers [75, 81–89] during 1980–1986. Other lesser used methods involve ring opening reactions and template reactions. Most of the ring opening reactions focus on cyclophosphazenes and tetraaminophosphorane derivatives [75].

SCHEME 33 Cyclocondensations were developed under high dilutions



Kyba & coworkers, 1980–1985 [77–80]

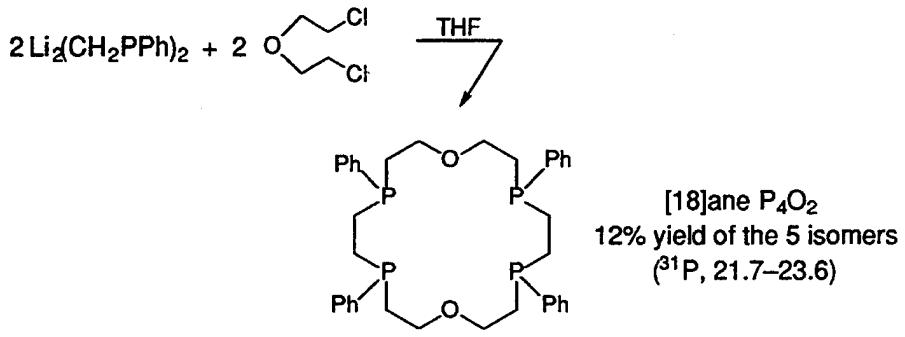


Ciampolini & coworkers, 1980–1986 [81–89]

Of the many metal complexes that are known [75], Scheme 34 shows the first crown ether phosphorus macrocycle encapsulating low spin cobalt(II) in both a square pyramid and an octahedron [90, 91].

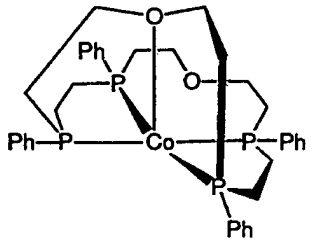
An interesting reaction takes place between a polyoxy macrocycle and hexamethylphosphoric triamide. Instead of the expected pentacoordinate phosphorus product, hexacoordination is observed in the form of zwitterionic *p–t*–butylcalix[4]arene–$P(H)NHMe_2$ [92], Scheme 35. An X-ray structure of the lithium salt has been obtained [93].

SCHEME 34 Macrocycle–Transition metal complexes

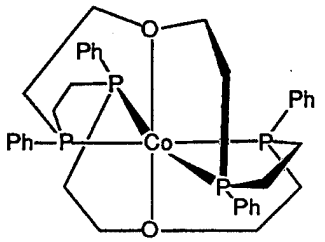


First Crown Ether Phosphorus Macrocycle

Low–Spin d^7 Co(II) Complexes



Square pyramid, Co–O = 2.26Å



Octahedron, Co–O = 2.35Å

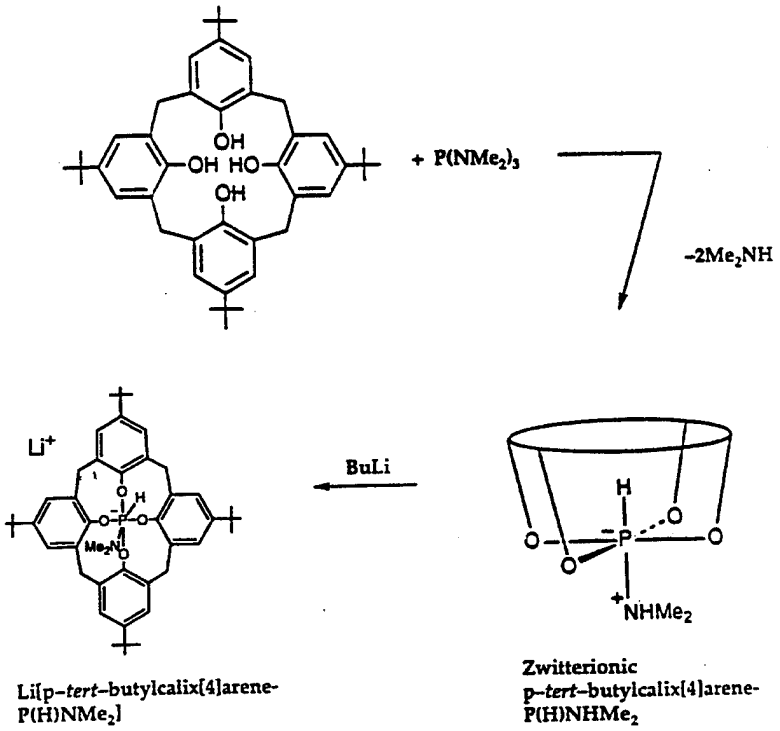
$[Co(\alpha\text{-}[18]aneP_4O_2]^{2+}[BPh_4]_2$

$[Co(\beta\text{-}[18]aneP_4O_2)]^{2+}[BPh_4]_2$

Ciampolini et al., 1980 [90], 1982 [91]

In our excursion through phosphorus chemistry, little mention had been made of compounds having a coordination number of six, although the number in this class is growing. Burgada and Setton have provided a recent summary of this topic [94]. We record here representative members formed by donor action for the most part and whose X-ray

SCHEME 35 First Calixarene–Hypervalent main group atom structure



Li[p-*tert*-butylcalix[4]arene-P(H)NMe_2]

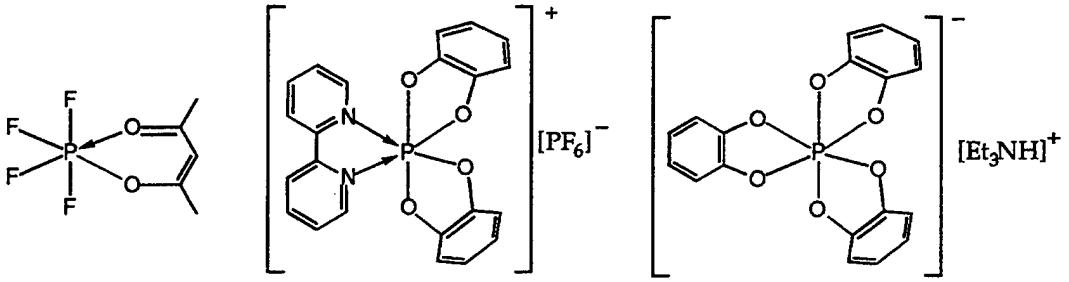
Zwitterionic p-*tert*-butylcalix[4]arene-P(H)$NHMe_2$

^{31}P, –120

Lattman and coworkers, 1990 [92], 1991 [93]

structures have been determined, Schemes 36 [95–97], Table 6 [98–102], and Scheme 37 [103a]. Sulfur induced hexacoordination (Scheme 37) is the latest example where a range of structures have been formed [103] whose geometries lie progressively from a square pyramid toward an octahedron. Just as pentacoordinate phosphorus compounds [104a] have

SCHEME 36 Hexacoordination (X-ray)

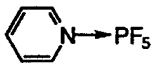
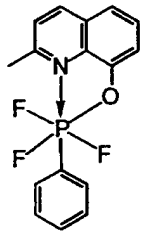
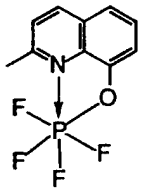
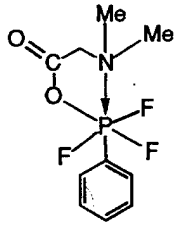


Sheldrick & Hewson, 1978 [95]

Sheldrick, Schmidpeter, von Criegern, 1978 [96]

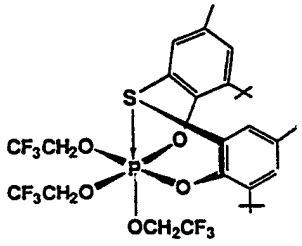
Allcock & Bissell, 1973 [97]

TABLE 6 Nitrogen induced hexacoordination

	P–N, Å		P–N, Å
	1.885(4)		1.980(3)
$H_3N \rightarrow PF_5$	1.842(2)		
	1.911(4)		2.013(4)
		P–N covalent	1.85

Schmutzler, Sheldrick, Schomburg & coworkers, 1974–1989 [98–102]

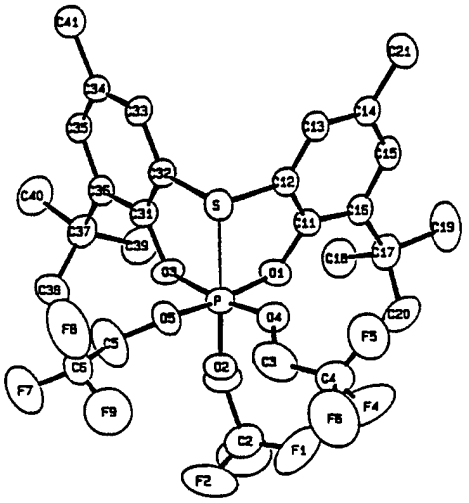
SCHEME 37 Sulfur induced hexacoordination



P–S = 2.362(2)Å

P–S Σ cov radii = 2.14Å

Σ van der Waals' radii = 3.75Å

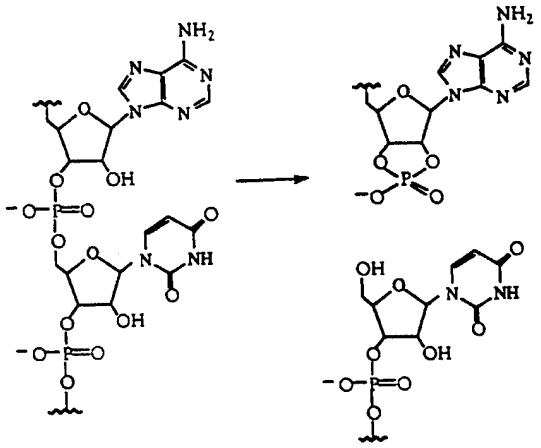


Holmes, Prakasha, & Day, 1993 [103a]

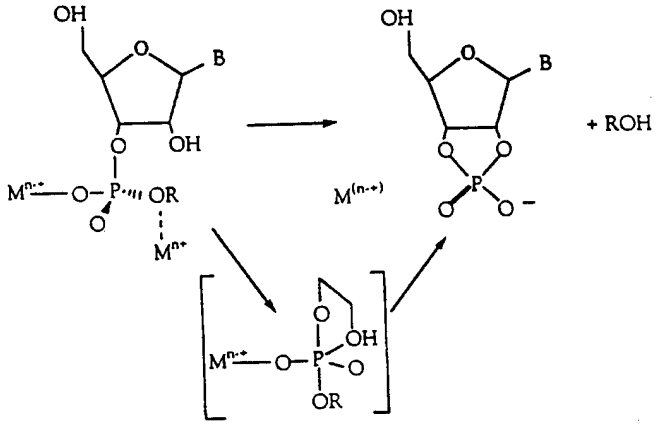
been found to provide useful models for nucleophilic displacement reactions at tetracoordinate centers [104b], hexacoordinate compounds should have applicability as models for nucleophilic displacements at pentacoordinate phosphorus centers.

In the area of enzyme action with phosphorus substrates, models are widely used to mimic catalytic features [104b]. An overview by Janet Morrow [105] discusses recent work on catalysts for substitution reactions of phosphorus(V) constituents of nucleic acids involving metal ion interactions. The metal ions assist by binding to the phosphate to increase its susceptibility to nucleophilic attack or by binding to the leaving group to assist its departure, Scheme 38 [105]. Hydrolytic cleavage of phosphate ester bonds by a number of important enzymes are known to use two metal ions [106–110]. In this connection, Tsubouchi and Bruice [111] reported a remarkable 10^{13} rate enhancement in the hydrolysis of a monoalkyl phosphonate ester assisted by two lanthanum cations. The two La^{3+} ions provide the first example of double metal cooperativity consisting of a proposed in-line intramolecular attack of metal-bound hydroxide in a TBP activated state and Lewis acid activation of the departing oxyanion leaving group, (Scheme 39), producing (8–hydroxy–2–quinolyl)methanol.

SCHEME 38 RNA cleavage by phosphate ester transesterification

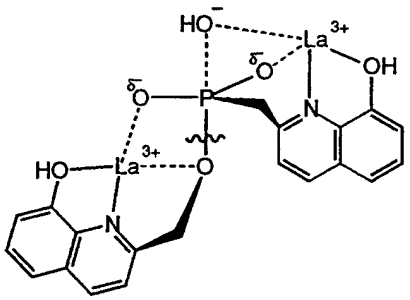


Metal Ion Catalyzed RNA Transesterification



Morrow, 1994 [105]

SCHEME 39 Phosphonate ester hydrolysis enhanced 10^{13} by lanthanide ions

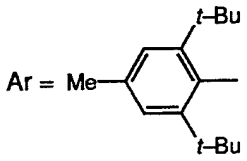


Proposed Intermediate

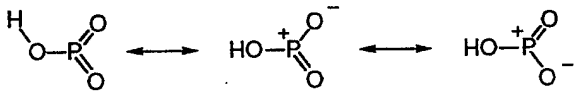
Tsubouchi & Bruice, 1994 [111]

Throughout this presentation, ^{31}P chemical shifts have been recorded and serve admirably to give an indication of the extent of coordination at phosphorus and structural changes encountered on going from the solid state to solution [112]. As discussed by Gorenstein [113], in connection with nucleic acid chemistry, ^{31}P NMR has come to be a powerful probe in providing valuable information on the phosphodiester backbone conformation present in nucleic acids and nucleic acid complexes in solution which at times may not be the same as that provided by X-ray diffraction in the solid state.

On the theoretical side, considerable progress in the interpretation of experimental ^{31}P chemical shifts has been made through computational methods. Quin and Chesnut [114a] and Chesnut and Rusiloski [114b] have summarized recent work in this area and provide an illustration on the extent of agreement achieved for isotropic shieldings at optimized geometries for some simple phosphorus compounds based on Ditchfield's gauge including the atomic orbital (GIA) coupled Hartree–Fock method [115], Table 7. The error is about 28 ppm over a range of 950 ppm. The agreement is deemed close enough to have predictive value. In this connection, the authors [114] cite evidence for a ^{31}P shift observed at 238 ppm which was assigned to the first phosphenite, ArO–P=O. The calculated shielding value



for a model compound (Ar = Ph) in a perpendicular *syn* form was 254 ppm which tends to confirm the structural assignment to the phosphenite. Also future experiments are encouraged to detect both the unknown metaphosphoric acid and the unknown phosphinidene oxide, H–P=O.



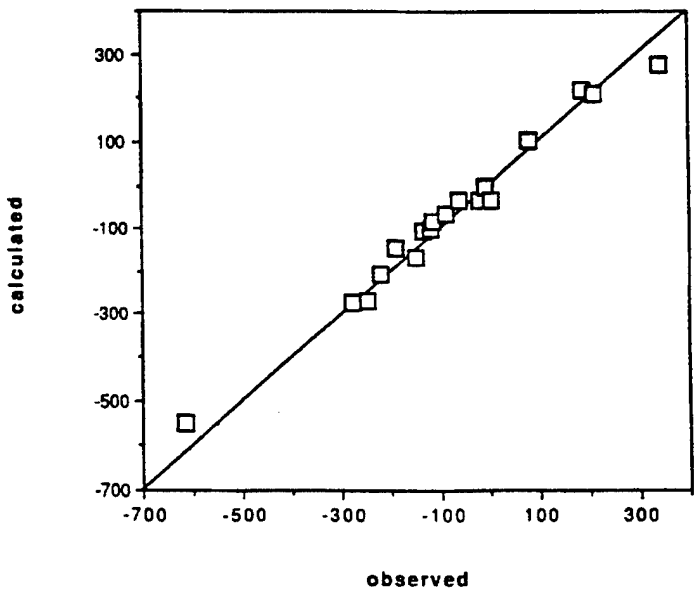
Values of 48.9 ppm for the fully planar form of the metaphosphoric acid and 649.3 ppm for the phosphinidene oxide have been calculated [114].

So can we say anything significant about the future of phosphorus chemistry. Each of you is in an unique position, with somewhat different perspectives, about new directions that phosphorus chemistry might take. It is difficult and no doubt hazardous to make such predictions. So much depends on unforeseen events, those rather rare but special occurrences that when properly recognized and followed up on may give rise to entirely

TABLE 7 ^{31}P chemical shifts

molecule	calc. [a]	obs.
P_4	-617.3	-551.4 [b]
PH_2^-	-335.1	(-279.4)
H_3SiPH_2	-277.1	-274
PH_3	-249.2	-266.0 [b]
H_2PPH_2	-222.1	-204
PF_6^-	-191.7	-143.7
CH_3PH_2	-149.7	-163.5
PH_4^+	-134.0	-105.3
$(CH_3)_2PH$	-115.7	-99
PF_5	-114.3	-80.2
$(CH_3)_3P$	-87.9	-63.3 [b]
OPF_3	-58.1	-35.0 [b]
HCP	-19.5	-32
PO_4^{-3}	-4.5	0.0 [c]
C_6H_5CP	4.6	-32
PF_3	83.4	105.7
PCl_3	189.4	217.1 [b]
C_5H_5P	211.7	211
rmse		28.3

a. At optimized geometries.
b. Gas phase result.
c. 85% H_3PO_4.



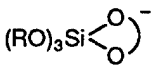
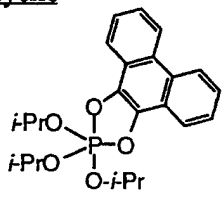
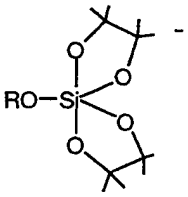
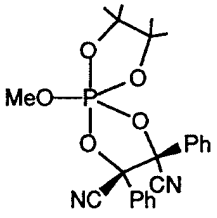
Quin and Chesnut, 1995 [114a]

new areas of chemistry. However, we can expect that the next quarter of a century should be at least as spectacular as the last in providing new discoveries leading to developments that at present cannot be anticipated. What I can say is that the chemistry of all the coordination types will enjoy continued exploration and advancement along with their synthetic and structural elucidation.

I feel there is a special need for the assistance afforded by theoretical methods of all types including computer graphics to better understand mechanistic features of reactants, intermediates, proposed transition states and products. Also in our planning, it would serve us well to look at related chemistries, perhaps not even in the same periodic family, that can give us additional perspective and insight not otherwise readily available and lend to a more rewarding and rapid advance of our research. Comparisons of this type that have proven useful in this way are found between isoelectronic phosphorus and silicon pentacoordinate molecules in our own research [104a, 116–118] (Table 8) and in structural analogies between SiO and PN species, as discussed by Schmidpeter and coworkers [119], Table 9. I appeal in particular to the younger members of the community to take a broad view of research and not spend your entire research career on too narrow a focus.

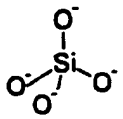
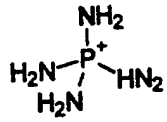
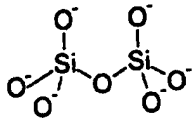
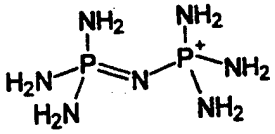
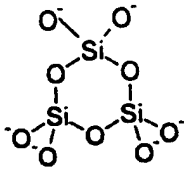
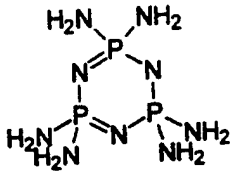
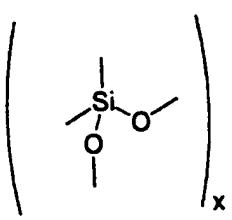
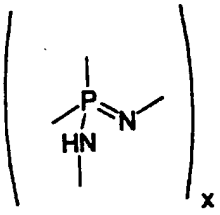
At the entrance of Bell Telephone Laboratories in Murray Hill, New Jersey, where I had been employed before joining university life once more, there is an inscription at the base of a statue of Alexander Graham Bell which may be particularly apropos to end my lecture: "Leave the beaten track occassionally and dive into the woods. You will be certain to find something you have never seen before." (Alexander Graham Bell)

TABLE 8 Comparative stability of pentaoxy silicates and pentaoxy phosphoranes [104a, 116–118]

Acyclic			
$Si(OR)_5^-$	detected but not isolated	$P(OPh)_5$	X-ray
Monocyclic			
	no known examples		X-ray (many other examples) with rings from 5 to 8 membered
Bicyclic			
	A few examples studied by X-ray		X-ray (many others with rings from 5 to 8 membered

All Si are K^+,18-crown-6 salts.

TABLE 9 Isoelectronic SiO and PN species

SiO_4^{4-}			$H_8PN_4^+$
$Si_2O_7^{6-}$			$H_{12}P_2N_7^+$
$Si_3O_9^{6-}$			$H_{12}P_3N_9$
$(SiO_2)_x$			$(HPN_2)_x$

Schmidpeter, Horstmann & Schnick, 1995 [119]

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ORAL PRESENTATIONS

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FLUORHYDROXYAPATITES OF NORTHERN EUROPE AND THEIR THERMAL TRANSFORMATIONS

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Abstract Peculiarities in the composition, structure and thermal properties of fluorhydroxyapatites of Northern Europe have been studied by XRD, FTIR, chemical and thermal analyses.

Key Words: Phosphate rock, fluorhydroxyapatite, properties, thermal transformations.

A belt of apatite containing rocks in Northern Europe is known mainly from Kola apatite rock which is a typical igneous fluorapatite relatively well corresponding to the ideal formula $Ca_{10}(PO_4)_6F_2$. The apatites of Kovdor (North Karelia), Siilinjärvi (Central Finland) and Kiruna (North Sweden) deposits being already exploited and of Sokli deposit (North Finland) discovered recently represent fluorhydroxyapatites (F,OHAp) $Ca_{10}(PO_4)_6F_{2-n}(OH)_n$.

As a result of rock enrichment apatite concentrates (ApC) containing 32-37 % of P_2O_5 are obtained. They differ, to some extent by the composition and structure of the apatitic mineral, but essentially by the origin and quantity of the accompanying minerals (Table). In spite of a higher reactivity these ApC are more complicated raw materials for processing in comparison with the high quality Kola ApC. Nevertheless, Siilinjärvi ApC is used for the production of phosphoric acid by wet method, Kovdor ApC for obtaining feed phosphates by thermal processing.

The content of fluorine in Siilinjärvi and Kiruna Ap is approximately the same ($n = 0.5$-0.7), in Kovdor Ap much lower ($n = 1.3$-1.4). The main accompanying minerals in Kovdor ApC are calcite, dolomite and forsterite, in Siilinjärvi ApC calcite and flogopite, and in Kiruna ApC calcite, talc and magnetite.

Differences in the structure and thermal properties of the Ap have been studied by the methods of XRD (DRON-4), IR spectroscopy (Nicolet FTIR with FSD), thermal (MOM) and chemical analyses. For XRD and IR studies the ApC were previously treated by triammonium citrate solution for the elimination of calcite and dolomite.

TABLE Characteristics of apatite concentrates

Chemical composition, %	Kola	Kiruna	Siilinjärvi	Kovdor
P_2O_5	39.6	31.5	36.4	36.5
CaO	52.0	51.5	53.1	51.1
MgO	0.2	0.8	1.4	2.7
F	3.3	2.1	2.4	1.0
SiO_2	0.7	3.0	0.5	1.4
CO_2		6.5	4.4	3.4
Fe_2O_3	0.4	1.9	0.5	0.5
Molar ratio F/6P	1.87	1.49	1.48	0.61
Unit cell parameters, Å				
a, ±0.002	9.384	9.403	9.402	9.403
a*,±0.005		9.394	9.398	9.400
c, ±0.005	6.893	6.904	6.904	6.884

* calcined at 1350 °C in air.

The XRD patterns of the apatites are typically apatitic, with slight shifts in peak positions and intensities. The unit cell parameter *a* changes from 9.421 to 9.376 Å in accordance with the increase in fluorine content in the Ap (Table). Changes in the unit cell parameters are influenced also by the other substitutions and by differences of the ion positions in the Ap structure, specified by means of IR spectra.

In IR absorption spectra of the igneous Ap beside the typical bands of PO_4^{3-} asymmetric deformation ν_4 at 605, 570 cm^{-1}, symmetric valence ν_1 oscillation at 963 cm^{-1} and asymmetric valence ν_3 oscillation at 1042, 1093 cm^{-1}, also other bands are usually revealed, belonging to the OH-groups on the hexagonal axis of the Ap crystal, to P-O-P bond and to CO_3^{2-} group in the PO_4^{3-} position or on hexagonal axis.

A comparison of the Ap spectra in the domain of valence oscillations of OH-group testifies that the maximum spreading of OH...F (3543 cm^{-1}) and OH...O (3566 cm^{-1}) bonds occurs in Kovdor Ap (Fig.1a). The half-width of these bands gives an evidence of a lower regularity of the ions on the hexagonal axis and of the presence of defects. In Siilinjärvi Ap also OH...F and OH...O bonds were detected, but the integral intensity of the bands is lower and the bands are narrower and thus the regularity of the structure is higher. In Kola and Kiruna Ap where the fluorine content is higher, only OH...F band occurs. These data are in agreement with the data of libration oscillations of the OH-group in the studied Ap (Fig.1a). Only in the Kovdor Ap spectrum the

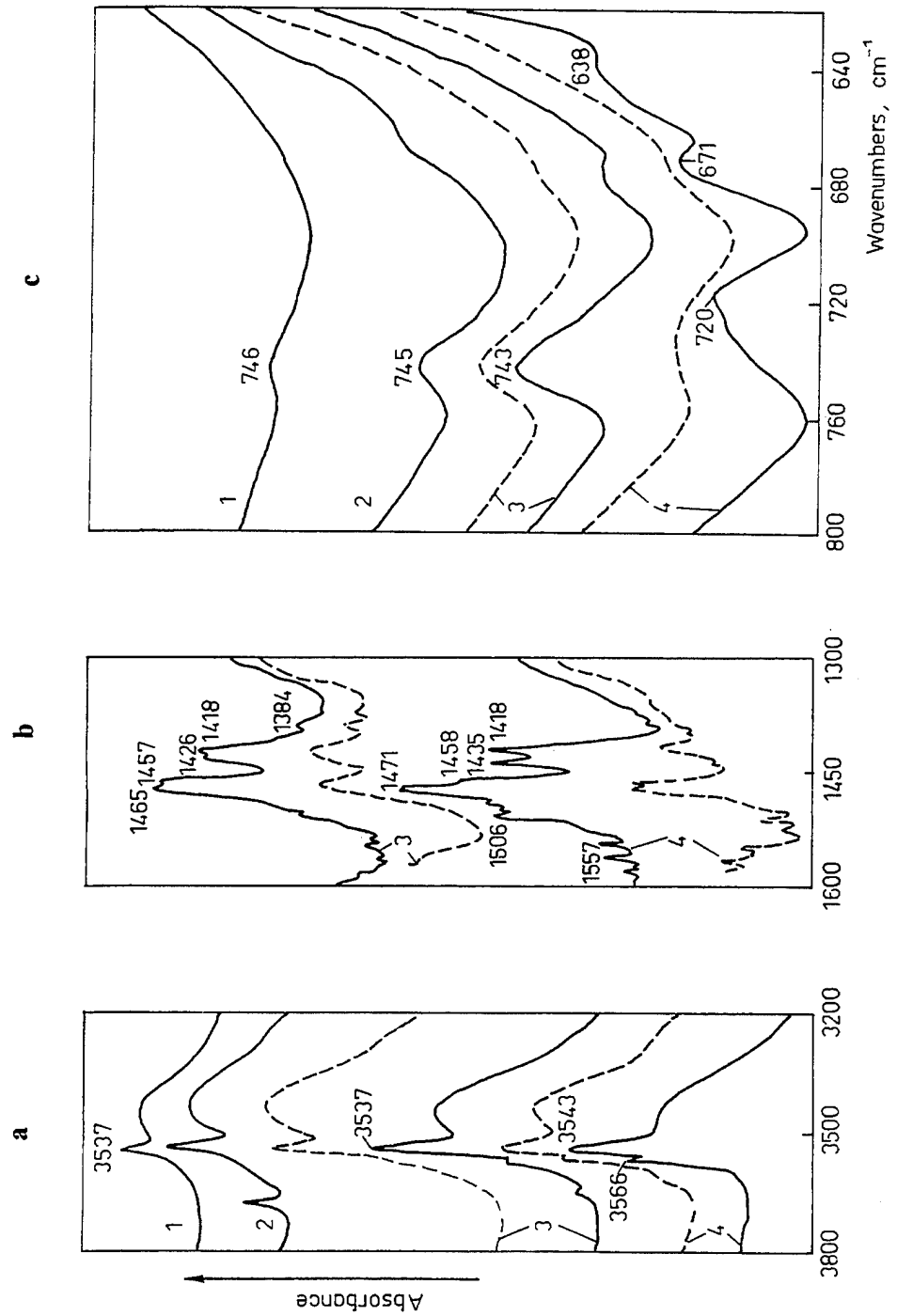


FIGURE IR spectra of Kola (1), Kiruna (2), Siilinjärvi (3) and Kovdor (4) apatites.
—— initial sample; - - - - - sample calcined at 1350 C

bands at 671 and 638 cm^{-1} belonging to librations of the OH-groups in the OH...F and OH...O bonds, respectively, were both distinctly fixed. In the spectra of the other Ap only weak bands at 671 cm^{-1} were seen.

In Fig.1c the bands at 720 and 745 cm^{-1} belonging to the symmetric valence oscillations of P-O-P bridge bonds, formed by the condensation of PO_4^{3-} tetrahedron, are also well seen. The band at 720 cm^{-1} is well expressed only in case of Kovdor Ap. In Kola Ap spectrum only the band at 745 cm^{-1} exists and the P-O-P bond oscillation has the lowest intensity.

Due to the low content, identification of CO_3^{2-} group in Ap structure and its belonging to the A or B type of carbonateapatite (substitution for OH-groups or for PO_4^{3-} ions, respectively) is more complicated. Fig.1b. represents baseline corrected spectra of the Ap studied in the domain of CO_3^{2-} ion oscillations. There are probably at least 7 bands: at 1559, 1540, 1506, 1471-1465, 1458-1456, 1434-1426 and 1417-1419 cm^{-1} from which can be concluded that they all contain CO_3^{2-} ions both at A and B positions. The Kovdor Ap contains CO_3^{2-} ions as well as OH^- ions, to a maximum extent.

On calcination of ApC the main thermoeffect with the maximum at 860 °C is connected with decomposition of carbonates. Thereafter, at 1100 °C, decomposition of Ap begins, fixed by a weight loss in TG curves. The weight loss at 700-900 °C is the biggest for Kiruna ApC, at temperatures higher than 1000 °C for Kovdor ApC, which corresponds to the highest content of carbonates and OH group.

The XRD patterns of Kovdor and Kiruna Ap calcined at 1350 °C show the appearance of ß-$Ca_3(PO_4)_2$ formed as a result of decomposition of F,OHAp. The decrease in the unit cell parameter *a* (Table) indicates that the Ap structure is changing into FAp structure. This phenomenon is confirmed also by the decrease in the band intensity at 720 cm^{-1}, that belongs to the P-O-P bond, and by relocation of this band to 736 cm^{-1}. The decrease in the band intensities at 3543 and 3566 cm^{-1} (Fig.1a), and the appearance of a new band at 435 cm^{-1} is an indication of a decrease in OH...F and OH...O bonds and the appearance of molecular oxygen in the channels of Ap structure. The intensity of CO_3^{2-} bands has sharply decreased as a result of calcination, especially of those at B position (at 1471, 1458, and 1435 cm^{-1} for Kovdor Ap and 1465, 1457, and 1426 cm^{-1} for Siilinjärvi Ap, Fig.1b.). That conforms with the higher endurance of A type CO_3^{2-} group substitution in Ap on calcination.

Similar changes in the F,OHAp structure occur during thermal processing of ApC for obtaining feed phosphates or fertilizers.

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PHYSICAL PROPERTIES OF CALCIUM PHOSPHATES GLASSES WITH VARIOUS CaO/P_2O_5 MOLE RATIOS

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Abstract

The physical properties of calcium phosphate glasses with various CaO/P_2O_5 mole ratios, Vicker's surface hardness, weight loss percentage after dipping Ringer's solution were investigated in this study. The best surface hardness of crystallized glass has an average hardness of 670Kg/mm^2 and the minmum weight loss percentage of crystallized glass were lower than 1%. The major crystalline phase that developed after heat treatment of these glasses was β-$Ca(PO_3)_2$ which characterized by X-ray powder diffraction method, and we found that the rod-like (3-5 μmD x 60 μmL) β-$Ca(PO_3)_2$ crystals from the photograph of SEM, the oxides composition of crystal was examined by EDS analysis also.

INTRODUCTION

Calcium phosphates ceramics are well known in bio-implant material applications because of their good biocompatibility, but the product of these ceramics is insufficient to make them useful as bone implant materials. Recently studies have been devoted to improving the mechanical properties of calcium phosphates.
β-$Ca(PO_3)_2$[1-2] fiber is expected to be for new composite-biomaterials. In this study, we tried to find the β-$Ca(PO_3)_2$ crystalline by changing the glass composition from traditional melting glass rod. The physical properties of calcium phosphates with various CaO/P_2O_5 mole ratios will be discussed.

MATERIALS AND METHODS

Batch mitures with CaO/P_2O_5 = O.73, 0.85, 1.0, 1.1 in mole ratio were prepared by using $Ca(H_2PO_4)_2 \cdot H_2O$, $CaCO_3$ and H_3PO_4. The composition of raw material were listed in Table 1. The mixtures were mixing with ethanol for 30 min. in a ball miller, after drying, the mixtures were melted for two stage in a platinum crucible at 850°C for 30 min.,and then 1250°C for 2 hour. The melts were poured onto a preheated graphite plate (280°C), then cooled to room temperature.
The glasses obtained from graphite plate were reheated at nucleation temperature maintaining 2 hours then at crystallization temperature for another various hours. The crystalline phases in the resultant products were identified by X-ray diffraction analysis (XRD).The morphologies of the crystalline were observed by scanning electron microscopy (SEM), and the chemical composition of crystalline were examined by EDS analysis. The physical properties such as Vicker's surface hardness, weight loss percentage after dipping in Ringer's solution for 14 days were examined also.

RESULTS AND DISCUSSION

The X-ray diffraction analysis of the resultant products, after various heat treatment procedure were showed as Figure 1, we found that the intensity of characteristic peak of β-$Ca(PO_3)_2$ enhancing with the duration time of heat treatment at crystal growth stage. The β-$Ca(PO_3)_2$ crystal was appeared at lower CaO/P_2O_5 mole ratio calcium phosphate glass.

The surface micrograph of the resultant product of glass D show as Figure 2. It was possessed the rod-like (3-5 μmD x 60 μmL) crystalline of β-$Ca(PO_3)_2$, the chemical composition of β-$Ca(PO_3)_2$ crystalline was examined by EDS, the energy-dispersive X-ray analysis of glass D was shown as Figure 3, the weight percentage composition of CaO/P_2O_5 was similared with the composition of β-$Ca(PO_3)_2$. We also found the glass-crystal interface show as Figure 4.

The Vicker's surface hardness of the resultant products after heat treatment were shown in Table 2. The Vicker's surface hardness of resultant product of glass C appeared the highest Vicker's surface hardness, 670 Kg/mm^2. On the other hand, the density of these glass-ceramics were between 1.7 to 2.5 g/cm^3.

The weight loss percentage of the resultant products after heat treatment procedure, then dipping in Ringer's solution for 14 days were shown as Table 3, the weight loss percentage of the resultant product of glass D has a big weight loss percentage, the maximum value is 38.3%, but the weight loss percentage of the resultant product of glass B was lower than 1%.

CONCLUSION

In this work, the following conclusions can be drawn:

(1) The major crystalline phase of glass D that developed after heat treatment procedure was β-$Ca(PO_3)_2$, the shape of β-$Ca(PO_3)_2$ crystalline are rod-like type with 5μm diameter and 60μm in length.

(2) We obtained the β-$Ca(PO_3)_2$ crystalline by traditional melting and heat treatment method.

(3) The heightest Vicker's surface hardness of these glasses resultant was 670 Kg/mm^2.

(4) The physical properties of these glass-ceramics are in sufficient to make them useful as bone implant materials.

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Figure 2. The surface micrograph of the resultant product of glass D.

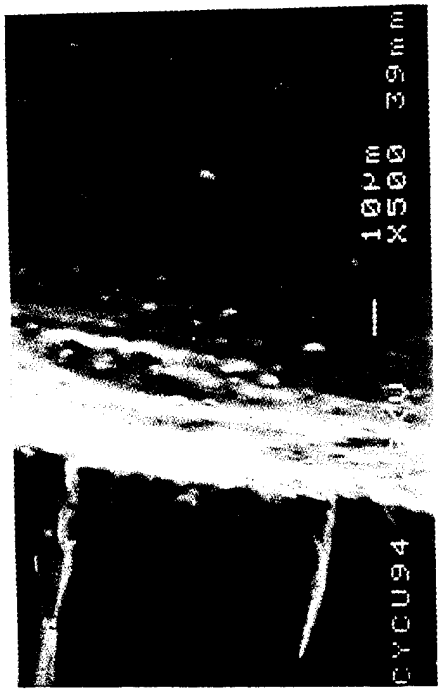


Figure 4. The glass-crystal interface of the resultant product of glass D.

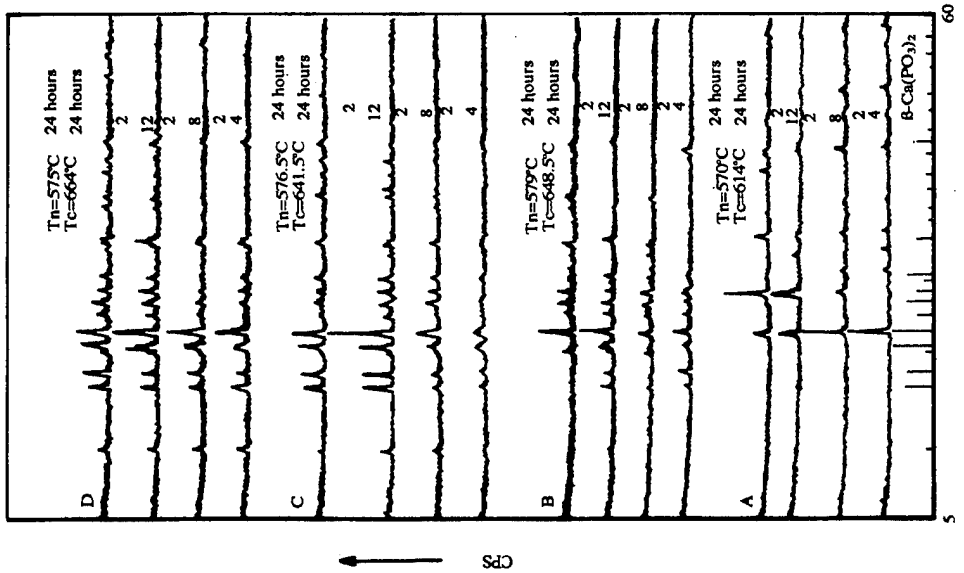


Figure 1. X-ray diffraction pattern of the resultant products.

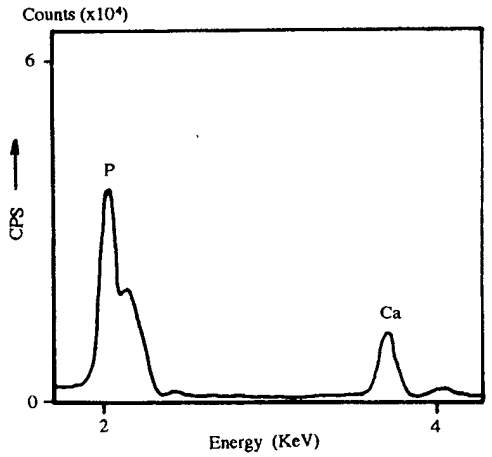


Figure 3. Energy-dispersive X-ray analysis of ß-$Ca(PO_3)_2$ crystalline

ELMT APP.CONC ERROR(WT%)

CaK: 0 3.433 .040

P K: 0 6.234 .091

ZAF CALCULATIONS

20.00 KV TITL = .00 ELEV =40.00 AZIM = .00 CONSIN =1.000

Spectrum: *INITIAL START-UP*

Last elmt by STOICH.,NORMALISED

ELMT	ZAF ratio	%ELMT	Error	ATOM.%	% OXIDE	FORMULA
CaK :	0.956	20.597+-	.240	11.324	28.820	CaO
P K :	1.151	31.062+-	.454	22.101	71.180	P_2O_5
O K :	0.000	48.341+-		66.575		
TOTAL		100.000		100.000	100.000	

Table 1 Composition of calcium phosphate glasses.

Glass	Composition		
	$Ca(H_2PO_4)\cdot H_2O$	$CaCO_3$	H_3PO_4
A	90.9	9.1	0
B	100	0	0
C	73.9	0	26.1
D	53.8	0	40.2

Table 2. Vicker's surface hardness and density of resultant product

Sample	Duration Time of Nucleation (hours)	T_n(°C)	Duration Time of Crystallization (hours)	T_c(°C)	Hardness (kg/mm^2)	Density (g/cm^3)
A	2	570	0	614	-	2.27
A	2		4		212	2.21
A	2		8		230	2.23
A	2		12		235	2.23
A	24		24		257	2.23
B	2	579	0	648.5	-	2.30
B	2		4		331	2.22
B	2		8		352	2.18
B	2		12		378	2.19
B	24		24		405	2.21
C	2	576.5	0	641.5	-	2.41
C	2		4		427	2.16
C	2		8		483	2.22
C	2		12		672	2.25
C	24		24		583	2.27
D	2	575	0	664	-	1.99
D	2		4		304	2.00
D	2		8		343	2.01
D	2		12		372	2.00
D	24		24		457	1.78

Table 3. Weight loss percentage of resultant product after dipping in Ringer's solution for 14 days

Sample	Duration Time of Nucleation (hours)	T_n(°C)	Duration Time of Crystallization (hours)	T_c(°C)	Wt. loss % of resultant product
A	2	570	4	614	2.2
A	2		8		5.3
A	2		12		4.3
A	24		24		9.7
B	2	579	4	648.5	0.8
B	2		8		0.6
B	2		12		0.6
B	24		24		0.2
C	2	576.5	4	641.5	6.2
C	2		8		8.5
C	2		12		8.1
C	24		24		7.1
D	2	575	4	664	23.7
D	2		8		27.0
D	2		12		21.4
D	24		24		38.3

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CALCINATION OF NEGEV PHOSPHORITES AND POSSIBLE CAUSES FOR TECHNOLOGICAL PROBLEMS

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Abstract Carbonate removal in the apatite structure was observed at temperatures from 600 to 900°C. The carbonate ions are also partially relocated from the orthophosphate site, into others such as interstitial positions and OH site. Hydroxyl groups form hydrogen bonds along the hexagonal axis; partial condensation of the orthophosphate groups takes place. Oxidation of organic-rich phosphorites, with a high S content in the organic matter, during calcination, causes the introduction of SO_4 in the apatite structure in orthophosphate sites. Similarly SiO_4 may also be introduced in these sites. In all cases the residence time during calcination is of great importance. Flash calcination is not only significantly cheaper than conventional calcination but is preferable because of the very short residence time of the phosphorites at high temperatures.

Key words: Phosphorite, Flash Calcination, Apatite, Substitutions in Apatite

INTRODUCTION

Calcination is an efficient beneficiation method for phosphorites with a high carbonate and/or high organic matter content. The advantages of calcination are: the decomposition coefficient of the phosphate increases, flotation properties of some phosphorites are improved, consumption of sulfuric acid decreases, the filtration rate of the precipitated phospho-gypsum increases, abundant foaming in the reactor is eliminated, the humidity of the phospho-gypsum is decreased [1]. Thermal beneficiation enables the inclusion of some types of poor quality phosphate rock, which would have been almost impossible to process by acidic treatment, in the production of mineral fertilizers. The drawbacks of calcination are its high price and in some cases calcination causes a worsening of the indices of acidic treatment or of

flotation properties. This shows the possibility of different changes of the properties of phosphorites by thermal treatment sometimes even for phosphorites characterized by almost the same chemical composition. The reason may be connected with the differences of the real (detailed) structure of apatites [2]. Therefore the mineralogy of phosphorites and the crystallochemistry of apatites are of great importance for prediction of the properties of calcined product.

METHODS

Phosphorites from various deposits of Israel - Nahal Zin, Saraf, Arad, Oron, Yorkeam - were supplied by the Rotem-Amfert-Negev Company and the Geological Survey of Israel. The samples included a suite of phosphorites from Nahal Zin deposit, before and after flash calcination (900°C during a few seconds). Some samples were subjected to thermal treatment in the laboratory at temperatures from 600°C to 950°C for periods from a few seconds up to several hours. Admixtures of phosphorites with gypsum or with quartz, 10:1 w/w, were prepared and analyzed after thermal treatment. Chemical analysis, Fourier Transform Infrared spectroscopy (FTIR) and X-Ray (powder) Diffraction (XRD) were used to characterize the samples.

RESULTS AND DISCUSSION

In Nahal Zin phosphorites, after flash calcination, about half of the original calcite (9%) was decarbonated, calcium oxide (hydroxide) formed and transformation of gypsum to anhydrite took place. The amount of organic matter decreased significantly and its composition changed. Trace element concentrations also changed. The contents of Cd, Cr, Mo, Ni, V and Zn decreased while the contents of Ba, Eu, La, Sr and Y increased (Table 1).

Structural Changes In Apatite

Structural changes in apatite were registered after flash calcination: the amount of structural carbonate was drastically reduced (more than 50%) together with a corresponding reduction of F, the F/P_2O_5 ratio was reduced from 0.095 to 0.088. As a result the P_2O_5 content in the calcined rock increased by a little more than 10% from 29.5% to 33% (Table 1). The actual beneficiation is better, since CaO and MgO are separated by wet slaking of the calcined rock. The ousting of most of the structural

Table 1

A - Crystallite size (XRD), structural CO_2 (XRD) and major element composition(ICP-AES)

Sample No.	size of cryst. along the a direction in A	c direction in A	CaO %	P_2O_5 %	CO_2^1 %	CO_2^2 %	F %	F/P_2O_5
25	280	550	51.4	30.5	8.3	4.1	2.99	0.098
26	750	1530	55.1	33.6	3.7	1.5	3.02	0.090
27	270	660	52.4	30.1	7.5	4.2	2.71	0.090
28	790	1480	55.5	33.4	3.0	1.5	2.86	0.086
29	290	540	51.4	29.1	7.9	3.7	2.97	0.102
30	830	1090	55.0	32.6	3.1	1.8	3.08	0.094
31	370	640	50.9	27.8	7.5	3.5	2.71	0.097
32	840	1250	54.7	32.6	3.1	1.4	2.83	0.087
33	310	550	52.5	29.8	8.6	3.8	2.70	0.091
34	820	1240	54.6	31.7	3.1	1.6	2.71	0.085

1 - Total CO_2. 2 - Structural CO_2.

B - Trace elementcomposition(ICP- AES)

Sample No	Ba ppm	Cd ppm	Cr ppm	Eu ppm	La ppm	Mo ppm	Ni ppm	Sr ppm	V ppm	Y ppm	Zn ppm
25	749	29	117	0.3	16	23	46	2800	164	54	474
26	1056	17	74	0.5	18	16	35	3076	136	60	408
27	430	31	119	0.2	17	38	47	2660	161	55	453
28	736	18	70	0.4	18	25	32	2997	131	60	404
29	800	30	108	0.4	17	35	47	2748	159	57	471
30	691	18	69	0.5	19	27	42	2952	127	63	411
31	568	31	122	0.3	16	26	57	2592	168	53	487
32	726	20	73	0.5	18	29	42	2970	138	60	422
33	581	32	105	0.3	16	35	54	2562	154	54	473
34	764	19	74	0.1	18	27	42	2898	122	58	430

Samples 25, 27, 29, 31 and 33 are field samples (FEED) and samples 26, 28, 30, 32 and 34 are samplesafter flash calcination.

carbonate increased the crystallinity of the apatites, and the sizes of their crystallites (Table 1). Only one type out of the observed crystallochemical type of the apatites (FTIR) in Negev phosphorites was found in the flash calcined Nahal Zin phosphorites.

After flash calcination, carbonate ions were not only ousted from the structure, but also partially relocated from one site (orthophosphate group) of the structure to others, interstitial and along the hexagonal axis.

Orthophosphate groups were partially condensed to pyrophosphate: vibration bands of the P-O-P bridge bonds appeared in the IR spectra. Hydroxyl groups formed hydrogen bonds with fluorine on the hexagonal axis of the structure. The structural changes of the apatites during flash calcination caused changes in the properties of calcined phosphorite; the solubility of the concentrates decreased by 50%. After prolonged calcination, sulfate (SO_4) and silicate (SiO_4) enter the apatite structure, in the vacant phosphate positions produced by the ousting of the carbonate, at 800°C and sometimes already at 700°C. Appearance of the bands at 530, 930, 1150 cm-1 in the IR spectra of calcined apatite when no other phases is present (according to X-ray diffractions) is indicative of isomorphous substitution of phosphorus by sulfur and/or silicon. The organic matter in the Negev phosphorite is rich in sulfur (10% by weight of organic matter). During calcination a partial decomposition of organic matter occurs, S is liberated, some of it enters the apatite structure as SO_4. We found a correlation between the concentration of organic matter in the original samples and the amount of SO_4 in the structure of the calcined product. The residence time during calcination is of great importance. Entering of SO_4 and SiO_4 in the apatite structure takes place only at 950°C with flash calcination. This shows that use of flash calcination at 950°C is not desirable in spite of the more complete liberation from carbonate at this temperature.

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NEW ASPECTS OF SOLID STATE TRANSFORMATION OF VANADIUM PHOSPHATES USED AS CATALYSTS FOR SELECTIVE OXIDATION OR AMMOXIDATION REACTIONS

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Abstract The influence of anion doping on the formation and properties of vanadyl pyrophosphates starting from $VOHPO_4 \cdot 0{,}5\ H_2O$ as well as the formation of ammonium containing vanadyl pyrophosphates from different vanadium monophosphates under the conditions of the ammoxidation process have been studied. Structural aspects of solid state transformations of these compounds and catalytical properties of various in this way obtained vanadium phosphates are discussed.

Vanadium phosphates of different structures are suitable precursors of very active and selective catalysts for the oxidation of C_4-hydrocarbons to maleic anhydride as well as for the ammoxidation of methylaromatics and methylheteroaromatics to the corresponding nitriles. Among the wide variety of vanadium containig phosphates the hemihydrate $VO(HPO_4) \cdot 0{,}5\ H_2O$ and the oxovanadium(IV) diphosphate, $(VO)_2P_2O_7$, play an outstanding role, especially for the selective oxidation of butane.

In earlier studies it was found that sulfuric acid has a directive influence to the formation of $VO(HPO_4) \cdot 0{,}5\ H_2O$ from aqueous solutions[1]. As we have found in further investigations, sulfate is incorporated statistically in the crystal lattice. On heating of this sulfate-doped precursors catalysts for the selective oxidation of butane are obtained which show increased catalytic performance compared to sulfate-free samples.

$$2\ VO(HPO_4) \cdot 0{,}5\ H_2O \xrightarrow{470°C} (VO)_2P_2O_7 + 2\ H_2O$$

The yield of $VO(HPO_4)\cdot 0,5\ H_2O$ and the content of incorporated sulfate depends to a high degree on the starting compound and on the amounts of sulfuric acid used[2]. Methane sulfonic and benzene sulfonic acid also act directive to the formation and crystallization of the hemihydrate. Whereas sulfate is incorporated into the hemihydrate lattice up to about 10% substitution of HPO_4^{2-} by SO_4^{2-} probably from steric reasons CH_3SO_3H will inserted only in small extent and $C_6H_5SO_3H$ not at all.

The differences concerning the behaviour of sulfate incorporation between different starting materials indicate that structural elements of the used vanadium phosphates are still present in the aqueous solutions influencing the doping process. Furthermore, sulfuric acid and the sulfonic acids, respectively, stimulate not only the nucleation of $VO(HPO_4)\cdot 0,5\ H_2O$ but also the cristal growth resulting in samples with low cristallinity.

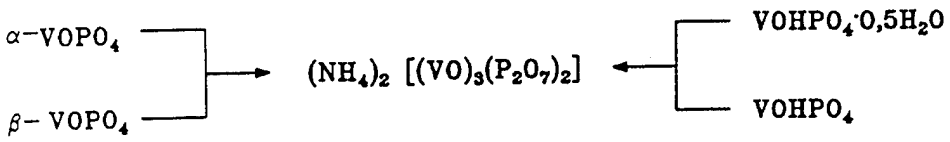
On heating of precursors obtained in this way samples of $(VO)_2P_2O_7$ are formed which show X-ray patterns with distinct broader reflections than it was found for undoped specimens (Table 1)

TABLE 1 Position and Full Width Half Maximum (FWHM) of the {020} and {204} X-ray reflections for $(VO)_2P_2O_7$ samples with varying doping agents

	{020}		{204}	
Doping agent	Position [2Θ]	FWHM [2Θ]	Position [2Θ]	FWHM [2Θ]
-	22.942(2)	0.280(5)	28.447(1)	0.206(3)
H_2SO_4	22.893(4)	0.498(12)	28.427(2)	0.298(5)
CH_3SO_3H	22.897(9)	0.940(33)	28.423(3)	0.354(8)
$C_6H_5SO_3H$	22.871(8)	1.082(33)	28.453(3)	0.415(8)

The influence of the degree of sulfate doping on the structure of the hemihydrate and the vandyl pyrophosphate was also studied by ESR spectroscopy. In the case of the hemihydrate the continuous change of line width and relative signal intensity in dependence of the sulfate content point to a statistical incorporation of the SO_4 tetrahedra. By studying the dehydration of different sulfate doped samples of the hemihydrate in a high-temperature resonator it was found that differently from the $VO(HPO_4)\cdot 0,5\ H_2O$ the arrangement of sulfate in the lattice of $(VO)_2P_2O_7$ does not occur in a statistical way but in form of local VO_6-SO_4 clusters.

Recently, it was found that the interaction of various vanadium monophosphates with the ammoxidation feed leads to structural transformations of the precursor, generating new phases, e.g. NH_4^+-containing vanadium diphosphates[3].



Now, the structural transformation of vanadium phosphate hemihydrate, $VO(HPO_4)\cdot 0,5\ H_2O$ into ammonium vanadyl pyrophosphate $(NH_4)_2[(VO)_3(P_2O_7)_2]$ during the ammoxidation of substituted methylaromatics was studied in detail by FTIR, XRD, and Raman spectroscopy. This solid state transformation can take place in an NH_3/O_2 environment without participation of aromatics. It probably proceeds via an intermediate phase which has a lamellar structure. The transformation is finished within 10 hours under the reaction conditions. Treatment only with NH_3 leads to destruction of the structure of the hemihydrate. The first step seems to be the formation of an intercalation compound which will be then transformed into the layer-like β-$(NH_4)_2[(VO)_3(P_2O_7)_2]$. This compound is not stable under the conditions of ammoxidation and invert to the α-modification:

$$VO(HPO_4)\cdot 0,5\ H_2O \Rightarrow \underset{\text{compound}}{\text{intercalation}} \Rightarrow \beta\text{-}(NH_4)_2[(VO)_3(P_2O_7)_2] \Rightarrow \alpha\text{-}(NH_4)_2[(VO)_3(P_2O_7)_2]$$

From stoichiometrical reasons one or more vanadium-rich compounds should be formed during the transformation. The investigation by FTIR and Raman spectroscopy suggests the formation of vanadate-like compounds but other vanadium compounds as the oxides V_2O_4 or V_4O_9 may also be formed:

$$8\ VO(HPO_4)\cdot 0,5\ H_2O + 10\ NH_3 + 0,5\ O_2 \rightarrow 2\ (NH_4)_2[(VO)_3(P_2O_7)_2] + 2\ '(NH_4)_3VO_4' + 3\ H_2O$$

$$10\ VO(HPO_4)\cdot 0,5\ H_2O + 8\ NH_3 + 0,5\ O_2 \rightarrow 2\ (NH_4)_2[(VO)_3(P_2O_7)_2] + V_4O_9 + 12\ H_2O$$

However, V_2O_4 is infrared and Raman inactive. To clear up the kind of vanadium-rich compound further investigations are in progress. From the catalytic tests it is evident

that this up to now unknown vanadium compound plays an important role for the catalytic performance of the catalyst system. This was shown by comparison of the catalytic activity and selectivity of the catalyst, obtained from the hemihydrate during the ammoxidation and a pure α-$(NH_4)_2[(VO)_3(P_2O_7)_2]$, prepared from ammonium hydrogenphosphate and vanadium pentoxide under special conditions. This different behaviour of the two catalysts can be explained by a cooperative mechanism involving the known crystalline α-$(NH_4)_2[(VO)_3(P_2O_7)_2]$ phase and the up to now unknown non-crystalline vanadium-rich phase (Remote Control Mechanism).

Furthermore, the thermal behaviour of the ammonium vanadyl diphosphate phase has been studied by using temperature programmed methods in combination with a quadrupol mass spectrometer. In the following scheme the results are summarized:

$$\alpha\text{-}(NH_4)_2[(VO)_3(P_2O_7)_2] \longrightarrow \underset{\textbf{(A)}}{[(VO)_3(P_2O_6NH_2)_2]} + 2\,H_2O$$

$$2\ \alpha\text{-}(NH_4)_2[(VO)_3(P_2O_7)_2] \longrightarrow \underset{\textbf{(B)}}{2\,[(VO)_3(P_2O_6OH)_2]} + 4\,NH_3$$

$$\mathbf{A} + 2\,\mathbf{B} \longrightarrow 2\,(VO)_3[P_3O_9N] + 3\,VO(PO_3)_2 + 4\,H_2O$$

$$3\ \alpha\text{-}(NH_4)_2[(VO)_3(P_2O_7)_2] \rightarrow 2\,(VO)_3[P_3O_9N] + 3\,VO(PO_3)_2 + 6\,H_2O + 4\,NH_3$$

$$2\,(VO)_3[P_3O_9N] \longrightarrow V_4[P_2O_7]_3 + N_2 + V_2O_3$$

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THE SOLID-STATE NMR OF P–S AND P–Se COMPOUNDS – AN IMPORTANT TOOL FOR THE STRUCTURE INVESTIGATION

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Abstract The efficiency of the solid-state NMR spectroscopy is demonstrated on various examples of P-S and P-Se compounds. Experimentally determined ^{31}P nuclear magnetic shielding values are discussed on the base of IGLO calculations.

INTRODUCTION

The fast development of NMR instrumentation made it possible that the applied spectroscopist nowadays uses solid-state NMR spectroscopy as an important tool for the structure investigation. In many cases this method provides information comparable or complementary to those of the X-ray structure analysis. As most of the nuclear spin interactions in solids are tensor quantities special requirements concerning measurement [high-power dipolar decoupling, cross-polarisation (CP), magic angle spinning (MAS)] and spectra interpretation have to be met.

In the examples discussed below only two of the nuclear spin interactions - the chemical shift and the dipolar interaction - differ considerably from those in solution. The scalar interaction is negligible since for all compounds the indirect spin-spin coupling constant (J_{PP}) is less than 50 Hz. Quadrupolar interactions are not present.

The chemical shift is different along various directions. Solid-state NMR spectroscopy yields the three principal values of the shielding tensor. The orientation of the shielding tensor in the molecular coordinate system is principally available from single-crystal NMR experiments, quantum mechanical calculations and in some favourable cases from dipolar spectroscopy. The microsymmetry around the investigated nucleus can provide partial information.

RESULTS

The ^{31}P solid-state NMR spectroscopy under CP-MAS conditions is preferably used e.g. for the investigation of compounds being practically insoluble, the determination of the number of crystallographically independent molecules in a unit cell and the determination of the number of chemically nonequivalent phosphorus atoms in a molecule.

On the example of the well-known LAWESSON reagent, 2,4-bis(*p*-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane the existence of different modifications and the influence of short intermolecular S···S distances on the ^{31}P nuclear magnetic shielding tensor is shown.[1] The LAWESSON reagent can either crystallise as solvate or in form of solvent-free crystals.[2] Although, the presence of solvent molecules in the lattice has a negligible influence on the molecular structure, isotropic chemical shift δ_{iso} and the principal tensor component σ_{33} are remarkably different (27 and 70 ppm, resp.) for the both forms. Considering the crystal packing it becomes obvious that shorter intermolecular S···S distances in the solvent-free lattice account for this result.

Solution NMR investigations of perthiophosphonic acid anhydrides have the disadvantage that under these conditions dynamic processes may proceed.[3,4] To determine the composition of the solid product (monomer or dimer, *cis* or *trans* isomer) ^{31}P CP MAS spectra are well qualified. Both, monomer and dimer, have a shielding anisotropy of several hundred ppm, but they differ in the isotropic chemical shift δ_{iso} and the principal values σ_{11} and σ_{33} by the order of 300 ppm.[4] The distinction of the configuration isomers is possible since the *cis* isomer can never possess a centre of symmetry and hence, a more complex MAS spectrum results.

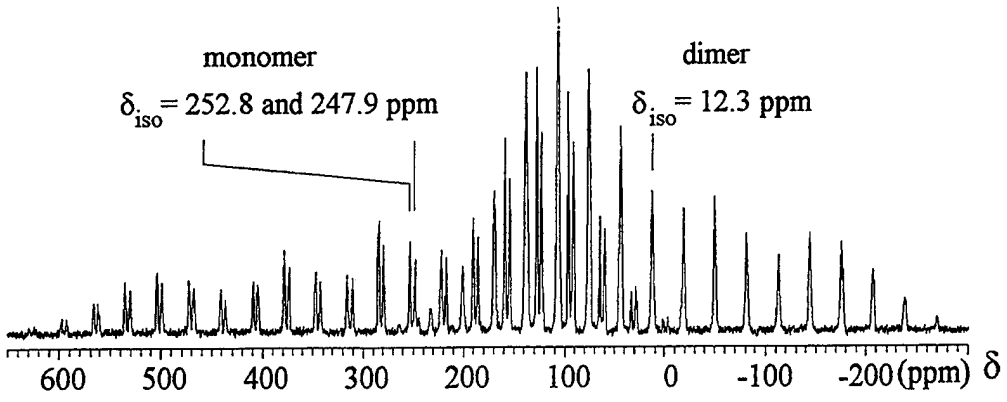


FIGURE 1 ^{31}P CP MAS spectrum of a monomer/dimer mixture of $[(CF_3)_2C_6H_3PS_2]_n$.

In Figure 1 the ^{31}P CP MAS spectrum of a monomer/dimer mixture of the perthiophosphonic acid anhydride $[(CF_3)_2C_6H_3PS_2]_n$ is shown. According to the number of sideband systems it follows that the unit cell of the monomer contains two crystallographically independent molecules whereas in the unit cell of the dimer only crystallographically equivalent molecules with equivalent P atoms are present. The small frequency-dependent splitting of the sideband system of the dimer is in agreement with the *cis* configuration of this isomer (see Figure 2).

The dipole-dipole interaction of two P nuclei in a molecule can be used to determine the orientation of the principal axes system of the shielding tensor with respect to the dipolar vector.[5] The analysis of static powder spectra as demonstrated on the example of a new, recently isolated four-membered ring compound, 2,4-bis(2,4,6-tri-isopropyl-phenyl)-1-oxa-3-thia-2,4-diphosphetane, yields data being in good agreement with the results of quantum mechanical calculations[6] applying the IGLO method.[7] Numerous calculations of the nuclear magnetic shielding tensor[8] of different four-coordinated P–S compounds with one P=S double bond have shown that in all cases principal axis *3* which corresponds to the most shielded component is directed nearly along the P=S bond (see Figure 2).

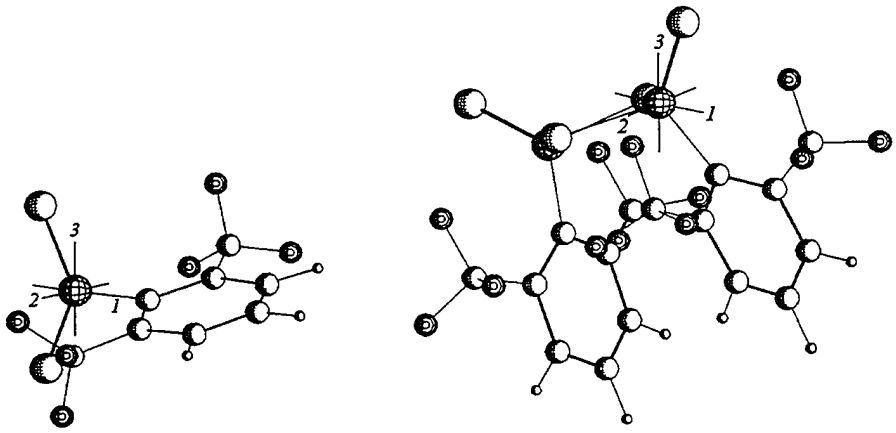


FIGURE 2 Molecular structure and orientation of the principal axes of the ^{31}P shielding tensor for monomer (left) and dimer (right) of $[(CF_3)_2C_6H_3PS_2]_n$.

Using the ovaloid presentation[9] for the shielding tensor (see Figure 3) it can be shown very descriptively how the shielding changes along various directions. Here, the distance between the origin and any point on the surface represents the shielding value in the given direction and hence, the principal values σ_{ii} are reflected by the section of the corresponding axis *i*.

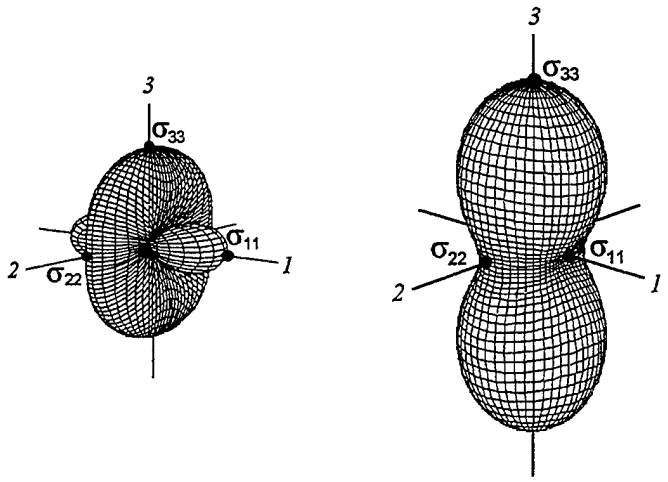


FIGURE 3 Graphical presentation of the ^{31}P shielding tensor for monomer (left) and dimer (right) of $[(CF_3)_2C_6H_3PS_2]_n$.

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Qualitative and quantitative study of various forms of phosphorous in storm and runoff waters in Toulouse (31) and Florensac (34), France

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ABSTRACT

Storm water and runoff water has been analyzed. Phosphorous was measured in three forms : orthophosphates, hydrolysable phosphate (polyphosphates), and total phosphorous. The difference [total phosphorous] - {[hydrolysable phosphorous] + [orthophosphates]} gives a good idea of the organic origin phosphorous content.

The qualitative and quantitative assessment of different phosphorous amounts enabled us to find that the irreducible part (organic soluble phosphorous) is about 23% of total phosphorous for runoff waters. Annual loads of orthophosphates, total phosphorous and so phosphorous known as organic were evaluated in the case of the motorway site at 3,3 kg of total phosphorous of which 0,60 kg of orthophosphates and 1,1 kg of soluble phosphorous known as organic for a catchment area of 1 hectare: motorway runoff waters are three times less loaded in total phosphorous than treated waters. As the urban site is much more loaded than a motorway site, it seems very important to supervise urban runoff waters.

INTRODUCTION

The work described was undertaken in collaboration with the Compagnie Générale des Eaux and more particularly its research center Anjou-Recherche. It concerns the phosphorous amounts in the storm and runoff waters in the city of Toulouse and in the mediterranean motorway site (A9). The goal of this work was to carry out a qualitative and quantitative assessment of the various forms of phosphorous per site and per different kind of sampling waters. Another goal was to differentiate between the phosphorous form considered irreducible and the phosphorous forms (1) which are possible to reduce through appropriate treatments.

1 METHODOLOGY

1.1 Sampling

Runoff water: For the three Toulouse sites, the study was made on the first thirty litres of runoff water which reached the mouth of the sewer from the start of the rainfall event (2).
For the motorway site, the (2 x 3 lane) motorway road bed surface area is 13000m^2. recovered in a drain channel lower down.
Storm water: Rain gauges were installed at five sites round Toulouse
For the motorway site, the cone of the rain gauge was not protected during dry spells and so collected all that fell (wet and dry).

1.2 Analyses

The phosphorous was measured in three forms : orthophosphates, hydrolysable phosphorous (polyphosphates) and total phosphorous. The difference [total phosphorous] - {[hydrolysable phosphorous] + [orthophosphates]} gives a good idea of the organic origin phosphorous content. We note that the polyphosphates which come first from detergents change through hydrolysis into orthophosphates and the kinetics of change depend on the ambient conditions (temperature, pH, weather etc.,).

Orthophosphates measurement

Ammonium molybdate, double antimony tartrate and potassium react in an acid medium with the orthophosphates to produce phosphomolybdic acid. This is reduced through ascorbic acid and produces a blue complex. Colorimetric measurement is carried out at 630 nm wave length by means of a UV - Visible Perkins Elmer lambda 2 spectrophotometer. The measurement range extends to 0.01 to 1 mg/l.

Polyphosphates measurement

Polyphosphates are converted into orthophosphates by hydrolysis on boiling in a 15% sulphuric acid medium. Spectrophotometer measurement is done after addition of soda until a pH value of 2 is obtained. Phosphorous concentration coming from hydrolysable phosphates was calculated by the difference between the phosphorous content measured in this way and the orthophosphate content previously determined.

Total phosphorous measurement

The sample was mineralized by hydrolysis at 480°C in a concentrated sulphuric acid medium in the presence of sodium persulphate as catalyst. After neutralization with concentrated soda at a pH = 1.5 to 2.5, the orthophosphates liberated by mineralization were measured by colorometer by means of a UV - Visible Perkin Elmer lambda 2 at 700 nm wave length.

The total soluble phosphorous was measured on filtered water. The total phosphorous corresponds to the total soluble phosphorous content increased by the phosphorus content in the suspended matter. It was measured for a more limited number of samples.

2 RESULTS AND DISCUSSION

2.1 Qualitative and quantitative assessment of different phosphorous amounts according to the source of analyzed waters.

Total phosphorous can be found in sediment form and in soluble form. Total soluble phosphorous contains soluble orthophosphates, polyphosphates, and the soluble part of the organic phosphorous. Total organic phosphorous content is equal, then, to the difference between the total phosphorous and the orthophosphates and polyphosphates in the suspended solids and the soluble phase. It is not possible to directly reach it with the carried out analysis because the orthophosphates contained in the sediments cannot be known. On the other hand, the organic soluble phosphorous is completely defined by the difference between the total soluble phosphorous amount and the soluble orthophosphates and polyphosphates amounts. The means obtained for each site are shown in the Tables 1 and 2 . The sites « Argoulets, Palayre and South Ring Road » whose means are very close together, have been regrouped under the name « South East » which corresponds to the geographical characteristics.

The mean values obtained for each site are shown in Tables 1 and 2.

Mean contents per site	unity	South South-East	North ring road	Saint Simon (South-west)	Motorway A9
Orthophosphates	(mgP/l)	0,14	0,18	0,12	0,04
Total soluble phosphorous	(mgP/l)	0,59	0,29	0,43	0,31
Organic phosphorous	(mgP/l)	0,44	0,11	0,31	0,27

Table 1: Storm water

Mean contents per site	unity	Urban	North ring road	Semi-urban	Motorway A9
Orthophosphates	(mg P/l)	1,17	0,79	0,41	0,13
Total soluble phosphorous	(mg P/l)	2,10	1,30	0,69	0,38
Organic phosphorous	(mg P/l)	0,93	0,51	0,28	0,25
Total phosphorous	(mg P/l)	2,83	1,34	0,62	0,68

Table 2: Runoff water

The insoluble part can , for the most part, be eliminated by settling. The soluble part can be treated by a physico-chemical process which consists of precipitation of phosphates inducted by, for example, alumina sulphate and ferric chlorid (flocculation process).
Concerning organic phosphorous, no simple or cheap process allowing its elimination is known for the moment. Consequently it represents the part of the phosphorous irreducible in water treatment. Some work is being done at the moment to characterize this phase.
Therefore, it is interesting to note what the respective percentages are (figure 1) for the insoluble and soluble parts as well as for the organic soluble part in the runoff water, knowing that rainfall, when it flows on the ground, fills up primarily with orthophosphates.
The phosphorous irreducible amount remains between 19 and 27 % of the total phosphorous amount. Approximately one quarter of the total phosphorous pollution inducted by the runoff water is never actually treated.

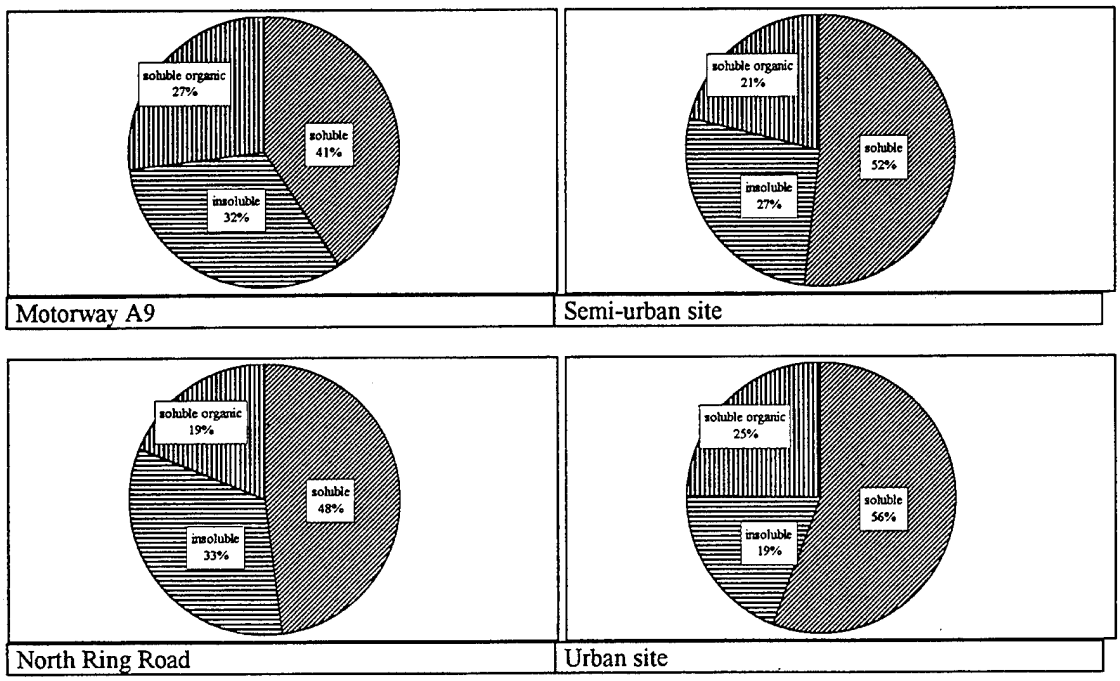


figure 1 :Respective percentages of different parts **of phosphorous in runoff waters**

2.2 Comparison of loads

Annual loads of orthophosphates, total phosphorous and so phosphorous known as organic were evaluated in the case of the motorway site for a catchment area of 1,3 hectares (table 3).

Year 1993-1994	Yearly soluble load	Yearly particule-like load	Total yearly load	Yearly soluble load/ha	Yearly particle-like load/ha	Total yearly load/ha
PO4 kgP	0,8	?	?	0,6	?	?
Porg kgP	1,4	?	?	1,1	?	?
Ptot kgP	2,2	2,1	4,3	1,7	1,6	3,3

Table 3 : Phosphorous loads (motorway site A9)

The irreducible phosphorous percentage is about 30% for the samples collected during one year of analysis. The percentage previously mentioned for the concentration values is very close to this last percentage.

Sampled waters	Year 1993-94	Total annual load (KgP)	Number of Equivalent/ inhabitant
runoff waters	Motorway A9	4,3	2600*
waste waters	Inlet B400	8271,0	400000
	Inlet B150	3148,0	150000
	General outlet	2641,0	550000

Table 4:Total phosphorous annual loads of runoff waters (A9) and waste waters (Toulouse 1994)

The total phosphorous loads obtained for the runoff waters are clearly inferior to those obtained for the waste waters (table 4). In order to compare them, it is necessary to evaluate the total annual load of COD (Chemical Oxygen Demand) knowing that 100 g of COD corresponds to 1 equivalent/inhabitant. The annual load of COD for the motorway catchment area studied is 261 kg which corresponds to 2600 equivalent/inhabitant. Motorway runoff waters are therefore three times less loaded in total phosphorous than treated waters.
As the urban site is four times loaded in total phosphorous than the motorway site (table 2), it seems very important to supervise urban runoff waters which are therefore close to treated waters..

3 CONCLUSION

71 samples of storm water were analysed. By site or overall, 14% of samples have a total phosphorous content higher than 1 mg P/l. This content is never higher than 2 mg/l.Orthophosphate contents were always less than 1 mg/l.
Samples were taken of run off water at four sites. 57 samples were analysed. Phosphorous contents were higher at the urban site (mean total phosphorous content : 2,8 mg/l) than at the semi urban site (mean total phosphorous content : 0,62 mg/l), at the ring road site (mean total phosphorous content : 1,30 mg/l) and at the motorway site (mean total phosphorous content : 0,68 mg/l) without allowing for atmospheric fallout (rain and dry deposits). We note that in one case, at the urban site, the total phosphorous content reached 8 mg/l. Phosphorous contents in suspended matter were calculated for 33 samples. In 65% of the samples analysed the phosphorous content was higher than 1 mg/l and in 25% of cases higher than 2 mg/l.
The qualitative and quantitative assessment of different phosphorous amounts enabled us to find that the irreducible part (organic soluble phosphorous) is about 23% of total phosphorous for runoff waters.
Annual loads of orthophosphates, total phosphorous and so phosphorous known as organic were evaluated in the case of the motorway site at 3,3 kg of total phosphorous of which
0,60 kg of orthophosphates and 1,1 kg of soluble phosphorous known as organic for a catchment area of 1 hectare. These values were compared to mean values obtained in 1994 at the city of Toulouse purification plant outlet. If we take the number of equivalent inhabitants as the point of reference (100 g of COD corresponds to 1 equivalent/inhabitant), motorway runoff waters are three times less loaded in total phosphorous than treated waters. As the urban site is much more loaded than a motorway site, it seems very important to supervise urban run off waters.

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NOVEL ALKENYL SUBSTITUTED CYCLOPHOSPHAZENES FOR THE SYNTHESIS OF THERMALLY STABLE POLYMERS

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ABSTRACT. The synthesis of some new alkenyl substituted tetrachlorocyclophosphazenes is discussed. The reaction of acetyl chloride with a hydridocyclophosphazene yielded a vinylacetate derivative or a carbon-bridged bicyclophosphazene. Elimination reactions with $(NPCl_2)_2NP(^iPr)C(CH_3)_2OSO_2CH_3$ yielded a propene derivative and an ANSA compound. X-ray structures of the bicyclophosphazene and ANSA compound are presented. The vinylacetate and propene derivatives did not homopolymerize under radical conditions. Copolymerization with styrene resulted in polymers with a maximum incorporation of 17 mol% for the vinylacetate derivative and 18 mol% for the propene derivative. In TGA studies high char yields up to 64 wt% were observed for the homo- and copolymers of the vinylbenzyl substituted tetrachlorocyclophosphazene. XPS studies showed the residue to contain P, N and C.

INTRODUCTION

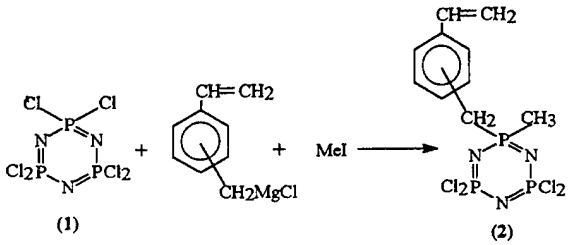
Over the past years a large number of polymerizable cyclophosphazene derivatives have been reported as well as their polymerization behavior[1]. The incorporation of these inorganic compounds in an organic polymer is of interest as it allows for a large variety of substitution reactions. Furthermore these (co)polymers exhibit interesting thermal properties such as flame retardancy[1]. Most of the synthesized cyclophosphazene monomers have the polymerizable group linked to the inorganic ring with a phosphorus-oxygen bond. A disadvantage of the phosphorus-oxygen bond is the possibility of rearrangement reactions resulting in degradation of the polymer[2].

Objective of this research is the synthesis of organic backbone polymers with phosphazene side groups with a direct P-C bond.

RESULTS AND DISCUSSION

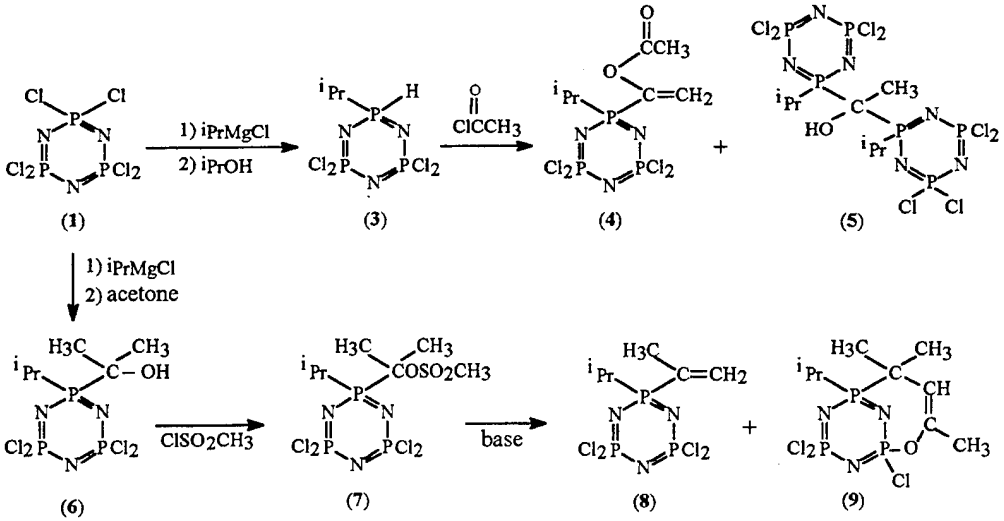
The strong electron-withdrawing nature of the cyclophosphazene necessitates the shielding of the double bond from the inorganic ring. To achieve this two strategies can be followed. The first is the use of a spacer group between the double bond and cyclophosphazene ring. Another approach is to compensate for the electronegative effect of the phosphazene group by an electron-donating substituent.

An example of a monomer with a spacer group is given below[3].



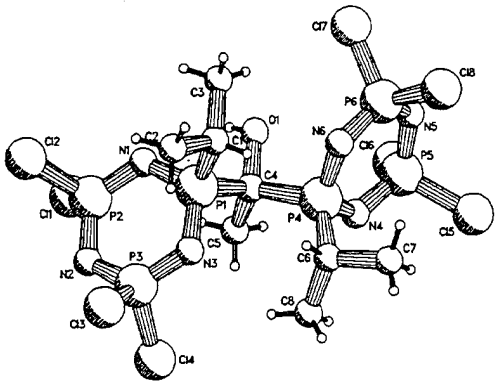
The obtained reactivity ratios from radical copolymerization reactions of methyl methacrylate (MMA) and the vinylbenzyl substituted cyclophosphazene (**2**) showed that the polymerization behavior of (**2**) resembles that of styrene[3].

Examples of the second class of monomers are the vinylacetate (**4**) and the propene derivative (**8**). Reaction schemes for their preparation are given below.

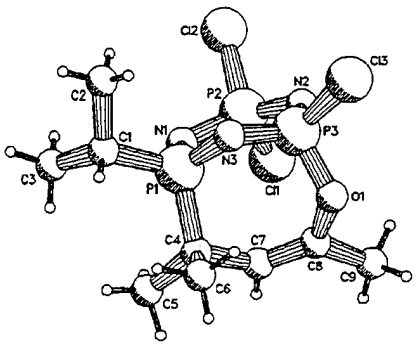


By using different ratios of acetyl chloride to (**3**), either the vinylacetate derivative (**4**) or a carbon-bridged bicyclophosphazene (**5**) was obtained. The structure of (**5**), which is given below, was confirmed by a single-crystal X-ray structure determination.

The synthesis of (**8**) involves multiple steps. Although (**8**) can be obtained from (**6**) by dehydration, yields are low for this direct procedure. Therefore the hydroxyl group in (**6**) was transformed in OSO_2CH_3 being a better leaving group. The elimination of the sulphonium group with a base proceeds smoothly and gives (**8**) in good yields. However apart from the expected product (**8**) a small quantity of another compound (**9**) was present in the reaction mixture. This compound was found to be an ANSA derivative of which the X-ray structure is presented below.



(**5**)



(**9**)

From the ^{13}C NMR data of (**4**) and (**8**) it follows that the electron-withdrawing effect of the phosphazene ring on the double bond is indeed weakened by the acetyl and methyl groups. The larger electron-donating capacity of the acetyl group is reflected by the smaller chemical shift of the vinyl ß-carbon atom compared with that of (**8**)[4].

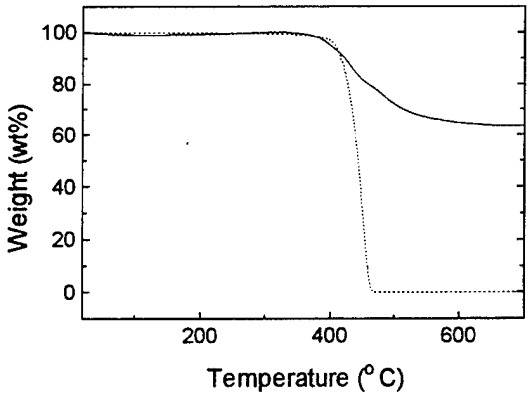
In contrast to the styrene derivative (**2**), homopolymers of (**4**) and (**8**) could not be obtained under radical conditions. This is most probably due to the fact that two steric demanding groups are present at the double bond. For the same reason polymers obtained from the copolymerization of (**4**) and (**8**) with MMA consist mainly of MMA. In a copolymerization experiment with MMA and 5 mol% of (**4**) in the feed, the incorporation of the phosphazene monomer in the polymer amounted only to 0.3

mol%. With the propene derivative (**8**) a similar result was obtained.

Copolymerizations of (**4**) and (**8**) with styrene resulted in much higher incorporation to a maximum of 17 and 18 mol%, respectively. The molecular weights of these polymers decreased with increasing phosphazene content. With feed contents of (**4**) of 40 mol% or higher (60 mol% for (**8**)) no polymer was formed. This phenomenon can be explained from steric reasons rather than from the phosphazene ring acting as a transfer or terminating agent.

All polymers derived from styrene and the phosphazene monomers presented here are self-extinguishing and do not liquefy when placed into a flame. Upon heating, a black brittle material remained which can be heated until glowing without any visible change. In particular the homopolymer of (**2**) is of interest. The polymer is stable up to 410 °C. At higher temperature decomposition takes place in one step with a loss of weight of 36 wt% (see TGA-plot). XPS spectra of the polymer before and after heating to 900 °C under N_2 flow indicate that weight loss is due to the evolution of HCl. The remaining residue is composed of P, N and C. The polymers described here may possess interesting flame retardant properties.

TGA-plot of the homopolymer of (**2**) (-) and styrene (...)



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STRUCTURAL CHEMISTRY OF NON - CYCLIC PHOSPHAZENES

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Abstract The crystal structures of some open-chained trichlorophosphazenes, the $NPCl_3$ groups attached to carbon, were determined at low temperature (90K, 100K), and the structures were compared in order to show the conformational variability of these compounds. This investigation comprises the structures of the cations in $[Cl\text{-}C(NPCl_3)_2]PCl_6$ and in $[CH_3\text{-}C(NPCl_3)_2]SbCl_6$, and the molecular structures of 2,2,4-trichloro-6-trichlorophosphazeno-1,3,5,2λ^5-triazaphosphorine, $C_2Cl_6N_4P_2$, and of a triclinic and a monoclinic modification of 2,4,6-tris(trichlorophosphazeno)-1,3,5-triazine, $C_3Cl_9N_6P_3$.

INTRODUCTION

From a synthetic and structural viewpoint phosphazene polymers constitute the broadest and most versatile of the known inorganic macromolecular systems. Since for polymers only limited structural data can be obtained it is reasonable to take small molecules as model compounds and to get precise data from single-crystal X-ray structural analyses of them. Most structural data of phosphazenes are known from the cyclic compounds which are not good model compounds for the polymers because of their ring constraints.

Concerning the important chlorophosphazenes, crystal structures of some non-cyclic compounds are described in the literature: $[Cl_3PNPCl_3]^+X^-$, $X^- = PCl_6^-$ [1], $X^- = MoCl_6^-$, $MoOCl_4^-$ [2], $[C(NPCl_3)_3]SbCl_6$ [3], $[C(NPX_3)_3]SbBr_6$, $X = Br_{0.78}Cl_{0.22}$ [4], $(Cl_3C)_2C(Cl)NPCl_3$ [5], $(F_3C)_3CNPCl_3$ at 153K and at 208K [6], $Cl_2P(O)NPCl_3$ at 223K, $Cl_2P(O)NPCl_2NPCl_3$ and $[Cl_3P(NPCl_2)_3Cl]PCl_6$ [7]; $[ClP(NPCl_3)_3]^+X^-$, $X^- = Cl^-, PCl_6^-$ at 100K [8], $Cl_2P(O)NPCl_3$ at 100K [9], $[P(NPCl_3)_4]ICl_2 \cdot 2[(CCl_4)_x(CHCl_3)_{1-x}]$, x=0.67(2) at 105K and at 293K [10], $SO_2(NPCl_3)_2$ at 100K [11].

In this work the molecular structures of some open-chained trichlorophosphazenes, the $NPCl_3$ group attached to carbon were compared in order to show the conformational variability of these compounds.

STRUCTURE OF THE $[X\text{-}C(NPCl_3)_2]^+$ CATIONS

Chlorobis(trichlorophosphazeno)carbenium hexachlorophosphate, $[Cl\text{-}C(NPCl_3)_2]PCl_6$, may be obtained by reaction of cyanamide with PCl_5 [12]. There are two formula units in the asymmetric unit of the monoclinic cell. Both the cations show cis-trans conformations with respect to their Cl-C-N-P torsion angles instead of the most symmetric ($C2_v$-mm2) cis-cis conformation. A trans-trans conformation is not possible by sterical hindrance of the two $NPCl_3$ groups.

The related compound bis(trichlorophosphazeno)methyl-carbenium hexachloroantimonate, $[CH_3\text{-}C(NPCl_3)_2]SbCl_6$, can be synthesized by reaction of ethanamidine with PCl_5 [13]. Once again there are two formula units in the asymmetric unit of the triclinic cell, and both the cations show cis-trans conformations with respect to their C_{Me}-C-N-P torsion angles as predicted for this compound [13]. The comparison of the four independent cations in the two compounds shows the agreement in the conformation (see Fig. 1). Solely the arrangement of the PCl_3 groups is different in the two compounds.

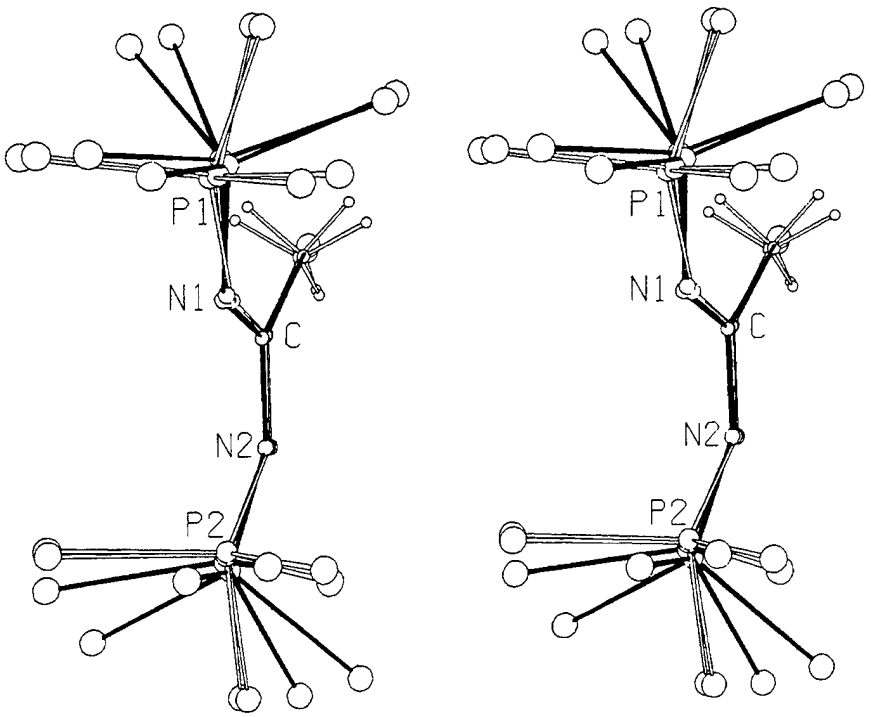


FIGURE 1 Stereographic projection of a fit of the cations in $[Cl\text{-}C(NPCl_3)_2]PCl_6$ (full lines) and in $[CH_3\text{-}C(NPCl_3)_2]SbCl_6$ (open lines).

STRUCTURE OF $C_2Cl_6N_4P_2$

The reaction product of dicyanodiamide with PCl_5 in a ratio of 1:2 is 2,2,4-trichloro-6-trichlorophosphazeno-1,3,5,2λ^5-triazaphosphorine and not 2,4,6-trichloro-2-trichlorophospha-zeno-1,3,5,2λ^5-triazaphosphorine as given in the literature [12]. This is confirmed by an X-ray structure analysis at 90 K. A least-squares fit between the atomic positions of the ring atoms and the adjacent atoms of the two independent molecules of the asymmetric unit demonstrates the low variability in conformation of the compound (see Fig. 2).

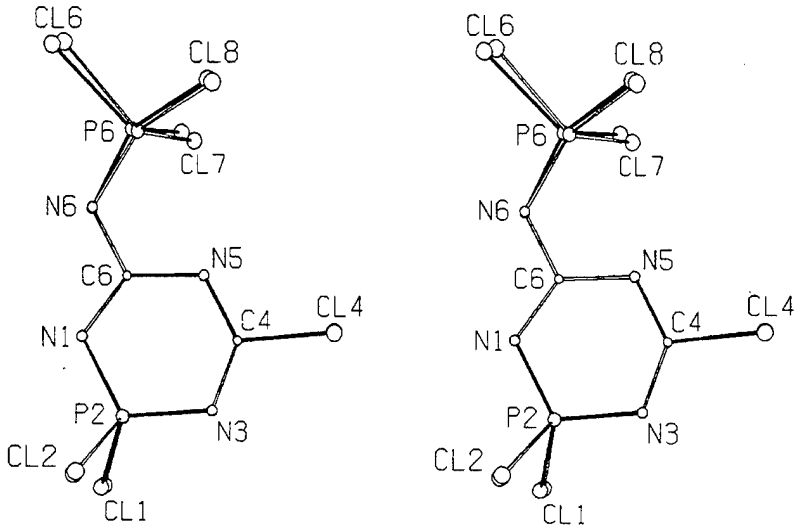


FIGURE 2 Stereographic projection of a fit of the two independent molecules in the asymmetric unit of $C_2Cl_6N_4P_2$.

STRUCTURE OF $C_3Cl_9N_6P_3$

By reaction of melamine with PCl_5 a triclinic and a monoclinic modification of 2,4,6-tris(trichlorophosphazeno)-1,3,5-triazine with totally different cell constants may be obtained. They both contain solvent molecules and PCl_6^- anions and make difficulties in the refinements (R = 10.5%, 10.8%) due to disorder in the included solvent molecules. But since the $C_3Cl_9N_6P_3$ molecules scarcely suffer from disorder, and since there are two molecules in the asymmetric units of both modifications, the average of the very similar conformations of the four independent molecules (see Fig. 3) may be taken as the most stable conformation of the molecule. This conformation showing approximately C_s symmetry is characterized by the longest possible all-trans chains.

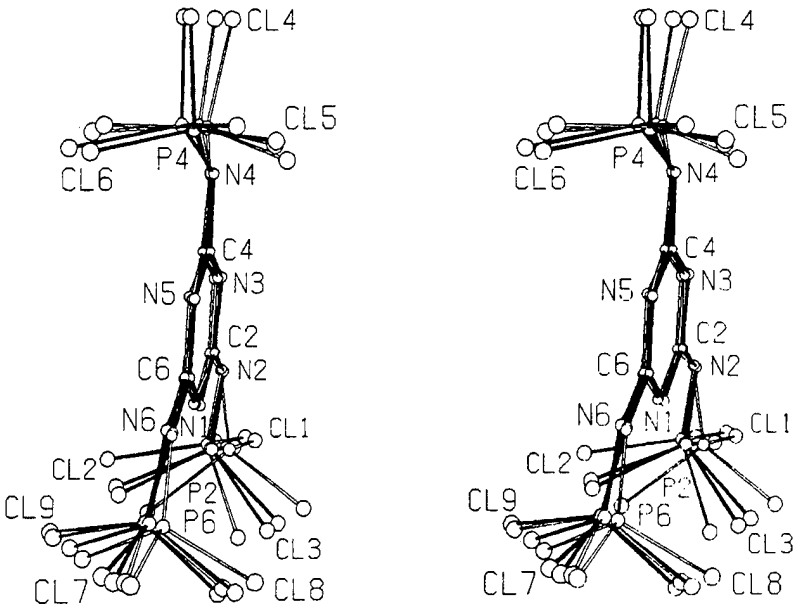


FIGURE 3 Stereographic projection of a fit of the four independent molecules in the triclinic (full lines) and monoclinic (open lines) modifications of $C_3Cl_9N_6P_3$.

The author thanks Prof. Kratky for the use of the diffractometer and Prof. Schmidpeter for the crystals of $[CH_3\text{-}C(NPCl_3)_2]SbCl_6$.

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A STUDY OF SYNTHESIS AND THERMAL PROPERTIES OF CYCLOTRIPHOSPHAZENE-CONTAINING POLYIMIDES

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Abstract New novel fire- and heat-resistant cyclotriphosphazene-containing polyimides were prepared from polymerization of bis(*p*-aminophenoxy)tetra(phenoxy) cyclotriphosphazene with 3,3',4,4'-benzophenonetetracarboxylic dianhydride (BTDA) and 3,3',4,4'-diphenylsulfonetetracarboxylic dianhydried (DSDA). The imidization of the polyamic acids and the thermal stabilities of the polyimides were evaluated by FTIR, differential scanning calorimetry(DSC), and thermogravimetric analysis(TGA). These polyimides, in which the cyclic triphosphazene structure is preserved, showed good thermal stability and fire-resistance.

INTRODUCTION

Organocyclotriphosphazene materials are known to exhibit good thermal stability. The presence of phosphorus and nitrogen atoms in the backbone as well as the ether linkages in the form of phenoxy groups introduced in the cyclotriphosphazene as side groups have resulted in the development of a new class of hybrid inorganic-organic phosphazene polymers, such as polyurethanes[1], polyamides[2], polysulfones[3], maleimide resins[4-7], and epoxy resins[8] etc.. These studies have shown that incorporation of a substituted cyclotriphosphazene ring into the polymer backbone has signficantly improved heat- and fire-resistance. Therefore, it is expected that incorporation of substituted cyclotriphosphazene ring into polyimide backbone can give the merits of cyclotriphosphazene and polyimide. In this study, the reactive bis(*p*-aminophenoxy)tetra(phenoxy)cyclotriphosphazene was synthesized as a precursor for incorporating the cyclotriphosphazene ring onto the traditional organic polyimide. The preparation and the properties of the phosphazene-containing polyimides prepared are discussed in this report.

EXPERIMENT

Synthesis of bis(*p*-nitrophenoxy)tetra(phenoxy)cyclotriphosphazene, (3), and bis(*p*-aminophenoxy)tetra(phenoxy)cyclotriphosphazene, (4):

(3) and (4) were synthesized following the procedures reported before[2].

Preparation of polyamic acids:

Diamine(4) was reacted with equimolar amount of dianhydride a and b separately in DMAc at ambient temperature under N_2 to give the polyamic acids 5a and 5b respectively.

Imidization of polyamic acids:

The polyamic acid 5a in THF was cast on a glass plate and dried at room temperature overnight under vaccum. It was then heated in oven at 100℃ for 1h, 200℃ for 1h, and 250℃ for 1h to convert to the corresponding polyimide 6a. 5b were imidized in an analogous procedure to obtain 6b.

RESULTS AND DISCUSSION

Synthesis and characterization of polyimides:

The bis(*p*-aminophenoxy)tetra(phenoxy)cyclotriphosphazene (4) was synthesized according to the procedure outlined in Scheme I. As shown in Scheme II, compound (4) was reacted with BTDA and DSDA separately to give the polyamic acids 5a and 5b. The corresponding polyimides 6a and 6b were then obtained by the imidization of 5a and 5b respectively.

Fig.1 shows the FTIR spectra of polyamic acid 5a and that of polyimide 6a. It is seen that the cyclotriphosphazene is intact in both polymers. The four typical characteristic imide bands at 1780cm^{-1} (C=O, imide), 1726cm^{-1} (C=O,phenyl), 1370cm^{-1} (C-N-C, imide), and 721cm^{-1} (C-N-C, out-of-plane bending) were found for the polyimide. In order to find a proper temperature for the imidization, the band at 1370cm^{-1} was followed with temperature variation using 949cm^{-1} (P-O-C) as the reference band. It was found that for 30 minutes heating, the absorbance at 1370cm^{-1} is increased with increasing temperature and reaches a steady absorbance at about 200℃ as indicated by the plot of absorbance ratio vs. temperature in Fig.2. This suggests that although the imidization occurs initiially at 100℃, polymer 5a can be imidized as effectively as at 250℃. Furthermore, the DSC thermogram of 5a shows an endothermic peak between 100℃ and 150℃ indicating the melting process occured. Therefore, it is believed that the imidization took place concurrently with melting process between 100℃ and 200℃. In order to make sure the imidization was complete, heating at 100℃ for 1h, at 200℃ for 1h, and 250℃ for 1h were conducted for converting polyamic acid 5a in the form of film

to the polyimide 6a. Similar results were obtained for polyamic acid 5b and the corresponding polyimide 6b.

Thermal properties of the polyimides

The glass transition temperatures (Tg) of the polyimides measured by DSC are only 140℃-160℃. It reveals that the polyimides can be processable at relatively low temperature. The thermal stabilities of the polyimides 6a, and 6b were investigated by dynamic TGA(Fig.3). As listed in Table I, the temperature of 5% weight loss is at 400℃-410℃, and the temperature at which major thermal decomposition occurs in N_2 is at 410℃-450 ℃. This suggests that the synthesized polymers are thermally stable. In addition, the high char yield feature gives these polyimides good potential for use in fire-resistant application.

TABLE I. The thermal analysis data of the polyimide prepared.

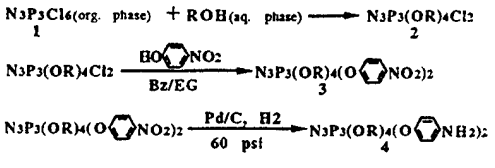
polymer	Tg (℃)	$T_{5\%}$ (℃)	T_{max} (℃)	char yield at 600℃(%)
6a	160.0	410.9	445.8	78.5
6b	142.4	402.8	413.5	74.0

ACKNOWLEDGMENTS

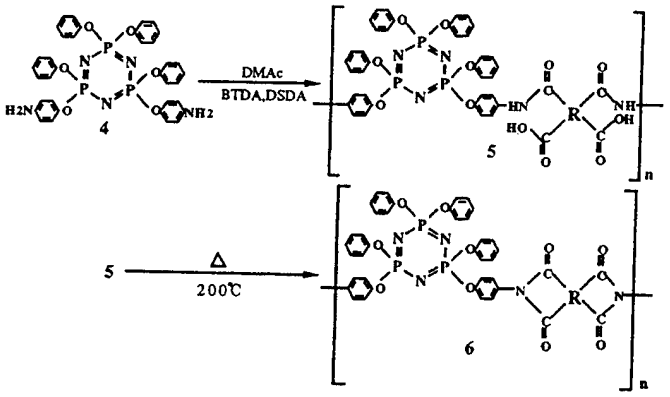
The authors wish to thank the National Science Council of R.O.C. for the financial support of this work under the project CS 84-0210-D-033-001 and Nippon Fine Chemical Company, Japan, for providing the hexachlorocyclotriphosphazene.

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Scheme I



Scheme II

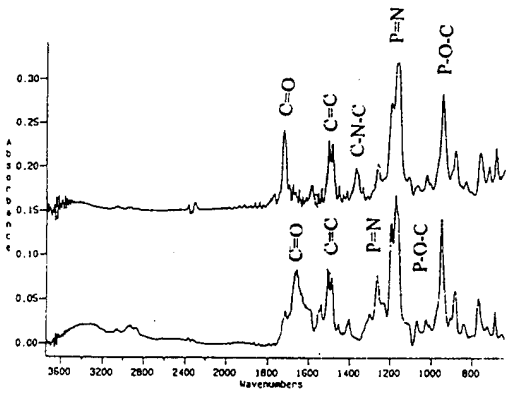


Fig.1 The FTIR spectra of polyamic acid 5a and polyimide.6a in the rang of 700-3600cm^{-1}

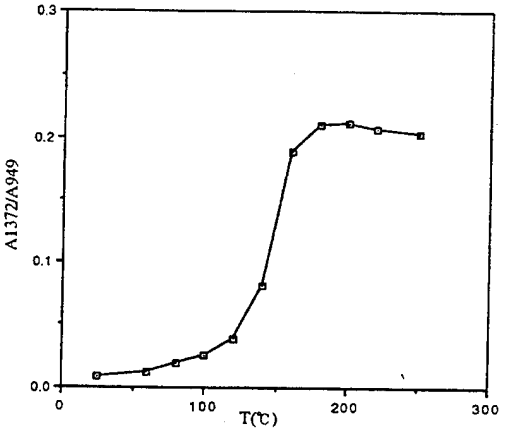


Fig.2 Dependence of the absorbance ratio at 1372cm^{-1} peak on different temperature during the course of imidization

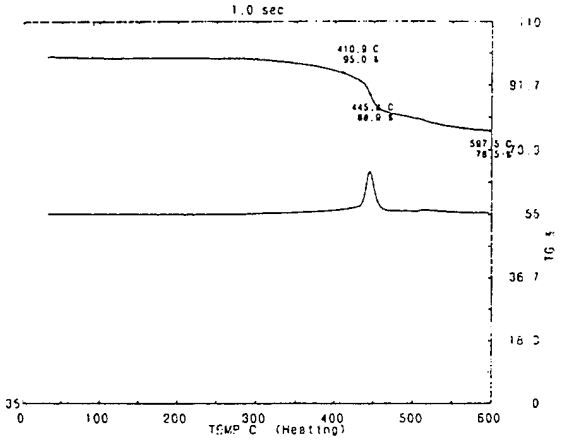


Fig.3 TGA thermogram of the polyamic acid 6a.

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NEW ORGANOFUNCTIONAL CYCLOPHOSPHAZENE DERIVATIVES

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Abstract The rational design, synthesis and polymerization of the methacrylphosphazenes $N_3P_3Cl_5O(CHR)_x(CHR')_yOC(O)CMe=CH_2$ (x=y=1,2, R=R'=H; x=1, R=Me, y=1, R'=H; x=1, R=H, y=1, R'=Me) is reported. Another new type of alkenyloxy derivative is prepared from 5-nonbornene-2-methoxide and $N_3P_3Cl_5$. The preparation of spirocyclic derivatives with methacrylate or protected hydroxyl groups is reported. Various functionalized ferrocene derivatives of the cyclophosphazenes have been prepared with particular attention being paid to the synthesis and electrochemical characterization of the $N_3P_3Cl_{6-n}(NMeCH_2C_5H_4FeC_5H_5)_n$(n=1,2,3,4) series.

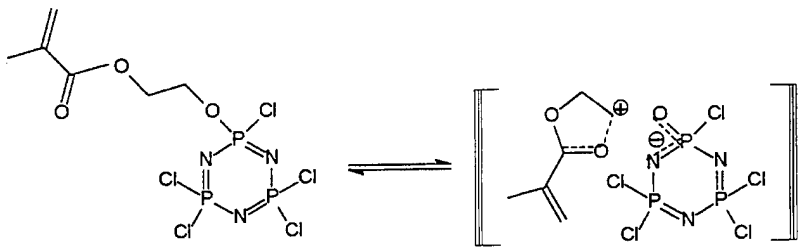
Key Words: cyclophosphazenes, organofunctional phosphazenes, exocyclic group polymerization, redox active phosphazenes

INTRODUCTION

The range of accessible synthetic transformations of polymeric and cyclic phosphazenes is significantly enhanced by the incorporation of substituents which can undergo further reactions. This expanded range of reactivity is directed towards property modification of poly(phosphazenes)[1], the formation of polymerizable cyclophosphazene monomers[2] or providing substituents suitable for classical step polymerization[3]. In this paper, we report a series of new cyclophophazenes with organofunctional substituents which can serve as sites for addition polymerization, step polymerization or redox behavior.

RESULTS AND DISCUSSION

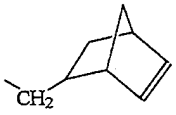
Previous work in our research group has focused on the synthesis of carbon chain polymers with cyclophosphazenes as substituents.[2] The polymerization and copolymerization of $N_3P_3Cl_5OCH_2CH_2OC(O)CMe=CH_2$ (**1**) was explored as an entry to the important acrylate polymer series.[4] While polymerization proceeded as expected, a phosphazene/phosphazane rearrangement was slowly occurring in the monomer. We have reported detailed study of the mechanism of this rearrangement.[5] The process proceeds through a transition state in which the developing carbocation is stabilized by interaction with the carbonyl group of the methacrylate. This model allows for the rational design of stable methacrylate monomers since an extension



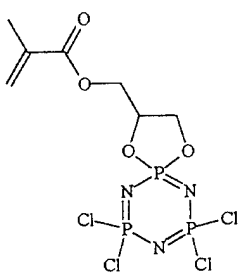
of the alkane chain length of the ester will produce species which are not prone to rearrangement due to the requirement of forming highly strained dioxo rings in the transition state. This proposal was verified by the synthesis of **2-5**. Very slow rearrangement occur for **2-4** and none

$$N_3P_3Cl_6 \quad + \quad ROH \longrightarrow N_3P_3Cl_5OR$$

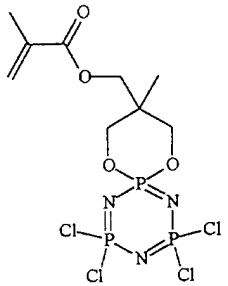
R = R'OC(O)C(CH$_3$)=CH$_2$; R' = (CH$_2$)n [n = 2 (**1**), 3 (**2**), 4 (**5**)]
CH$_2$CH(CH$_2$) (**3**), CH(CH$_3$)CH$_2$ (**4**)

R =  (**6**)

is noted for **5**. The new methacyrlate monomers undergo homopolymerization and copolymerization with methylmethacrylate. While the homopolymerization of **2** proceeds without detectable rearrangement of the monomer, continued heating of the polymers leads to some phosphazene/phosphazane tautomerization. Polymerization of **5** in the presence of 5% of the crosslinking agent $CH_2=CMeC(O)O(CH_2)_4OC(O)CMe=CH_2$ gives a soluble, high molecular weight product. Finally, the chlorine atoms in the **5**/methylmethacrylate copolymer may derivatized with sodium trifluoroethoxide. The reaction of 5-norbornene-2-methanol (endo/exo mixture) with $N_3P_3Cl_6$ produces the novel exocyclic olefin derivative **6** in very high yields. The remaining chlorine atoms do not undergo any further reaction with the norbornene-2-methanol



7



8

even under forcing conditions. Exocyclic spirocyclic entities have the advantage of fixing the geometry and providing a more rigid ancor for the organofunctional unit. Both five (**7**) and six (**8**) membered spirocyclic units containing the methylmethacrylate unit have been prepared . The reaction of methylmethacrylate with solketal in the presence of titanium (IV) isopropoxide followed by acidification leads to **7** upon reaction with $N_3P_3Cl_6$. Treatment of tris(hydroxymethyl)ethane with dimethoxypropane followed by coupling with methacrylchloride and subsequent acidic work-up to remove the protecting group gives the diol which upon reaction with $N_3P_3Cl_6$ gives **8**. Homopolymerization and copolymerization with methylmethacrylate of **8** proceeds to give well behaved high molecular weight materials while **7** only gives ologiomers. The chlorine atoms in **8**/methylmethacrylate may be derivatized with sodium trifluoroethoxide. Spirocyclic materials have also been obtained from 1,3-diamino-2-hydroxy propane which has the hydroxyl group protected with a trimethylsiloxy moiey. The ^{31}P NMR of **9** exhibits a ABX pattern rather than the expected A_2X.

$$N_3P_3Cl_6 + NH_2CH_2CH(OSiMe_3)CH_2NH_2 \rightarrow N_3P_3Cl_{6-2n}[NHCH_2C(OSiMe_3)CH_2NH]_n$$

n=1 (**9**), 2 (**10**)

The origin of the AB behavior at the $\equiv PCl_2$ centers is due to the disposition of H and $OSiMe_3$ centers at the 4 position of the spirocycle. The ^{31}P spectrum of **10** is even more complex due to the fact that stereoisomers based on the arrangements of spirocyclic groups relative to one another occur. Both **9** and **10** represent cyclophosphazenes with protected hydroxyl functions which are structurally constrained to avoid intramolecular reactions. The reaction of $NH_2CH_2CHOSiMe_3$ with $N_3P_3Cl_6$ gives the know spirocycle $N_3P_3Cl_4NHCH_2CH_2O$ demonstrating the viability of the intermolecular reaction possible when substituents are not locked in place.

Techniques for generation of phosphazene monomers and polymers with redox active substituents is also of interest. Our ultimate goal is the synthesis of polymeric materials which have electron transfer properties so we have focused on phosphazenes in which a ferrocene unit is separated from the phosphorus center by a saturated spacer group. The reactions of ferrocenyl methoxide and ferrocenyl 2-propoxide lead to the monosubstituted phosphazene[5]. The reactions of N-methyl-2-ferrocenylmethylamine with $N_3P_3Cl_6$ give rise to a series of stable well behaved ferrocenylamine derivatives.

$$N_3P_3Cl_6 + CpFeC_5H_4CH_2NHMe \rightarrow N_3P_3Cl_{6-n}(CpFeC_5H_4CH_2NMe)_n$$

$$n=1\text{-}4$$

The reaction followed a mixed geminal/non-geminal pathway which is solvent dependent. The trans isomer is the dominant non-geminal species. Cyclic voltametry studies show that each of the N-methyl-2-ferrocenylmethlamino derivatives undergoes a single reversible oxidation process indicating the electronic isolation from the phosphazene is sufficient so that all centers oxidize at a similar potential. An analogous poly(phosphazene) derivative containing the ferrocenylmethylamino and trifluoroethoxy derivative has been prepared and characterized.

ACKNOWLEDGEMENTS

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OLIGOMERIC PHOSPHATE ESTERS AS FLAME RETARDANTS

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Abstract. In this paper, some Akzo Nobel contributions to organophosphorus flame retardant chemistry are discussed in the context of some current and future issues affecting various end use applications. Current issues of greatest concern include toxicity, environmental impact and performance characteristics such as fogging in automotive applications. Future concerns will no doubt focus on environmental issues and recycling as well as new indices of fire performance such as rate-of-heat release. One approach to the right molecules is through oligomeric phosphate esters. Specifically, those that are formed by the reaction of oligomeric pyrophosphates with cyclic ethers.

As a consequence of the current technological revolution, synthetic polymers and composites continue to replace traditional materials such as metal, wood, glass, etc., especially in electrical, electronic, transportation, construction and home furnishings applications. Once it was established that synthetics could do the job, another wave of change began in which lower cost polymers are being formulated and "engineered" to replace higher cost polymers by improving properties and pushing service capabilities to higher performance levels. One particular characteristic of synthetic polymers that has always needed improvement has been and continues to be fire performance.

Factor in the present worldwide concern for the environment and the rapidly growing emphasis on recycling and we get an exciting challenge to produce cost-effective, halogen-free flame retardants. Certainly, high on the list of candidate compounds to meet these challenges are organophosphorus compounds.

In some areas, such as the flame retarding of polyurethane foams, organophosphorus materials have a longstanding history of use. The compounds used though have generally contained combinations of phosphorus and halogens in the form of simple haloalkyl phosphates. In recent years, concern for the health and safety of workers and consumers brought about greater emphasis on the toxicity of materials. Several years ago tris(dibromopropyl) phosphate was found unacceptable due to its chronic toxicity. More recently tris(chloroethyl) phosphate has also come under attack for toxicity reasons. Tris(chloroethyl) phosphate now falls into labeling category R40 in Europe. This label carries the words "possible risk of irreversible effects".

From a performance perspective, tris(chloroethyl) phosphate and tris(monochloroisopropyl) phosphate are too volatile for today's more stringent automobile seat cushion requirements. They will fail the new fogging test criteria which measures the propensity of additive materials in flexible polyurethane foam to volatilize and collect on vehicle windows. Tris(chloroethyl) phosphate can also cause unacceptable discoloration in polyurethane foams, especially in the new, more efficient production techniques which make larger and less dense foam buns. Even though tris(monochloroisopropyl) phosphate is more volatile than its chloroethyl analog this is generally not a problem when it is used in rigid polyurethane foams.

A few higher molecular weight chloroalkyl phosphates have been commercialized over the years. Even though they are more permanent, they can cause problems in some disposal or recycling schemes. The potential disposal problems and the toxicity testing likely to be required for registration on the various international chemical inventories such as the EINECS, the TSCA or the MITI lists discourages further exploration of any new chloroalkyl phosphate compounds. Simple molecules containing only phosphorus and no halogens such as dimethyl

methylphosphonate, often referred to as DMMP, are also very effective flame retardants, but their low molecular weight results in relatively high volatility. DMMP also falls into the European labeling class R46 which carries the warning "may cause heritable genetic damage". Similarly, triphenyl phosphate and its various alkylated derivatives, though nonvolatile enough to pass the automotive fogging test requirements, are still volatile enough to collect in exhaust hoods over thermoplastic processing equipment when they are used in various engineering plastics. This evidence of volatility together with the discovery a decade ago of a unique but apparently harmless monocyte esterase inhibition in some workers exposed to these polymer processing operations [1] has encouraged the search for even less volatile materials.

The pursuit of reduced volatility of organophosphorus flame retardants has taken numerous paths over the years. In one approach, virtually nonvolatile salts are prepared from highly volatile precursors such as DMMP . At least one of these compounds has been reported to be in commercial development but does not seem to have found much actual use.

A second approach, making reactive molecules that become part of the polymers in which they are used, has enjoyed some commercial success over the years [2], most notably in polyester fibers, and in polyurethane foams. This approach can be expensive and leads to specific, niche compounds rather than to materials with broad applicability.

A third approach, one that we at Akzo Nobel have emphasized, is the preparation of higher molecular weight compounds, specifically oligomeric versions of some of the simple compounds mentioned earlier, such as dimethyl methylphosphonate and trischloroethyl phosphate. Earlier phases of our work in this area have been reported at a previous International Conference on Phosphorus Chemistry by Weil [3]. The work previously reported covered aliphatic oligomeric phosphates and phosphonates. I will discuss our extension of this work into aromatic analogs.

As previously described, we approach the oligomeric phosphates by reacting simple trialkyl phosphates or phosphonates with phosphorus pentoxide to obtain alkyl esters of a mixture of oligomeric metaphosphoric and metaphosphonic acids also referred to as metaphosphates and metaphosphate/phosphonates. This mixture is then reacted with ethylene oxide until all of the pyrophosphate groups disappear and are replaced by ethyleneoxy bridges. This appears to be easily explained by the insertion of ethylene oxide into the pyrophosphate bond as suggested by Weil et al [3].

Bright, Jaffe and Walsh [5] point out that this suggestion was based, in part, upon the diagnostic chemistry and, in part, upon infrared monitoring of the reduction in the concentration of the pyrophosphate bonds resulting from the processing and that the reduction in concentration or the disappearance of the anhydride groups is not unequivocal evidence that ethylene oxide inserts into the anhydride bond. Since the more stable of these linkages may resist titration by the usual alcoholic KOH method, measurement of the HCl acid number is very useful [4]. In this procedure, residual pyro moieties and labile five-membered cyclic ester groups are hydrolyzed with a measured amount of excess HCl and then back-titrated.

Walsh also points out that in this oligomeric system, there are other pathways for the opening of the anhydride linkages and, there was no clear identification of the formation of the products expected from an insertion reaction of ethylene oxide into the anhydride linkage.

Weil suggests [3] that ethylene oxide inserts into the anhydride linkages formed in a side reaction during the condensation of tris(2-chloroethyl) phosphate. However, insertion is not the only pathway available for removal of the anhydride linkage and, perhaps because of the difficulty in analyzing such reaction mixtures, a product of such a reaction was not unequivocally identified.

Extending this chemistry to the aryl phosphates we have demonstrated clearly and unequivocally the insertion reaction of epoxides into the pyrophosphate linkage [6]. Under carefully controlled conditions, ethylene oxide was added to tetraphenyl pyrophosphate to form ethylene bis(diphenyl phosphate) as the sole reaction product. The reaction proceeds at 70°C when ethylene oxide is added to molten tetraphenyl pyrophosphate during a 10-hour period. Pyridine

was found to be an effective catalyst. The yield is 87.4%; m.p., 38-40°C; purity, 97.2 by HPLC.

Similarly the reaction of tetraphenyl pyrophosphate with propylene oxide leads to an 80% yield of the corresponding insertion product, as an oily liquid. The reaction time was six hours at 70°C; purity, 96.7% by HPLC. Magnesium chloride and stannous octoate were also shown to be effective catalysts for this insertion reaction.

The tetraphenyl pyrophosphate was prepared by hydrolytic condensation of diphenyl chlorophosphate and the subsequent alkylene bis(diphenyl phosphates) form a series of mixed aliphatic aromatic phosphates. These are "dimeric" versions of the commercial "monomeric" alkyl diaryl phosphate plasticizers which are noted for their low-smoke-generation characteristics but this "dimeric" series is higher in phosphorus content and in molecular weight.

The high reactivity of the strained three-membered epoxide ring suggested that the insertion into pyrophosphoric linkages might be unique for epoxides. This is not true and the insertion reaction is not restricted to epoxides. Four-membered-ring cyclic ethers, oxetanes, will also insert into the pyrophosphate bond of tetraphenyl pyrophosphate [6].

Neopentyl glycol bis(diphenyl phosphate) and dichloroneopentyl glycol bis(diphenyl phosphate) were prepared in 89% and 75% yield respectively by reaction of 3,3-dimethyl oxetane and 3,3-bis(chloromethyl)oxetane with tetraphenyl pyrophosphate using pyridine as catalyst. The oxetane ring may be slightly less reactive than the epoxide ring as suggested by the higher reaction temperature, 120°C, used in these reactions.

In retrospect, the reaction of aliphatic ethers with pyrophosphoric linkages may be a general reaction resulting in the formation of two phosphoric ester linkages. When the ether is a cyclic ether, the result is insertion of one molecule. By contrast when the ether is acyclic, the result is more complex. A well known example fitting this model is the autoclave reaction of diethyl ether with phosphorus pentoxide which results in a metaphosphate mixture from which triethyl phosphate is reactively distilled [7][8].

Aliphatic bridged oligomeric aryl phosphates have the desired low volatility and a reasonable phosphorus content but are still limited by the thermal stability of the aliphatic phosphate ester link. To overcome this shortcoming and better address the needs of the marketplace we have focussed on the development of a totally aromatic oligomeric phosphate. The current state of the art in thermally stable, easily recycled, halogen-free, non-volatile flame retardants is resorcinol bis(diphenyl phosphate). The commercially available products are mixtures of resorcinol-bridged diphenyl phosphate moieties containing oligomeric species with two to five phosphorus atoms per molecule. This mixture is reportedly made by reacting resorcinol with an excess of phosphorus oxychloride [9], then stripping off the excess phosphorus oxychloride and reacting the residue with phenol. The oligomer distribution is controlled by the amount of excess phosphorus oxychloride used initially. This oligomeric flame retardant, sold by Akzo Nobel as Fyrolflex®RDP, is very effective in polycarbonate blends with styrenic polymers, notably ABS [10] and in polyphenylene ether blends with high impact polystyrene [11]. Thin-walled, light-weight computer housings meeting the stringent UL94 V0 flammability test criteria incorporating this material have gained widespread commercial acceptance.

Another approach to achieving high molecular weight, oligomeric phosphorus compounds is based on the high temperature transesterification of dialkyl or diaryl methyl phosphonates [12][13][14]. Despite a flurry of patent activity in this area in recent years, no commercial products based on this technology have yet evolved.

As you can see there are several good synthetic approaches to building structures that will function as thermally stable and effective flame retardants. The problem is that any new flame retardant compound must also demonstrate minimal effects on the physical properties of a variety of polymers. This requires extensive testing and evaluation by compounders and end users. New compounds must also be listed on the various chemical inventories around the world. Unfortunately, there is not one but three sets of testing protocols necessary to gain acceptance worldwide. These are the requirements for listing on the EINECS (Europe) inventory, the TSCA

(US) inventory and the MITI (Japan) inventory. Many other countries have their own inventories but will usually accept test results acceptable for listing on one of the main three. In the past you could restrict yourself to a limited geographic market and concentrate on the listing requirements of that market. But today, and especially in the future, with the globalization of products and markets it is necessary to consider worldwide registration requirements. This is particularly true in those applications with the greatest growth, such as in electronic equipment and computers. The use of new polymers to replace metal and even other polymers requires flame retardants acceptable in any jurisdiction. It is not uncommon to have components made in many different countries, assembled in still other countries and finally sold everywhere. The problem does not stop there, because it is likely that each country or regional trading bloc will have its own rules on disposal and recycling of obsolete equipment. We are already seeing this in the still voluntary ecolabeling programs established in Germany (Blue Angel) and in Sweden (White Swan).

It is clear that the defining parameters for future flame retardant candidates present formidable challenges even before chemistry is considered. It is also likely that no other class of compounds has a better chance of meeting these challenges than organophosphorus compounds.

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FLAME RETARDANT ACTIONS OF TRIS(1,3-DICHLORO-2-PROPYL) PHOSPHATE IN FLEXIBLE URETHANE FOAM

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**IMI Institute for Research and Development, Haifa +Hebrew University (retired)

Abstract The flame retardant action of tris(1,3-dichloro-2-propyl) phosphate (TDCPP, widely used to flame-retard flexible urethane foam) appears to result in part from vapor phase physical action and in part from condensed-phase barrier-forming action.

INTRODUCTION

Flexible polyurethane foams, made typically with toluene diisocyanate and aliphatic polyols, often must pass flame retardancy requirements. An economical flame retardant, made on a large scale for this application, is tris(1,3-dichloro-2-propyl) phosphate (hereinafter designated as TDCPP). It is available from Akzo-Nobel as FYROL® FR-2 and from Albright & Wilson as ANTIBLAZE® 195. TDCPP is a liquid containing 49.1% Cl and 7.2% P, made from phosphorus oxychloride and epichlorohydrin.[1] The dichloropropyl groups are almost all 1,3-dichloro-2-isopropyl.

TDCPP is essentially a permanent flame retardant. The advantage of Fyrol FR-2 is that it is chemically very inert and practically does not interact with the tertiary amine and tin compounds used to catalyze the foam formation.

Curiously, despite the major use of TDCPP for over 30 years, little or no study has been made of its mode of action. There were some related studies on tris(2-chloroethyl) phosphate[2,3] and tetrakis(2-chloroethyl) ethylene diphosphate[4] in flexible foams. Briefly, the study on tris(2-chloroethyl) phosphate showed that most of the compound volatilized during burning but some reacted in; the flame retardant mode of action remained rather unclear. The more recent study on tetrakis(2-chloroethyl) ethylene diphosphate pointed to volatilization of the additive, and a gas phase mode of action together with some drip enhancement.[4]

RESULTS AND DISCUSSION

Evidence that all or most of the TDCPP was not bound during the foaming reaction was shown by the fact, not too surprising, that it could be extracted by methylene chloride.

Thermogravimetric analysis (TGA) at 20 /min. and an isothermal (230-5 C) large scale version thereof seemed to show loss of about all of the TDCPP prior to urethane decomposition. However, a fault of TGA as a means for studying flammability is that the rate of heating in TGA is orders of magnitude slower than in the burning process,[5] likewise, the surface to volume ratio is orders of magnitude higher in TGA than under real burning conditions.

Measurement of the fate of the TDCPP during actual burning did not give a simple result - surface tar analysis showed that much of the TDCPP vaporized but some remained behind in a chemically converted form. This still left open the question of the principal mode by which TDCPP flame retards. The vapor phase mode could be significant or could represent wastage of the additive. Furthermore, the vapor phase action could be physical or chemical or both.

A classical test of whether a flame retardant works in the condensed phase or in the flame zone is to generate a curve of oxygen index *vs.* concentration and then to compare this curve to a similarly run "nitrogen oxide index" curve *vs.* concentration.[6] The theory is that if the oxygen index *vs.* concentration and N_2O index *vs.* concentration curves have very different slopes or shapes, then the retardant must be acting as a flame chemistry inhibitor. Conversely, if the curves of oxygen index and N_2O index are very similar, then the retardant probably does not work by means of an effect on the flame chemistry. What we found was that the curves of oxygen index and nitrogen oxide index were quite similar. This is evidence against flame chemistry involvement. However, we want to point out that evidence against involvement in the flame chemistry does not logically prove that the retardant functions in the condensed phase. If the choice of oxidant has little effect and flame chemistry therefore appears not to be involved, there still remains the possibility of a vapor phase mechanism due to heat capacity, endothermic pyrolysis and gas-dynamic effects, independent of the flame chemistry.[7-10]

Further experiments to ascertain whether vaporized TDCPP can act as a flame inhibitor at first seemed to point to no vapor phase action at all. Injection of TDCPP into a flame from a burning non-flame-retarded foam using a syringe or vaporizing TDCPP from a wire loop surrounding the flame showed no evident sign of extinguishment.

However, we than found several simple demonstrations which indicate that there is a vapor phase fire-retardant action specifically when the TDCPP enters from the dark (preheat)

zone of the flame. One mode of this demonstration was conducted as follows: small bars of non-flame-retarded foam were carefully painted just on their sharp edges with the TDCPP. Thus, no TDCPP was inside the bars and we estimate that 95% of the lateral area of the bars also did not have TDCPP on it. To have any effect, it would have to evaporate from the treated edges. When these bars are held nearly vertically and ignited from the bottom up by a burner flame, the bars either self-extinguished or burned transitorially with an unstable flame. accompanied by a cloud of white smoke. Thus, when TDCPP is fed into the preheat (dark) zone of the flame, it does show a flame retardant effect. The importance of dark zone (preoxidative zone) endothermic processes in flame retardancy has only occasionally been noted in the literature.[11]

We propose that the effect is caused (1) by endothermic evaporation, absorption of sensible heat by vapors, endothermic pyrolysis (cracking) of the vapors, (2) by the decoupling of heat transfer from the flame as a result of the evident thickening of the dark zone, and (3) partly by the gas dynamic effect of an outgoing poor fuel simultaneously diluting the fuel, slowing the combustion reaction, and shortening the retention time in the combustion zone (the Damköhler number effect[12]). The phosphoric or condensed (*i.e.* dehydrated) phosphoric acid in the whitish smoke could be demonstrated by the classical phosphomolybdate blue color test. It represents not only a heat sink but the smoke could also serve as a site for radical recombination.

The question of the possible condensed phase action must now be considered. A tar on the surface of the self-extinguished TDCPP foam was always observed, accompanied by a small amount of sticky flexible char, but never a continuous char layer, contrary to what is usually seen in flame-retarded rigid urethane foams. The infrared spectrum of the tar shows it to be much like the original polyol, with only trace poorly resolved absorption in the carbonyl region characteristic of urethane and urea structures. The infrared spectrum of this tar was surprisingly close to that of the tar from nitrogen-quenched non-flame-retardant foam made with the same polyol. Any phosphorus component present was too weak for us to detect by infrared.

We had considered the possibility that pyrolysis of TDCPP at or near the surface of the foam might produce a surface film of phosphoric or polyphosphoric acid, which in some other flame retardant systems has been shown to be part of the flame retardant mode of action.[13] However, applying a pH indicator to the self-extinguished surface of a TDCPP-retarded foam showed a weakly-basic surface. Elemental analysis of the tar showed 1.02% Cl and 0.31% P, corresponding to an approximately a 3:1 atom ratio of Cl to P, whereas TDCPP has 6:1 Cl to P.

A ^{31}P nmr analysis of the tar showed that the phosphorus was present as neutral

phosphate and as salts of mono- and dialkyl phosphate esters, plus a weak but characteristic signal for a 5-membered cyclic phosphate ester.[14]

The limited amount of reaction which has occurred in the surface of the foam can be reasonably related to the chemistry analogous to reactions reported in the literature for other 2-haloalkyl phosphates, namely cyclization to 5-membered ring phosphates.[15,16]

From analysis of vapors from bulk pyrolysis of TDCPP foam, as others have found from pyrolysis of TDCPP itself,[17] we did identify the 1,2,3-trichloropropane byproduct. The 5-membered ring phosphates readily undergo ring opening. The products, instead of being P-N-bonded, are derived from ring opening with the nucleophile attacking at one of the ring carbons. This chemistry has been demonstrated in the case of the reaction of a tertiary amine with a cyclic 5-membered ring phosphate.[18] We consider that the most likely structures are arylaminopropyl acid phosphates, although zwitterionic structures cannot be excluded.

The question of the flame retardant effect of this surface tar was then examined. It was easy to establish that the surface tar from self-extinguished TDCPP foam had some moderate flame retardant action. By wiping it as smoothly as possible from self-extinguished surfaces of TDCPP foams onto bars of non-flame-retarded foam, self-extinguishing character in the horizontal position was produced at about 110% add-on, based on the weight of the bar. Significantly, a substantial part of the action of this tar was attributable to the polyol component of the polyurethane, since applying a 130% add-on of the phosphorus-free polyol itself produced flame retardancy. The surface tar from non-flame-retardant foam, although mostly polyol by infrared, was less effective, requiring about a 200% add-on to get flame retardancy. The TDCPP tar was observably *less flowable* when produced in massive amounts by continuous application of a burner, and did have some greater amount of coherent black somewhat flexible charry skin. We think that this material may have been responsible for a more coherent and obstructive tar/char layer when TDCPP is present.

Unlike some other polyurethane foam compositions where the flame retardants appear to enhance melt flow,[4] this appears *not* to be the mode of action of TDCPP in flexible foam; to the contrary, TDCPP actually *increases* melt viscosity.

CONCLUSION

Our final conclusion is that the flame retardant effect is produced by a combination of two actions: one, a vapor phase probably dark-zone action caused by endothermic effects and the outward flow of poor fuel, and a second action, the enhancement of the flame retardant barrier character of the tar, probably by physical obstruction of the surface. Both actions relate to the heat and mass flow effects of flame retardants.

Phosphorus flame retardants in general have a surprising number of possible flame retardant modes of action, encompassing several physical and chemical modes, occurring in both the condensed phase and the vapor phase modes, for all of which there are demonstrable examples.[19,20] The present case of TDCPP in flexible urethane foams exemplifies at least two such modes. Quantitative heat and mass balance studies would be needed to assess the relative contributions of each mode.

ACKNOWLEDGMENT

We want to thank Ms. Barbara Williams (Akzo Nobel, Dobbs Ferry, NY) for supplying samples of foam, Dr. Biing-Ming Su (also at Akzo Nobel) for ^{31}P nmr and Prof. Eli Pearce for providing laboratory facilities during M. Ravey's sabbatical at Polytechnic.

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THE NOVEL TETRAAMINOPHOSPHONIUM ION - STRUCTURE, CHEMICAL BONDING AND REACTIONS

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Abstract: The first representatives of tetraaminophosphonium salts $[P(NH_2)_4]Cl$ and $[P(NH_2)_4]I$ were synthesized and structurally characterized by X-ray crystal structure determination and ab initio calculations on SCF and B3LYP level. According to the theoretical results a stable D_{2d} conformation and a significant distortion of the PN_4 tetrahedra were observed in the solid. The short P-NH_2 distances (~ 161 pm) are in agreement with the calculations. Tetraaminophosphonium salts emerged as versatile educts for condensation reactions forming P-N sceletons and frameworks.

Key Words: tetraaminophosphonium salts, crystal structure, ab initio calculations, phosphorus nitrogen compounds

INTRODUCTION

The characteristic building units of solid phosphorus(V) nitrides are PN_4 tetrahedra [1]. For the synthesis of defined P-N solids from solution soluble educts would be desirable, which contain "isolated" PN_4 building blocks. Because of their unusual high formal charge PN_4^{7-} ions, as in Li_7PN_4, are not appropriate for this purpose and no experimental evidence has been found that these anions would exist in solution. The salt Li_7PN_4 is derived from the hypothetical acid H_7PN_4, which is suspected to be an unstable monophosphazene intermediate during ammonolysis of PCl_5 [2]. However, due to its high basicity and tendency to undergo condensation reactions it has not yet proven possible to isolate imidophosphoric acid triamide, H_7PN_4.

SYNTHESES

By using excess liquid ammonia for the ammonolysis the condensation can be suppressed and, according to Equation (1), only the product of substitution, the tetraaminophosphonium chloride is obtained [3].

$$PCl_5 + 8\,NH_3 \longrightarrow [P(NH_2)_4]Cl + 4\,NH_4Cl \qquad (1)$$

The pure product is obtained by reacting the byproduct ammonium chloride with diethylamine and removing the formed diethylamine hydrochloride (Eq. (2)).

$$NH_4Cl + (C_2H_5)_2NH \longrightarrow NH_3 + (C_2H_5)_2NH_2Cl \qquad (2)$$

An alternative preparation starts from phosphorothionic triamide $SP(NH_2)_3$ and thus avoids any risk of condensation [4, 5]. A two step sequence (Eq.(3)) leads from the molecule $SP(NH_2)_3$ to an ionic solid $[P(NH_2)_4]I$.

$$SP(NH_2)_3 \xrightarrow{CH_3I} [CH_3SP(NH_2)_3]I \xrightarrow[-CH_3SH]{+\,3\,NH_3} [P(NH_2)_4]I \qquad (3)$$

STRUCTURE AND BONDING

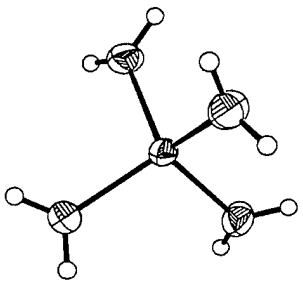


FIGURE 1 $[P(NH_2)_4]^+$ ion

According to the X-ray structure determination both salts contain the tetraaminophosphonium ion (Fig. 1). In $[P(NH_2)_4]I$ (P4/nbm, a = 842.6(2) pm, c = 486.7(2) pm, Z = 2, R = 2.23 %, wR = 1.34 %) the cations and anions resemble a CsCl analogous structure, while in $[P(NH_2)_4]Cl$ (Pbcn, a = 470.8(2) pm, b = 1622.3(3) pm, c = 756.3(2) pm, Z = 4, R = 2.94 %, wR = 1.64 %) a TlI analogous structure is found. In the tetraaminophosphonium cation (Table I) phosphorus and nitrogen form a markedly distorted tetrahedron with an unusual short P-N distance. Both, the distortion of the P-N tetrahedron as well as the short P-NH_2 distance have electronic reasons and can be explained using ab initio calculations on SCF or B3LYP level [6].

TABLE I Calculated and measured length and angles in $[P(NH_2)_4]^+$

Method	d (P-N)	HNH	NPN (2x)	NPN (4x)
SCF/SV	166.5 pm	115.3°	121.4°	103.9°
SCF/SVP	162.7 pm	114.2°	122.6°	103.3°
B3LYP/SV	168.5 pm	115.9°	124.4°	102.6°
B3LYP/SVP	164.6 pm	114.1°	124.6°	102.5°
$[P(NH_2)_4]I$	160.7(2) pm	114(4)°	124.3(1)°	102.7(1)°
$[P(NH_2)_4]Cl$	161.8(1) pm (2x)	116(2)°-118(2)°	123.8(1)°	102.2(1)° (1x)
	160.6(1) pm (2x)			102.8(1)° (1x)
				103.1(1)° (2x)

The D_{2d} conformation found in the crystal structures, is according to these calculations the most stable conformation of $[P(NH_2)_4]^+$. The enlargment of two NPN angles may be explained by a generalized anomeric effect, nitrogen lone pairs donate into antiperiplanar σ^* orbitals on phosphorus. The short P-N distances result from a significant charge transfer from phosphorus to nitrogen, corresponding to an electrostatic contraction of the P-N bonds, together with nearly planar amino groups and $d\pi p\pi$ -interactions [6].

REACTIONS

Depending on the reaction conditions, the tetraaminophosphonium cation may be used as a versatile educt for condensation reactions. By the influence of bases, the tetraaminophosphonium salts condense to triaminophosphazo-triaminophosphonium salts (Eq. (4)).

$$2\,[P(NH_2)_4]Cl \xrightarrow[\text{RT, 8 bar}]{NH_{3,\,liq.}} [(NH_2)_3PNP(NH_2)_3]Cl + NH_4Cl \qquad (4)$$

The crystal structure of this compound ($P\bar{1}$, a = 584.7(1) pm, b = 732.1(1) pm, c = 1092.0(2) pm, α = 71.05(3)°, β = 76.36(3)°, γ = 89.83(3)°, Z = 2, R = 4.75 %, wR = 2.47 %) shows a cation built up by two corner sharing PN_4 tetrahedra (Figure 2).

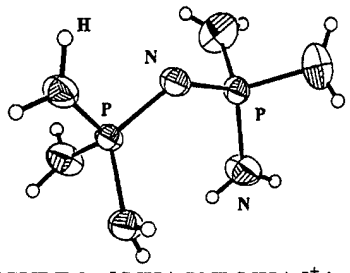
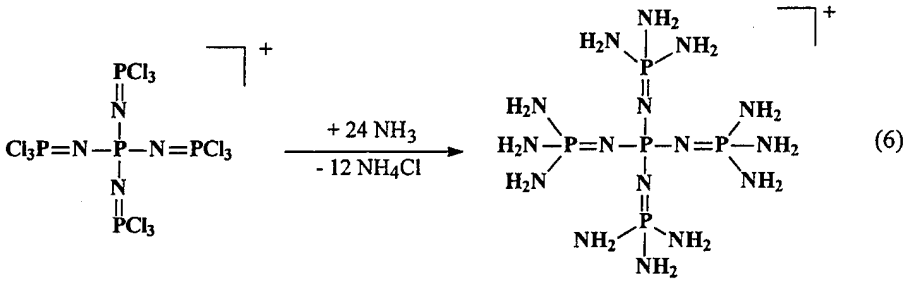


FIGURE 2 $[(NH_2)_3PNP(NH_2)_3]^+$ ion

Thermal condensation of tetraaminophosphonium salts leads dependend on the reaction conditions to linaer aminophosphazene polymers, HPN_2 or P_3N_5. The syntheses of P-N sodalites is possible by using this thermal condensation under influence of metal halides, e.g. $CoCl_2$ (Eq.(5)).

$$12\,[P(NH_2)_4]Cl + 7\,CoCl_2 \xrightarrow{800°C} Co_7[P_{12}N_{24}]Cl_2 + 24\,NH_4Cl \qquad (5)$$

By reaction of tetraaminophosphonium salts with phosphorus pentachloride $[P(NPCl_3)_4]^+$ is obtained, a product, which makes doubly branched phosphazenes accessible [7]. A dendrimeric structure is built up by ammonolysis of this product (Eq. (6)).



(6)

An extended dendrimer may be synthesized by repeated reaction with PCl_5 and subsequent ammonolysis. These results show, that $[P(NH_2)_4]^+$ is a useful educt to form P-N structures in solid state reactions or in solution.

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ENTHALPIES OF FORMATION AND BOND ENERGIES OF P(III) AND As(III) COMPOUNDS

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Abstract The enthalpies of vaporization and formation of halogenides of P(III) and As(III) compounds of different cyclic and acyclic structure have been determined. The hydrolysis of mentioned compounds have been carried out and formation enthalpies in condensed state and gaseous phase have been calculated. The Cl_2P-, Cl_2As-, ClP< – and ClAs< – group contributions in vaporization and formation enthalpies have been calculated on the basis of experimental data too. The appreciation of bond energies in chlorides of P(III) and As(III) has been given.

Key Words: *thermochemistry, vaporization, formation, phosphorus, arsenic, compound*

INTRODUCTION

Thermochemistry of vaporization, solvation, reaction and formation of P(III)–organophosphorus and As(III)–organo-arsenic compounds have been not studied detail, however such data are very useful in understanding the reactivity of these substances. The development of research into thermochemistry and thermodynamics of the mentioned class of compounds is restricted to an extremely small number of

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works conserning of the vaporization enthalpy [1,2]. The vaporization enthalpy magnitudes, contrary to the heats of solution, have not been similarly easy obtained especially in the case of heteroatomic compounds.

B.Solomonov and A.Konovalov [3] suggested for the determination of this energetical term the Equation (1) with the use of molar refraction and solvation enthalpy of compound in alkane (hexane) (in kJ mol^{-1})

$$\Delta H_{vap} = \Delta H_{soln}(C_6H_{14}) + 4.39 + 1.05\ (MR_D - \alpha) \qquad (1),$$

where α is a molar refraction correction for branched carbon atoms.

Such approach allows us to extend considerably the library of thermochemical data and gives a basis for quantitative determination of formation enthalpy (ΔH_f^o) of P and As compounds in liquid (l), solid (s) state and gaseous phase (g) according to Equation (2)

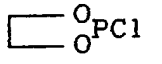
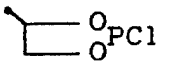
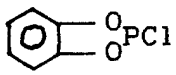
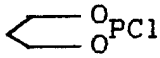
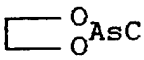
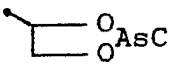
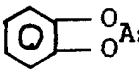
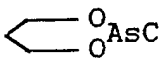
$$\Delta H_f^o(\ g\ ) = \Delta H_f^o(\ l\ \text{or}\ s\ ) - \Delta H_{vap} \qquad (2)$$

RESULTS AND DISCUSSION

Among the three-coordinated organophosphorus and -arsenic compounds the halogenides are most reactive but thermochemistry of its reaction have not investigated systematically. In present work we report the previously published enthalpies of vaporization [4] and also measured now the hydrolysis and formation enthalpies of some P(III) and As(III)-halogenides of acyclic and cyclic structure; thermochemical data are summarized in Table I.

On the basis of additive scheme and using the contributions for organic groups of molecules in ΔH_f^o we

TABLE I Thermochemical data for some halogenides in kJ mol^{-1} at 298.15 K.

Formula	ΔH_{vap}	$-\Delta H_f^o$ (l or s)	$-\Delta H_f^o$ (g)
$MeOPCl_2$	37.3	455.5	418.2±7.1
$PrOPCl_2$	45.2	532.7	487.5±7.0
$BuSPCl_2$	58.6	426.3	367.6±5.0 [a]
$(EtO)_2PCl$	48.5	683.2	634.7±8.4
$EtOAsCl_2$	47.1	558.7	511.6±9.8
$PrOAsCl_2$	52.2	574.0	521.8±10.5
$BuOAsCl_2$	55.7	590.8	535.1±12.0
	40.5	598.3	557.8±4.2
	41.4	630.2	588.8±5.4
	52.3	487.3 [b] 479.2	431.0±5.0 middle value
	44.5	655.6	611.1±7.5
	60.4	557.4	497.0±8.0
	59.8	588.7	528.9±7.3
	125.8	457.2	331.4±10.0
	62.0	565.4	503.4±8.3

[a] Calculated using the group contribution for $-PCl_2$.

[b] Reaction PCl_3 + catehol, see ref.[5].

calculated the same parameters in the vaporization and formation enthalpies for Cl_2P-, ClP<, Cl_2As- and ClAs< fragments. The calculated values in ΔH_{vap} are 22.2±0.7, 17.9±0.8 and 29.0±1.0 kJ mol^{-1} for the first, second and third-fourth groups correspondingly. The calculated contributions in ΔH_f^o are -290.0+1.8, -321.3±1.1, -328.2±3.0 kJ mol^{-1} for Cl_2P-, ClP< and Cl_2As- groups; for five- and six-membered As(III)-containing cycles the same contributions represent themselves as -202.0±4.0 and -226.5±3.3 kJ mol^{-1} correspondingly.

The energies of P-Cl, As-Cl, P-O and As-O bonds (E_b) in molecules of $ROPCl_2$ and $ROAsCl_2$ types have been calculated using the computer programm for minimization of ΔH_{at}^o- values (eqn.3) which have been worked up by us on the basis of least-square mathematical method

$$\Delta H_{at}^o = \sum \Delta H_f^o \text{ (atoms)} - \Delta H_f^o \text{ (mol)} = \sum E_b \qquad (3).$$

The calculated bond energies (± 1.7%) of P-CL, As-Cl, P-O and As-O compose as 307.1±5.7, 313.8±1.7, 418.4±11.4 and 400.0±3.4 kJ mol^{-1}.

These observations are important when interpreting the chemical behaviour of trivalent organophosphorus and -arsenic compounds.

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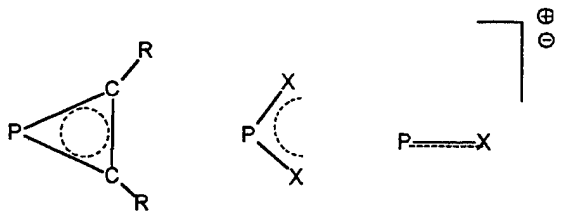
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CATION AND ANION STABILITIES OF LOW-COORDINATED Π-BONDED PHOSPHORUS SYSTEMS. AN AB INITIO QUANTUM CHEMICAL INVESTIGATION

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Abstract Quantum chemical calculations at RHF/6-31+g(d,p) with electron correlation (MP4SDTQ) corrections are reported on (a) a relative scale of model cations and anions derived from low-coordinated π-bonded phosphorus, (b) on band structure calculations (tight-binding approximation) of the P-iodine iminophosphane and (c) on lithiation to (unsolvated) corresponding structures derived from the anionic species.

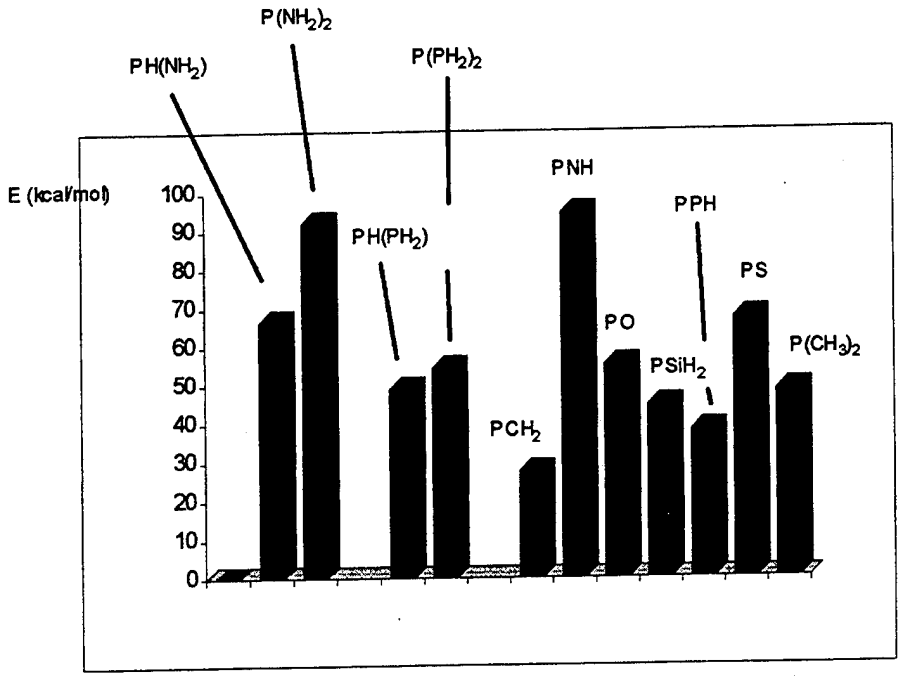
There is a particular interest in the experimental and theoretical investigations of bonding in cationic and anionic low-coordinated π-bonded phosphorus compounds of the type 1



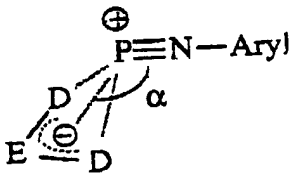
1 2 3

(R=alkyl, aryl etc.), 2 (X = NR_2, PR_2, Hal, alkyl), 3 (X = O, NR, CR_2) either as cations (in solution)[1] or in the crystal environment (triflate structures[2], periodic band structures). We explore the following aspects, on the basis of quantum chemical ab initio calculations:

(1) A relative scale of cation and anion stabilities (within the gas phase). These are given by corresponding group transfer reactions of a hydrid (proton) from PH_3 to the cationic (anionic) fragmental species under question, according to the reaction $PH_3 + PX_2^{(+)}$ (or $PX_2^{(-)}$) ---> $PH_2^{(+)}$ [$PH_2^{(-)}$] + PX_2H - ΔE. The largest cation stability possesses the diaminophosphenium cation, X = NH_2 (ΔE = 92.1 kcal/mol, exothermic, at MP4 (SDTQ(fc))/6-31+g(d) level, all details are given elsewhere[3]. In comparison with, the relative stability of the corresponding (closed shell) anion is nihil (2.4 kcal/mol). Further species with strong cation stabilities are: $P(PH)_2^{(+)}$ 54.4, $PNH^{(+)}$ 94.7 $PS^{(+)}$ 67.2, phosphirenyl cation 73.1 kcal/mol. Hence a large variation in cation stability is revealed (see following scheme for cation stabilities, exothermic energy balance, in kcal/mol).

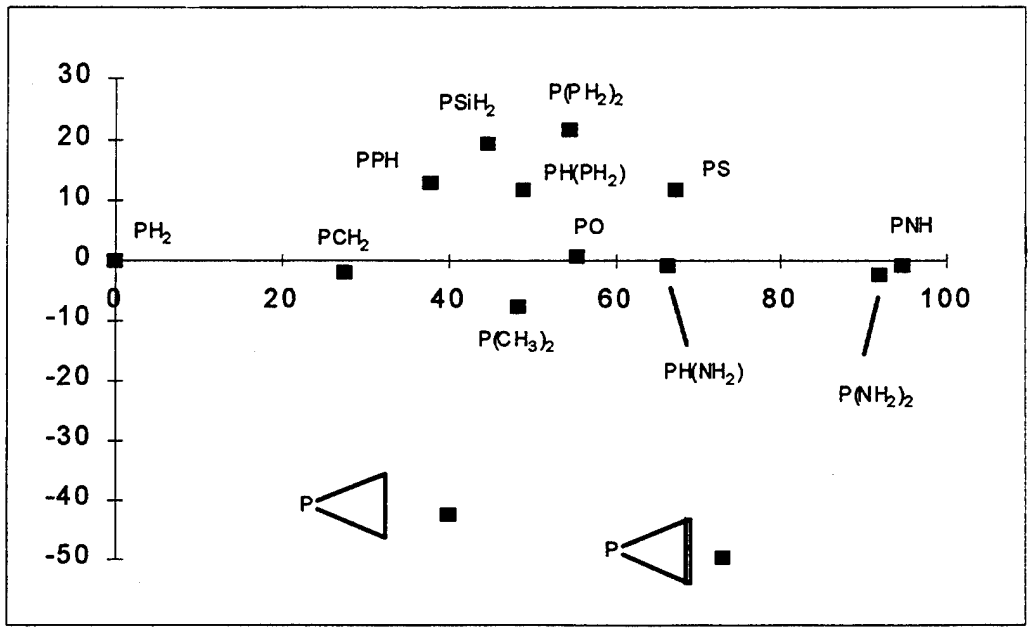


A detailed investigation of the electronic hypersurfaces of corresponding energy lowest singlets and triplets indicate that $PSiH_2^{(+)}$ possesses a triplet ground state[3,4] and reveals only a small tendency for adopting a bridged structure, as is known for the (isoelectronic) $P_2H^{(+)}$ cation. Continous medium effects were also explored within the Onsager model. They are in general much weaker than the Born effects. The strong cation stability of the $PNH^{(+)}$ cation is related to experimental work[5] on a variety of structures of donor-acceptor complexes of the following type (D = S, Se, t-BuN, O; E = R_2P, R = alkyl, aryl).



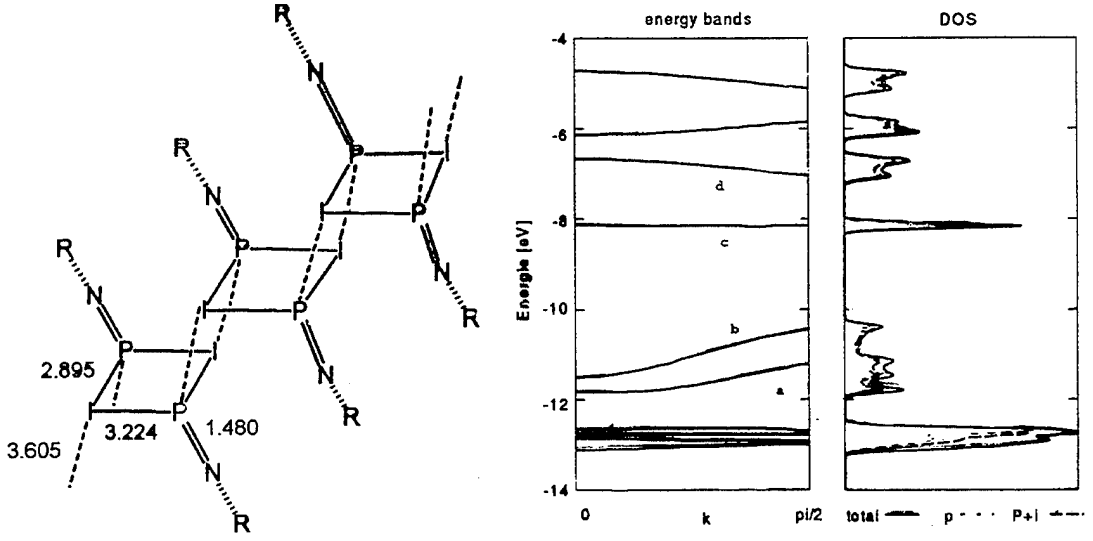
In the experiment[5] the PN-distances range from 1.53 (E = $(C_6H_{11})_2$, D = S) to 1.486 Å (D = S, E = t-Bu_2P), A detailed evaluation of the potential hypersurfaces are presented for the $N{=}CH_2^{(+)}$ and $P{=}CH_2^{(+)}$ cations. The former is lowest in energy in form of its acetylenic structural isomer $HNCH^{(+)}$ while for the latter the corresponding acetylenic isomer is unstable and rearranges to $P{=}CH_2^{(+)}$. This difference in structural stability is due to the stereochemically active lone pair in the corresponding phosphorus compound and is also apparant in the isoelectronic $Si{=}CH_2$.

A simplified plot of relative cation versus relative anion stabilities is given as follows,



indicating only a relative small variation in anion versus cation stabilities (positive values on the plot refer to extra stabilization energies and are actually exothermic in the group transfer reactions). In addition to the relative stabilities of the charged species the frontier orbital properties are evaluated[3].

(2) Formation of periodic band structures. The P-halogen substituted compounds, $XPCH_2$, XPNH (X=F, Cl, Br, I) are experimentally well known and possess according to the quantum chemical calculations energetically low lying π-orbitals at X[6] which are suitable for the formation of periodic band structures; e.g. a ladder structure of the following type (following scheme, left, ladder structure, right, band structure within the tight-binding approximation) obtained for the iodine compound.



Bonding is here rationalized and related to another periodic iodine-containing phosphorus compound, qualitatively on the basis of extended Hückel considerations within the tight-binding approximation. Thus, the compound possesses a large energy gap between the Fermi level and the lowest conduction band (right of the scheme), although it can be formally derived from the planar periodic structure, suffering Peierls distortion and causing significant σ/π orbital set mixing by folding to the ladder structure.

(3) Lithium affinities of anions. The lithiated structures (unsolvated) of a selected variety of anions are reported[3,4]. Considerably differences between lithiation at N versus P are drawn. The latter posseses a stereochemically active lone pair as already witnessed in a number of metal complexed compounds. Detailed investigations are reported on lithiation on the model compounds $N{=}CH_2^{(-)}$ and $P{=}CH_2^{(-)}$. Lithiation is in general more effective at N than at P, due to the larger ionic contribution in bonding in the former compared with the latter type of bonds. For some of the anions the electron affinities were also evaluated by successive attachment of an electron to the cations, under formation of radicals and anionic species. Some of the anions also prefer a triplet rather than a singlet ground state as an entity in the gas phase[3,4]. The lithium affinities (of the unsolvated species) do not correlate with the gas phase stabilities obtained by the group transfer reactions, rather the linkage of the (electropositive) lithium atom to the (more electronegative) nitrogen than the phosphorus atom is determining the stabilities.

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THEORETICAL STUDY OF PHOSPHONAMIDATES, PHOSPHONAMIDES AND SULFONAMIDES AS TRANSITION STATE ISOSTERES OF HIV PROTEASE

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Abstract Ab-initio calculations at the RHF/6-31+G* level are performed on the N-methyl(methyl) conformers of phosphonamidates, phosphonamides, and sulfonamides. Sulfonamides and phosphonamidates are found to have very similar conformers and energies as potential transition state isosteres. Local minima in both are separated by a 2.0 kcal/mol barrier. The anti conformation and molecular dipole moments of phosphonamides play a role in the transition state isostere as was previously evidenced in the hydroxyethylene based mimics.

Key Words: Phosphonamidates, phosphonamides, sulfonamides, HIV protease mimics.

INTRODUCTION

HIV protease plays a major role in the life cycle of the HIV virus and provides an attractive therapeutic target for the treatment of AIDS.[1] Of the various types of proteases which have been classified according to their catalytic mechanisms, the aspartic proteases are the most significant here.[2] The activity of these enzymes originates from the structural and electronic complementarity of the active site to the transition state of the substrate (Figure 1). Protease inhibitors are transition state isosteres for the hydrolysis of the amide bond and behave as stable structures which both mimic the transition state of a catalyzed reaction and will be more tightly bound than the substrate.[3,4] Successful transition state isosteres which are similar to the aspartate tetrahedral intermediate (hereafter called TI) in geometry, electron density and the hydrolysis of amide bond include the phosphonamidates, sulfonamidates, and hydroxyethylenes.[5,6,7]

Phosphonamidates ($PO_2CH_3NHCH_3$) and other phosphorous analogs have been used with success to prepare HIV protease inhibitors.[8] A disadvantage of the phosphonamidate moiety is its lability under acidic conditions.[9] The sulfur containing transition state (T.S.) analog on the other hand, has been shown to fragment the systems at temperatures between 46-49°C[10] but the corresponding sulfinamides are less prone to this. The sulfonamides SO_2RNHR (hereafter called SO_2) were investigated experimentally as HIV inhibitors and found to be only partially efficient.[11] In contrast, phosphonamidates analogs[12] (hereafter called PO_2) have been used with success in preparation of both HIV protease inhibitors and thermolysin inhibitors.[13] The PO_2 derivatives however are unstable under acidic conditions[14] and this initiated experimental trials on the phosphonamidate esters, phosphinates and phosphonate esters.[15]

By minimizing unfavorable strain energy and favoring compounds whose conformations require the least reorganization on enzyme binding, the focus here is first on resolving all possible conformations of PO_2, SO_2 and phosphonamides (hereafter called POH). In spite of the fact that both SO_2 and PO_2 possess the required tetrahedral structure to mimic the transition state, the PO_2 moieties appear to be superior inhibitors to

the SO_2. Finally, we compare these two species to POH and to understand their ability to function as isosteres.
GAUSSIAN92 calculations at the RHF/6-31+G* level of theory were performed.[16]

RESULTS AND DISCUSSION

Figures 1,2,3,4 and Tables I, II summarize the conformational studies on TI, POH, SO_2, PO_2 respectively. Some of the interconversions routes of various minima on the TI, POH, PO_2 and SO_2 surfaces are presented in these figures numerically. In Figure 1, minimum **1** may overcome the 10.2 kcal/mol barrier, **2**, to convert to minimum **3** which lies 3 kcal/mol above the global minimum Table III summarizes the ChelpG charges on various atomic centers of the global minima of TI, SO_2, PO_2 and the two minima (**1, 3**) of POH. Table III also tabulates the net dipole moments of the global minima of all these species.

The relative energies of conformers of TI and POH are given in Table I.

TABLE I
Energies of Minima and Transition States TI and POH (Kcal/mol)

Conformation		Relative Energy		ZPE Energies		dipoles (Debyes)
		TI	POH	TI	POH	TI
minimum	1	0.0	0.0	0.0	0.0	3.4
transition state	2	10.2	2.3	9.9	1.9	4.9
minimum	3	3.0	0.1	3.0	0.1	5.0
transition state	4	2.2	1.3	2.1	0.9	4.2
minimum	5	0.8	0.4	0.9	0.4	2.5
transition state	6	6.7	4.0	6.6	4.0	2.7
transition state	7		1.3		0.9	

FIGURE 1 Minima and Transition States of the Tetrahedral Intermediate (RHF/6-31+G*)

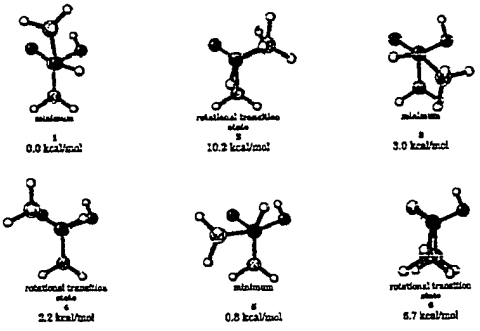
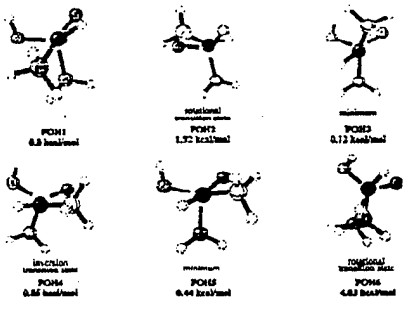


FIGURE 2 Minimum and Transition States of Phosphonamides (RHF/6-31+G*)



Figures 1 and 2 clearly show that a potential mimic for the global minimum of the tetrahedral intermediate is found in the POH local minimum 3. This conformer with the methyl groups anti to each other is only 0.12 kcal/mol above the global minimum of POH. Figure 2 also shows that the conversion from **1** to **3** on the POH surface only requires overcoming a 1.9 kcal/mol barrier, **2**, thus the POH provides a readily available transition state isostere. On the other hand, by comparing Figures 3 and 4 for the PO_2 and SO_2 to Figure 1 for TI, it is clear that no stable conformation with the methyl groups anti to each other exits. When the ability of any of the PO_2 or SO_2 conformers to rotate to the anti position is considered, preliminary results indicate that the sulfonamides are unable to match the anti configuration and are eliminated as potential transition state mimics. Phosphonamidates show a barrier of five kcal/mol in rotating to the preferred anti conformation and protonation of the phosphonamidates to match the isostere's configuration is currently under investigation.

Table I shows that the major difference between TI and POH is in the rotational barrier from **1** to **3**. In TI the barrier is 9.9 kcal/mol compared to a 1.9 kcal/mol barrier in POH. The facile conversion in POH explains its inhibitory effect as a transition state isostere and this may also facilitate the hydrolysis of the amide bond.

Molecular Dipole moments for all POH and TI conformers are given in Table I. While the conformational spaces of PO_2 and SO_2 are similar, their charge distributions differ significantly. The TI and PO_2 charges show some resemblances, indicating that PO_2 can mimic TI in hydrogen bonding and electrostatic interactions, while the SO_2 charges differs from both. Surprisingly, the global minima, **1**, on the POH and TI surfaces do not agree closely in individual charges or net dipole moment (Table 3).

TABLE II
Energies of Minima and Transition States of Sulfonamides and Phosphonamidates

conformation	PO_2 rel.	SO_2 energies	PO_2 zpe	SO_2 energies	POH ZPE	Comparison Energies	
minimum	1	0.0	0.0	0.0	0.0	0.0	0.0
transition state	2	1.5	1.5	0.9	0.8	1.3	0.9
minimum	3	1.1	1.3	1.0	1.1	0.1	0.1
transition state	4	6.7	7.5	6.4	7.0	2.3	1.9
transition state	5	8.1	9.6	8.1	9.6	4.0	4.0
minimum	6					0.4	0.4
transition state	7					1.3	0.9

TABLE III
ChelpG Charges for TI, SO_2, PO_2 AND POH

Structure		Central Atom 1	O2	O3	N	Net Dipole Debyes
TI	tetrahedral intermediate	1.27	-1.11	-0.86	-1.02	3.4
PO2	phosphonamidate	1.57	-0.99	-0.96	-0.91	5.3
SO2	sulfonamidate	1.33	-0.62	-0.66	-0.69	4.5
POH(1)	phosphonamide	1.35	-0.83	-0.74	-0.86	4.1
POH(3)	global minimum local minimum	1.49	-0.81	-0.78	-0.87	3.4

When charges in conformer **3**, the TI mimic on the POH surface, are compared to the TI global minima, there are some improvements at the O-H site while wide differences exist on the central atom. The net dipole moment of conformer **3** however, matches the tetrahedral intermediate exactly and uniquely. Global minima dipoles of PO_2 and SO_2 are higher than TI by over 1.0 Debye while the dipole moment of the POH global minimum, **1**, exceeds TI by 0.7 Debye. In SO_2 the conversion from **1** to **3** (Figure 3) appears similar to TI if it proceeds via transition state **5**.

FIGURE 3 Minima and Transition States of (N-Methyl) Methylphosphonamidate (RHF/6-31+G*)

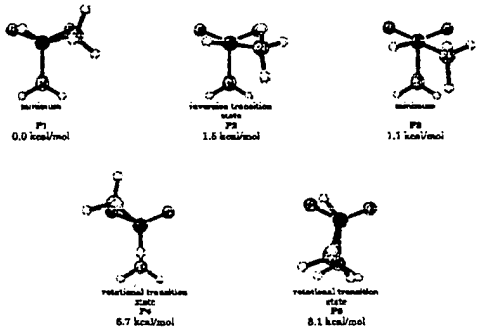
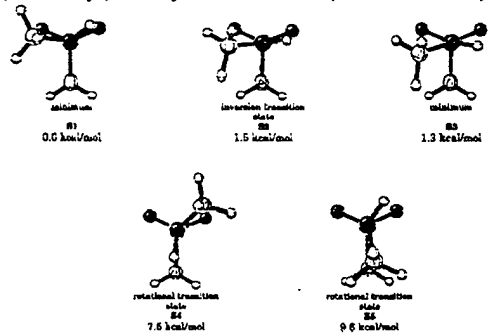


FIGURE 4 Minima and Transition States of (N-Methyl) Methyl-sulfonamide (RHF/6-31+G*)



It involves a high barrier of 7.5 kcal/mol compared to 9.6 kcal/mol in TI. The resulting conformations appear with the dihedral of about 60° for the methyl groups in SO_2 whereas on the TI surface they are anti and close to 180°. If a lower path is selected on the SO_2 surface (Figure 3), namely from **1** via **2** to **3**, the barrier heights resemble the POH values of less than 2 kcal/mol but again, the methyl groups in conformer 3 are not in the preferred anti conformation. In addition, the **1** to **3** conversion in SO_2 results in a dipole increase of 1.3 Debyes, whereas in the POH (conformer **3**) the dipole moment reduces by 0.7 Debye to exactly match the dipole moment of **1** in TI. All these factors explain why the sulfonamides are less efficient transition state isosteres.

The phosphonamidate surface (Figure 4) resembles SO_2 essentially since the global and local minima are in gauche-like conformations. Again, the net dipoles of both stable conformers exceed the TI dipole by up to two Debye units.

The conformational specificity of the POH anti methyl groups combined with a precise net dipole moment succeeds in matching the tetrahedral intermediate and creates a favorable transition state isostere.

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THE AROMATICITY OF PHOSPHORUS COMPOUNDS

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Abstract By using photoelectron spectroscopy and ab initio quantum-chemical methods it has been revealed that phosphorus is capable to build cyclic, stabilized, conjugated systems in any of its oxidation state, including σ^2,λ^3-, σ^3,λ^3-, σ^3,λ^5- as well as σ^4,λ^5-P. The conjugative ability of phosphorus - as shown on π-ionization energies and stabilization energies in isodesmic reactions - is similar to that of carbon.

Key words: σ^2,λ^3-phosphorus, σ^3,λ^3-phosphorus, σ^3,λ^5-phosphorus, σ^4,λ^5-phosphorus, aromaticity, photoelectron spectroscopy, ab inito calculations

INTRODUCTION

The chemistry of π-bonded phosphorus compounds remained nearly intact till the eighties. Apart from the experimental difficulties, the main reason of that was not the lack of interest, but the psychological effect of the "double bond rule" [1]. The great number of phosphinines, aza-, thia- and selenaphospholes synthesized in the eighties, however, showed that π-bonded phosphorus compounds do exist and presumably benefit from aromatic stabilization. Phosphole, on the other hand, is a non-planar, non aromatic molecule [2], as explained by the large inversion barrier about phosphorus, which cannot be compensated by the aromatic stabilization (if any) in the planar system.

In the present work a brief summary is given about the extent of aromaticity in compounds containing phosphorus in different bonding situations, characterizable by basic "bond types" shown in Scheme 1. The methods used were ultraviolet photoelectron spectroscopy and ab initio quantum chemical calculations. More details can be found in the references.



σ^2,λ^3-P σ^3,λ^3-P σ^3,λ^5-P σ^4,λ^5-P

Scheme 1

RESULTS, DISCUSSION

For the comparison of σ^2,λ^3- and σ^3,λ^3-phosphorus containig systems azaphospholes provide an excellent opportunity, as the aromaticity of an isomeric pair can be investigated. Comparing the photoelectron spectra of two alkylated 1,3-benzazaphospholes (**1** and **2**, Fig. 1) [3,4], it is apparent that their electronic structure should be completely different. Since the splitting of the ionization energies is much larger for the 1H-derivative **1**, this compound (containing σ^2,λ^3-phosphorus) seems to be the only aromatic molecule of the investigated pair.

Ab initio quantum chemical calculations on the similar azaphospholes (**3** and **4**) [5-7] revealed that only the 1H-derivative is planar in accordance with the photoelectron spectroscopic results. Furthermore, the alternation of the MP2/6-31G* bond length in the

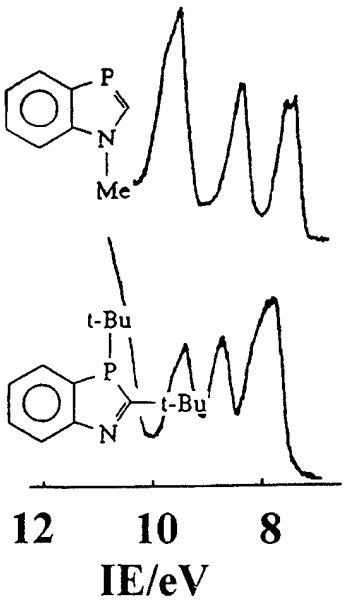


Fig. 1
Photoelectron spectra of alkylated 1H- and 3H-benzazaphospholes

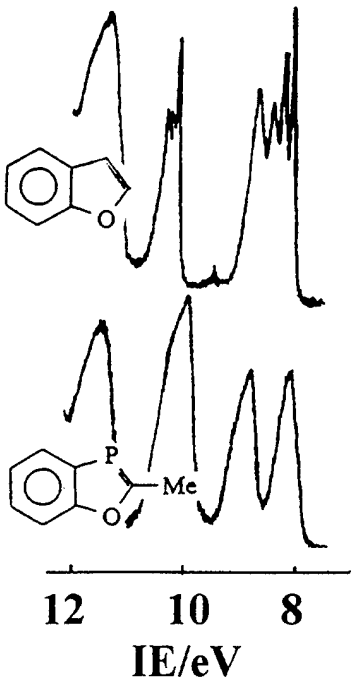
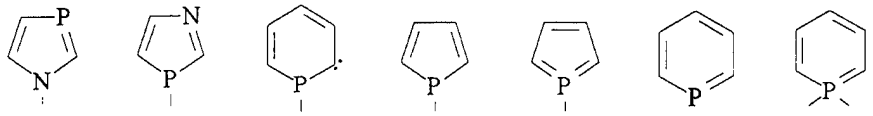


Fig. 2
Photoelectron spectra of benzoxazol and 1,3-benzoxaphosphole

ring is much smaller in this case [7], and the average double bond character (an aromaticity index introduced to measure the bond length shortening [8]) is considerably larger for **3** than for **4** (0.61 vs. 0.52, respectively; confer with the 0.68 for benzene). Semihomodesmic reaction [9] energies for 1H-1,3-azaphosphole indicate 25.45 kcal/mol aromatic stabilization (at the MP2/6-31G* level) [8].



3 **4** **7** **8a** **8b** **9** **10**

Comparing the assigned photoelectron spectra of compounds built with C=C and σ^2,λ^3-P=C units, the difference of the π-ionization energies has always been found less than a few tenth of an eV, while for the corresponding derivatives with N=C bond the difference is much larger [10]. As an illustration, the photoelectron spectra of benzoxazole (**5**) [11] and 2-methyl-1,3-oxaphosphole (**6**) [3] are shown in Fig. 2. Comparison of ring fragmentation rection energies of di- and triazaphospholes [10] resulted in similar conclusion.

Considering the abovementioned large conjugative ability of the σ^2,λ^3-P=C bond, it seems reasonable, that σ^3,λ^3-phosphorus is capable to take part in aromatic systems if planarized. Indeed, phosphinine-2-ylidene (**7**) has been shown to be planar [12] at all the levels of theories investigated. In case of this compound the carbenic centre (next to phosphorus) stabilizes the planar σ^3,λ^3-phosphorus atom. By the use of theoretical calculations phosphole (**8**) can be investigated in its planar form as well. The calculated NMR shifts [13], as well as the small alternation of the bond lengths [14] for the (artificially) planarized phosphole have shown the high aromatic character of this system. Furthermore, from the bond length distribution a significant contribution of a resonance form with σ^3,λ^5-phosphorus (**8b**) could have been concluded. By attaching different substituents on the phosphole ring the bond length distribution could be shifted towards the **8a** or **8b** structures. The attachment of the BH_2-substituent not only shifts the structure towards the **8a** form (if attached at phosphorus), or towards the **8b** form (if attached at the α-carbon atom), but lowers the inversion barrier in phosphole significantly (to 1.5 kcal/mol in case of 1-BH_2-phosphole [14]). It is of interest to note that by changing the substituents on the ring the σ^3,λ^3-phosphorus containing structure smoothly transforms to the σ^3,λ^5-phosphorus containing one, thus formally changing the valency of phosphorus.

Pentavalent phosphorus can exist in the σ^4,λ^5- form as well, this structure is considered as ylidic [15]. However, ylides can form formally aromatic structures, and their aromaticity according to Bird [16] is just slightly smaller, than that of their σ^2,λ^3-phos-

phorus containing counterparts. Indeed, the CC and CP bond lengths in σ^2,λ^3-phosphinine (**9**) are nearly identical to those in σ^4,λ^5-phosphinine (**10**) [17]. The homo-

$$C_5H_5X + 2CH_2{=}CH_2 + CH_2{=}XH \Rightarrow CH_2{=}CH\text{-}CH{=}CH_2 + CH_2{=}CH\text{-}CH{=}XH + CH_2{=}CH\text{-}X{=}CH_2 \quad (1)$$

desmic reaction (1) energies are of similar values for benzene (28.16 kcal/mol), σ^2,λ^3-phosphinine (27.24 kcal/mol) and σ^4,λ^5-phosphinine (20.55 kcal/mol) [17]. These facts show that although the behavior of σ^4,λ^5-phosphorus containing compounds is different from the "normal" double bonds in many respect, their conjugative ability is similar.

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PREPARATION OF PHOSPHORUS- AND FLUORINE-CONTAINING CALIX[4]ARENE DERIVATIVES, THEIR DICHLOROPLATINUM (II) AND CHLOROGOLD(I) COMPLEXES, CONFORMATIONAL ANALYSIS, SEPARATION OF THE CONFORMERS AND X-RAY CRYSTAL STRUCTURE ANALYSIS OF A CONE CONFORMER.

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Abstract: The reaction of the p-tert-butylcalix[4]arene **1** with Et_2NSiMe_3 was found to lead to the bis(trimethylsilyl) derivative **2**. Treatment of **2** with PF_2Cl gives the mono- and bis-difluorophosphite derivatives **3** and **4**, which undergo spontaneous elimination of Me_3SiF or PF_3 to yield the monofluorophosphite derivative **5**. **6** was allowed to react with P-chlorophosphorinone derivatives with formation of a mixture of the four possible conformers **11a - 11d**, and **12a - 12d**. In the case of **12a - 12d** the cone conformer **12a** was isolated. **12a** was allowed to react with $(COD)PtCl_2$ and $Au(C_4H_8S)Cl$ to form **13** and **14**.

Key Words: Calix[4]arenes; Supramolecular chemistry

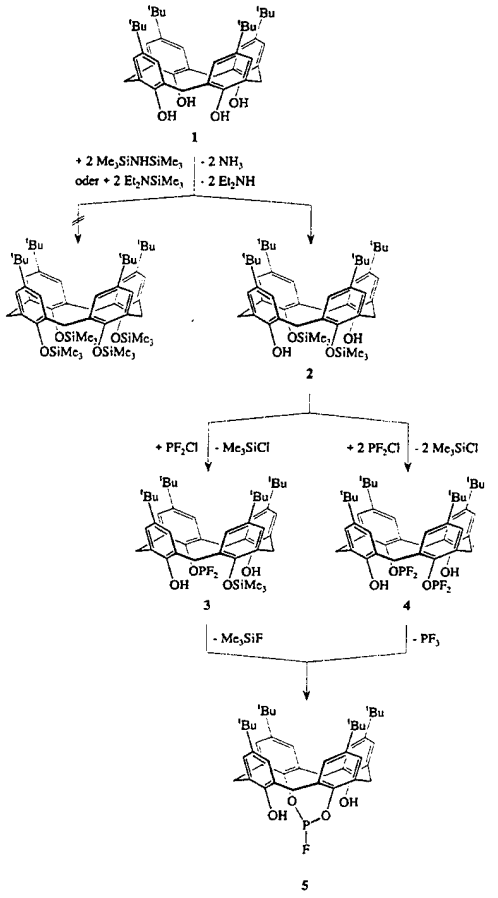
INTRODUCTION

The study of the chemistry of calixarenes including, especially, the calix[4]arenes [1], is attracting constantly increasing interest. Calixarenes are distinguished by some special features, e.g. a hydrophobic and a hydrophilic region, and a receptor space, and there is a possibility of functionalizing the donor atoms [2-7]. Phosphorus-containing calix[4]arenes, for example, are of special interest, as a result of the ability of phosphorus to exist in a variety of different oxidation states and/or coordination numbers [8-18].

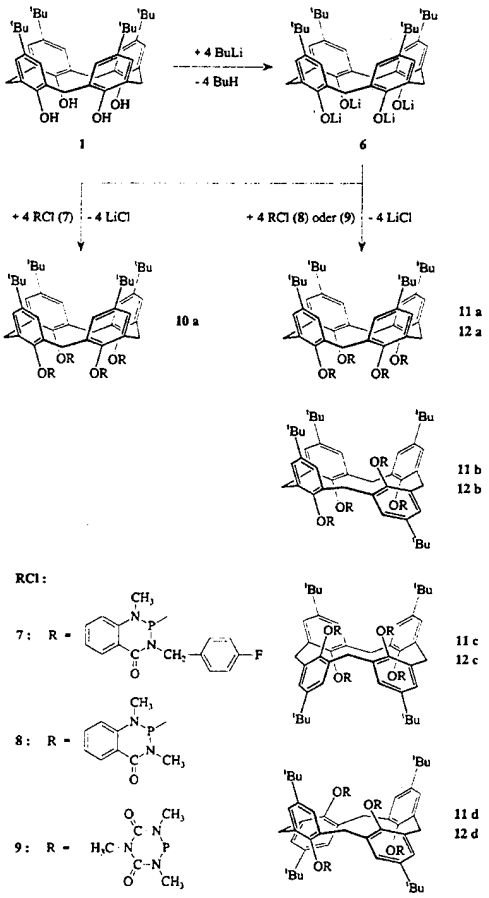
RESULTS AND DISCUSSION

In the reaction of **1** with Et_2NSiMe_3, **2** is formed (Scheme 1). The reaction of **2** with PF_2Cl in a 1:1 ratio led to the trimethylsiloxy-difluorophosphite derivative, **3** while excess PF_2Cl formed the bis(difluorophosphite) derivative, **4**. Both **3** and **4** are converted to the stable monofluorophosphite derivative **5**; while **4** loses PF_3 spontaneously upon standing in solution in hexane at room temperature over 6 h, the transformation of **3** into **5** requires 8 h heating in toluene solution at 50°C. Compound **5** is obtained from **3** with loss of Me_3SiF [19], as from **4**. The higher thermal stability of **3**, compared to that of **4**, is suggested to be due to the thermodynamically more favourable loss of PF_3, as against the formation of Me_3SiF.

Scheme 1



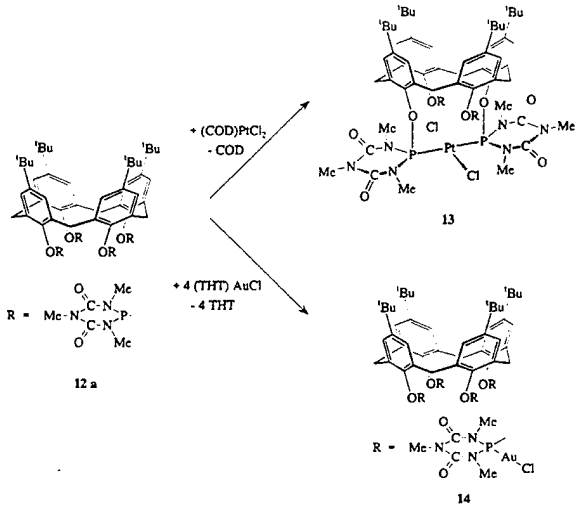
Scheme 2



The fourfold lithiation of **1** [6], followed by the action of **7** furnished the stable cone conformer **10a** (Scheme 2). Contrary to previous observations [20] no conformational changes occurred when **10a** was heated in refluxing toluene over 10 h. This must be due to the cone conformation being "frozen" through the bulky substituents at oxygen. The reaction of **1**, after fourfold lithiation [6], with **8** and **9**, lead to a mixture of all the four conformers **11a - 11d**, and **12a - 12d** (Scheme 2). The cone conformer **12a** was separated from the mixture through crystallization from acetonitrile/ n-hexane (3:1) or from a concentrated solution in THF. Because of the bulky groups at the oxygen atoms no spontaneous conversion of conformers at room temperature was observed. The conformers, **12b** and **12c**, could be separated by column chromatography at kieselgel [18]. The 1,3-alternating conformer **12d** could not be obtained in a pure state.

Preliminary attempts were undertaken at the study of the coordinating ability of calix[4]arenes, involving P(III) substituents. The formation of the trans-platinum(II) complex **13**, and of the tetrakis-gold(I) complex **14** is typical (Scheme 3).

Scheme 3



STRUCTURAL CONSIDERATIONS

Conformers **12a - 12d** could easily be distinguished by their characteristic ^{1}H- and ^{13}C-n.m.r. pattern. Depending upon the symmetry of each conformer the ^{1}H-n.m.r. spectra were found to exhibit for the $ArCH_2Ar$ resonances either a pair of doublets (**12a**), two pairs of doublets (**12b**), a singlet and a pair of doublets (**12c**), or a singlet (**12d**). In the ^{1}H-decoupled ^{13}C-n.m.r. spectra the $\delta(^{13}C)$ values were observed in the range, 31 to 37 ppm. The appearance of the ^{13}C-n.m.r. spectra of the carbon atoms of the methylene group was found to be affected by the orientation of the neighbouring aryl groups, i.e. one $\delta(^{13}C)$ value for **12a** and **12d** and two ^{13}C-n.m.r. signals (**12c** and **12c**). A single crystal X-ray structure determination was conducted for the cone conformer **12a**.

It is apparent from the ^{31}P-n.m.r. spectrum of **13** that only two of the four P(III) atoms coordinate to Pt(II). The value of $^{1}J(^{31}P^{195}Pt)$ (2728 Hz) suggests a trans-configuration. The identity of **14** was established by n.m.r. spectroscopy (^{1}H, ^{13}C, ^{31}P) and IR spectroscopy, mass spectrometry, and elemental analysis.

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SYNTHESIS OF DIPHOSPHINE DIOXIDES FOR EXTRACTION OF ACTINIDES USING SUPPORTED LIQUID MEMBRANES TECHNOLOGY

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Abstract A recurrent method for synthesis of linear and macrocyclic diphosphine dioxides has been applied to synthesize new phosphoryl ligands with P-C bonds, stable in strongly acidic aqueous solution and therefore useful for extraction and recovering of actinides from nuclear wastes. The influence of the structural parameters on their liquid-liquid extraction properties of plutonium and neptunium is studied. Plutonium and Neptunium can be removed from radioactive contaminated liquid wastes, using the supported liquid membrane technology with the more lipophilic organophosphorus extractants, which are a promising alternative to the CMPO (a carbamoylmethylphosphine), currently used for such extractions.

Key Words : diphosphine dioxide, actinide, extraction, supported liquid membrane, nuclear wastes.

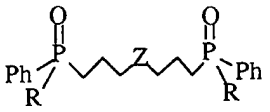
INTRODUCTION

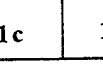
Nuclear fuel reprocessing operations produce medium level activity liquid wastes which are concentrated and disposed of in geological formations after embedding with regard to their activity associated with long-life radionuclides (actinides, strontium, ...).[1] Therefore it would be desirable to remove these very long-life radionuclides from the contaminated liquid wastes before embedding. This would allow these decontaminated wastes to be directed to surface repositories. One chemical separation process could be coupled transport through supported liquid membranes (SLM) using specific carriers.[2,3] Organophosphorus compounds have an exceptional ability for the extraction of hard cations, particularly actinides but monodentate organophosphorus compounds, even the most powerful ones, such as alkyl phosphine oxides only extract actinides (IV), (VI) and to a less extent (V), from low acidity media. Our strategy to improve actinide extracting power, consists in synthesizing cyclic diphosphine dioxides. Macrocycles of this types have been described but specific ways of synthesis are used.[4] It is interesting to dispose of a versatile synthetic method in order to design tailor-made ligands well-fitted to specific metallic cations extraction.

RESULTS AND DISCUSSION

Application Of The Recurrent Synthetic Method

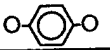
The use of the recurrent method earlier reported [5] allows us a stepwise approach to linear or cyclic organophosphorus extractants more and more efficient, controlling the size, type of bridges between the phosphorus atoms, number, type and position of heteroatoms, number and type of side chains (Figure 1).



Z \ R	Ph	$n\,C_{12}H_{25}$	$(CH_2)_nOR'$
CH_2CH_2	**1a**	**1a1**	—
O	**1b**	**1b1**	**1b2** *
	**1c**	**1c1**	**1c2** **

* n = 2, R' = Et ** n = 3, R' = Me

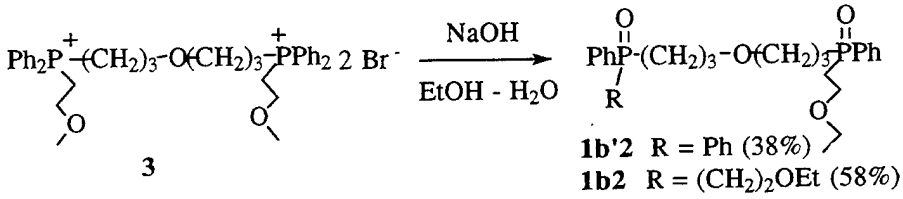


Z \ R		Ph	$n\,C_{12}H_{25}$
O	cis	**2ac**	**2cc**
	trans	**2at**	**2ct**
		**2b** ***	—

*** mixture of diastereoisomers

Figure 1 Diphosphine dioxides obtained with the recurrent synthetic method.

The recurrent method affords us the possibility to synthesize homologs of Lariat crown-ethers affording additional coordination sites in the side chains which can participate to the complexation of cations.[6] One (**1b'2**) or two (**1b2**) phenyl groups can be substituted by -$(CH_2)_2$-OEt thanks to the non specificity of clivage of the P-C bond in bis(β-functional)phosphonium salt **3** (Figure 2).[7]



3

FIGURE 2 Alkaline hydrolysis of bis (β–functional)phosphonium salt.

As a range of diphosphine dioxides were obtained, the influence of the structural parameters (bridges between the two phosphoryls, side chains and macrocyclic effect) on extractant properties could be studied.[8]

Extraction Results

The diphosphine dioxides obtained by the recurrent method have been first tested in liquid - liquid extraction of Pu (IV) and Np (V).[8b,c] The results obtained (Table 1) are to be compared with those of octyldiphenylphosphine oxide **4** (monodentate ligand) and to CarbamoylMethylPhosphine Oxide **5**, which is considered till now as the most powerfull extractant of actinides. [9]

	1a	1b	1c	1a1	1b1	1c1	1b2	1b'2	1c2	2at	2ac	2ct	2cc	4	5
D_{Pu}	0.06	0.11	17	12	20	35	35	14.2	30	0.1	0.5	28	41	0.16	22
D_{Np}	0.6	0.45	1	0.5	0.9	1.2	1.2	1	4.1	0.45	0.35	1.1	1.8	0.19	0.85

Table 1 Distribution coefficients D with extractants 10^{-2} M in NPHE.

The distribution coefficients D_{Pu} are increased by a factor of two when the extractant is cyclic. The replacement of the phenyl group by a less elecronegative alkyl group increased the D_{Pu} and leads to a better solubilization of the extractant in NitroPhenylHexylEther (NPHE). The replacement of a phenyl group by an ether substituent increased the extraction of plutonium, and compounds with two ether substituents are more effective than those with only one. The substitution of a methylene group by an oxygen atom or a hydroquinonic group in the bridge linking the two phosphoryl groups improved the extraction of plutonium; the hydroquinonic group leading to a more effective compound.

Compound **1c1** containing simultaneously alkyl groups linked to phosphoryl groups and the hydroquinonic groups in the bridge is a very effective plutonium extractant owing to the combination of the two effects. It must be noticed that only **2cc**, a macrocyclic compound, is more efficient.

Transport Experiments

The selective solvents used for extraction are often very expensive and thus limit the use of the techniques mentioned above; work was therefore carried out in this study on the use of selective solvents with liquid membranes technology. The use of neutral carriers E such as phosphine oxides leads to the coupled co-transport of cations and nitrate anions through the SLM.[2] When concentrates or fission product solutions are used as the feed solution [$NaNO_3$ (4M), HNO_3 (1M)] and demineralized water as the stripping solution, the concentration gradient of the nitrate anions will force the transport of actinide cations Ac^+ against their own concentration gradient, thus leading to increase their concentration in the stripping solution (Figure 3). The transport of ^{237}Np, ^{239}Pu from their synthetic aqueous solutions in $NaNO_3$ (4M) and HNO_3 (1M), was followed by regular measurement of the decrease of radioactivity in the feed solution by α spectrometry analysis. This allowed the determination for the constant permeabilities P

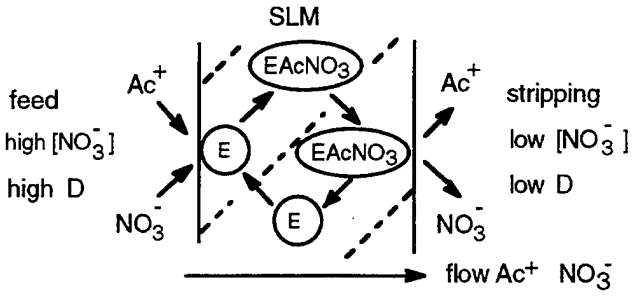


FIGURE 3 Transport Mechanism through SLM

(Table 2) for the actinide permeation through the SLM with the most promising compounds [8b,c] as described in the model of mass transfer proposed by P. Danesi.[3]

	1a1	**1b1**	**1c1**	**1b2**	**1c2**	**2ct**	**2cc**	**5**
P_{Pu}	2.37	2.47	1.95	0.37	0.94	2.17	3	3.44
P_{Np}	0.23	0.62	1.43	0.1	0.1	0.84	0.84	0.74

Table 2 Permeability P ($cm.h^{-1}$) with extractants 10^{-2} M in NPHE.

CMPO **5**, although exhibiting smaller distribution coefficients than **2cc**, is a slightly better carrier for plutonium (IV). In the case of neptunium (V), the hydroquinonic bridged compound **1c1** and to a less extent, macrocyclic compounds **2cc** and **2ct**, are better carrier than CMPO.

CONCLUSIONS

These transport experiments prove the interest of developing bidentate cyclic compounds such as **2cc** or bidentate linear compounds such as **1c1** to achieve the α decontamination on supported liquid membranes. Yet, as diphosphine dioxides are not efficient for the uptake of actininides (III) which are the more difficult to extract, we are developping further a new family of polyphosphine polyoxides whose first extraction results are particularly promising.

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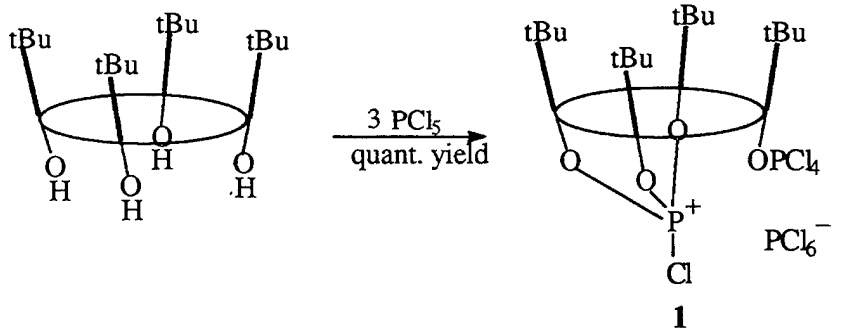
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P-BRIDGED CALIXARENE PHOSPHATE AND THIOPHOSPHATE - SYNTHESIS AND PROPERTIES

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Abstract The P-bridged calix[4]arene derivative **1**, formed from tert.butylcalix[4]-arene and phosphorus pentachloride, reacts with water, ethanol, sulfur dioxide, morpholine, hydrogen sulphide and mercaptan to give the new 1,2,3-bridged tert.-butyl-calix[4]-arene diphosphate **2a-c** and **3a**, dithiophosphate **2d, 2e** and **3b** and mono-thiophosphate **4**. The alkaline hydrolysis of **1** proceeds to the 1,2-bridged calixarene diphosphate **5**, which also is formed by acidic hydrolysis of **6**, obtained from tert.-butylcalix[4]arene and phosphorus oxychloride. The compound **7**, formed from tert.-butylcalix[6]arene and phosphorus pentachloride, reacts with water, ethanol and hydrogen sulphide to give the P-bridged tert.butylcalix[6]arene diphosphate **8a** and dithiophosphate **8b**.

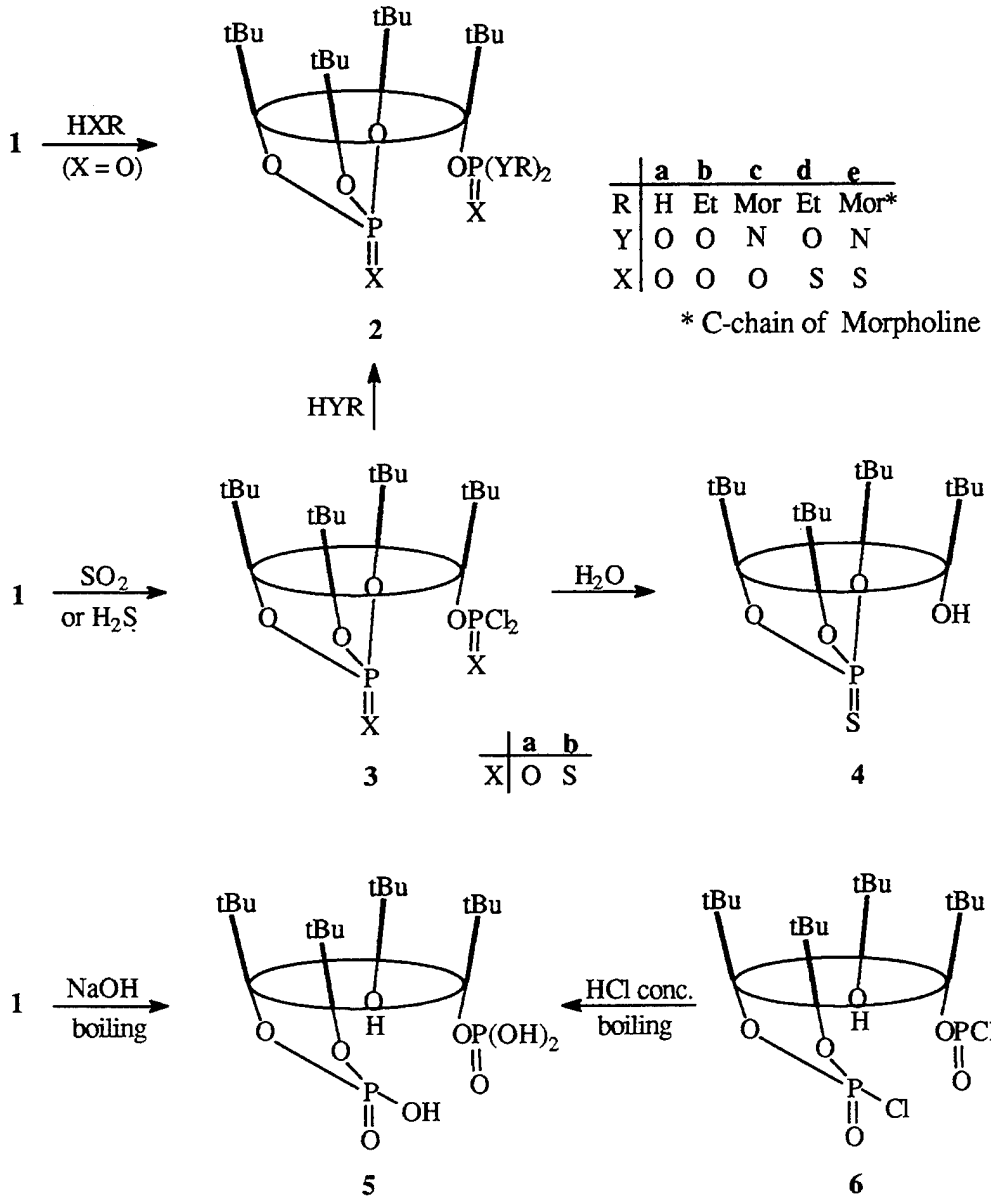
Tert.butylcalix[4]arene[1] reacts with 3 moles phosphorus pentachloride to give the compound **1**.[2] This P-bridged calixarene derivative has three different P atoms ($\sigma^4\lambda^5$,$\sigma^5\lambda^5$ and $\sigma^6\lambda^5$ phosphorus). **1** is a good starting material for the synthesis of calixarene phosphates and thiophosphates.[3]



1

δ (^{31}P) 8 ; - 66 ; - 296 ppm

The hydrolysis and the alcoholysis of **1** give the calixarene derivatives **2a** (δ -3,5, -22,3 ppm) and **2b** (δ -6,5, -22,5 ppm). These compounds have a cyclic and an acyclic phosphate group on the lower rim of the calixarene skeleton.



	a	b	c	d	e
R	H	Et	Mor	Et	Mor*
Y	O	O	N	O	N
X	O	O	O	S	S

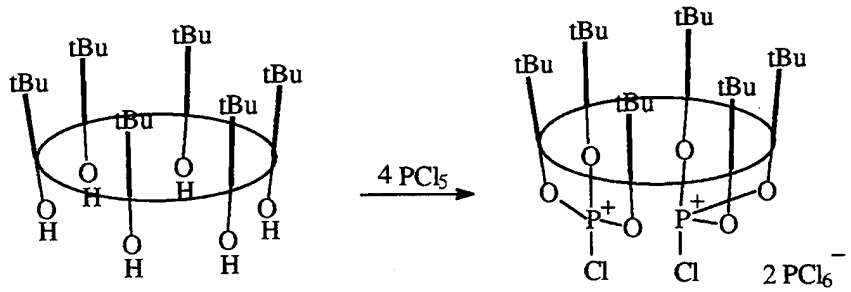
* C-chain of Morpholine

	a	b
X	O	S

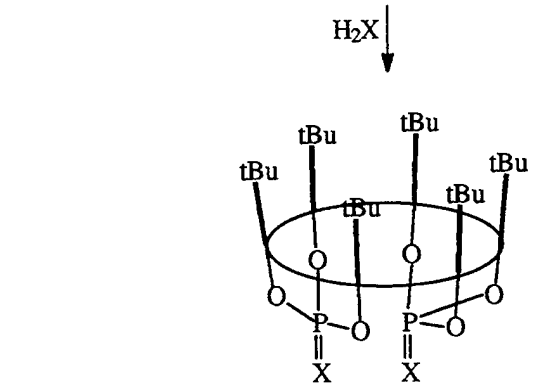
The reaction of **1** with sulfur dioxide proceeds to the dichloride **3a** (δ -2,5, -22,3 ppm), which reacts with water, alcohols and amines to produce the P-bridged calixarene diphosphate **2a**, **2b** and **2c** (δ 7,7, -22,0 ppm) in good yields. The reaction with hydrogen sulphide gives the corresponding dithio-dichloride **3b** (δ 46,9, 53,0 ppm). Its hydrolysis

proceeds under the splitting of the acyclic P-O bond to the monothiophosphate **4** (δ 46,0 ppm). The reaction of **1** with ethyl mercaptan gives **4** (δ 46,9 ppm), as well. The alcoholysis and the aminolysis of **3b** proceeds to the expected dithiophosphate **2d** (δ 46,6, 61,9 ppm) and **2e** (δ 46,1, 67,4 ppm). The X-ray structure investigations shown that the calixarene diphosphates **2b** and **2d** exist in the partial cone conformation in the crystalline state. All 1,2,3-bridged calixarene derivatives (**2, 3** and **4**) are stable compounds (m.p. 250-350°C) and they shown interesting results by NMR investigations (phosphorus, carbon, oxygen and proton NMR and addition of shift reagent).[4,5]

The splitting of the P-bridge of **1** is successful when boiled with 1n sodium hydroxide solution. The calixarene derivative **5** (δ -3,8, -8,8 ppm) was formed, which has a 1,2-bridge. The acidic hydrolysis of the trichloride **6** (δ 4,1, 1,4 ppm), formed from tert.butylcalix[4]arene and phosphorus oxychloride,[6] also proceeds to **5**.



7



	a	b
X	O	S

8

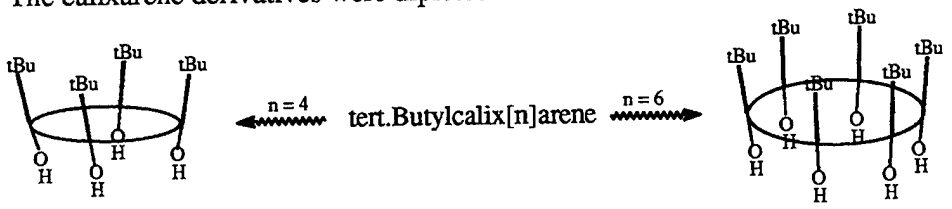
Tert.butylcalix[6]arene reacts with 4 moles phosphorus pentachloride to yield the calixarene derivative **7** (δ 12,7, 10,3, -296 ppm). It is a bis-chlorophosphonium salt with two P-bridges. The hydrolysis of **7** gives the calix[6]arene diphosphate **8a** (δ -22

ppm, m.p. 514°C), which was described by Grynszpan, Aleksiuk and Biali,[7] and the thiolysis with hydrogen sulphide gives the corresponding dithiophosphate **8b** (δ 46 ppm, m.p.512°C).

The calixarene diphosphates were tested as selective receptors for lanthanides.

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BIS(PHOSPHONIO)-ISOPHOSPHINDOLIUM CATIONS AS LIGANDS IN COORDINATION CHEMISTRY: ANIONIC BEHAVIOUR OF CATIONIC SPECIES

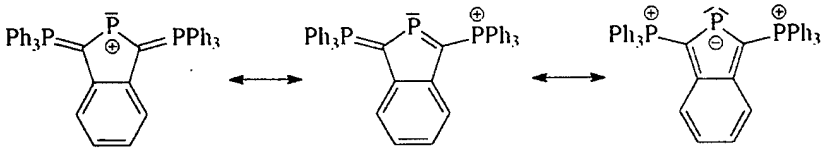
DIETRICH GUDAT, MARTIN SCHROTT, VOLKER BAJORAT, MARTIN NIEGER

Anorganisch Chemisches Institut der Universität Bonn, 53121 Bonn, Germany

Abstract Crystal structures and spectroscopic properties of the title cations and their reactivity towards transition metal carbonylates and coinage metals are discussed.

INTRODUCTION

The bonding situation in the bis(phosphonio)-isophosphindolium cation **1** may be described by a set of mesomeric structures containing both formulas with a positive (**1a**) and a negative charge at the two coordinate phosphorus (**1c**).[1] Accordingly, **1** resembles both an electrophilic phosphenium ion and a nucleophilic 2-phospha-allylic ion and thus forms a bridge between the two principal categories[2] of cations with two coordinate phosphorus.



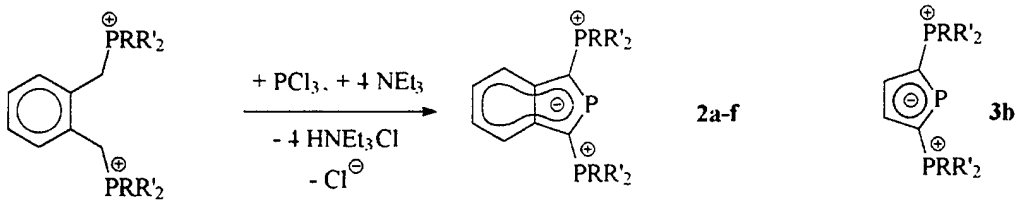
1a **1b** **1c**

Regarding that phosphenium ions form complexes[3] which can be considered as isoelectronic and isolobal to Fischer carbene complexes, the enhanced nucleophilicity of cations of type **1** as compared to a phosphenium ion[1] makes these species interesting ligands in coordination chemistry. Here, we report on a modification of the synthetic route to **1**[1] giving a more general access to the title cations. Their characterisation by spectroscopic methods and x-ray diffractommetry provides a detailed understanding of the bonding situation. Finally, the reaction behaviour of these compounds towards both nucleophilic and electrophilic transition metal compounds will be explored.

PROPERTIES OF BIS(PHOSPHONIO)-ISOPHOSPHINDOLIUM CATIONS

The synthesis of **1** was achieved via a multistep condensation reaction starting from PCl_3 and a xylylene-bisphosphonium salt.[1] Examining this reaction in more detail we found that

the cations **2a-g** are easily accessible when one or two of the peripheral phenyl moieties in the bisphosphonium salt are formally replaced by heteroaryl (**2a,b**)[4], vinyl (**2c**)[5], alkyl (**2d,e**)[4,6] or functionalized alkyl residues (**2f,g**)[6].



R' = Ph. R = 2-C_4H_3S (**a**). 2-C_5H_4N (**b**). C_2H_3 (**c**). Me (**d**). -$(CH_2)_2PPh_2$ (**f**). -$(CH_2)_2PSPh_2$ (**g**)
R = Me. R' = Ph (**e**)

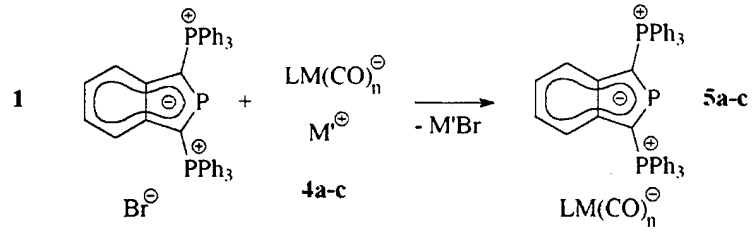
Limitations of this method are that no trialkylphosphonio substituted cations are accessible, and that alkyl groups in the phosphonio fragments may have no further activating functionalities ($SiMe_3$, CO_2R') on the α-carbon. The monocyclic bis(phosphonio)-phospholium cation **3b** was obtained in low yield by analogy via condensation of a butenylidene-bis(phosphonium) salt with PCl_3.[4] The cations **2** are isolated as halides whose anions are easily metathetically exchanged against $CF_3SO_3^-$, $CF_3CO_2^-$, or BPh_4^- anions.

Characterisation of **2a-f** by nmr spectroscopy revealed similar data as compared to **1**. The x-ray crystal structures of the salts **1**[$CpW(CO)_3$][7] and **2**[Br][5] revealed the presence of discrete cations and anions. The isophosphindole rings are planar, and the bond distances in the different cations differ not significantly. As expected, the endocyclic P-C distances are equal (av. 1.735 Å) and lie halfway between a single and double bond. The exocyclic P-C distances are comparable (av. 1.746 Å) and suggest that the ylide character in these bonds is very low. The distribution of the C-C distances in the ring suggests the presence of a delocalized π-electron system extending over both rings. This is further confirmed by the results of spectroscopic and quantum chemical[5] studies. Of particular importance are the UV/VIS-spectra which display three bands at 353, 336, and 262 nm attributable to transitions of the isophosphindole chromophore. The first excitation energy is similar as in 2-phospha-naphthalenes, and the position of the bands remains unchanged for all cations **2a-f**, indicating that electronic interaction of the π-system with the phosphonio fragments is unimportant.

On the whole, the results of structural and spectroscopic studies indicate that the bonding in the cations **1, 2** is adequately described as a delocalized 10π-electron system which extends over both condensed rings. The exocyclic P-C-bonds have essentially single bond character. The bonding situation at the two coordinate phosphorus atom constitutes a hybrid between an electrophilic phosphenium and a nucleophilic phospholide environment, in accord with a superposition of mesomeric formulas **1a** and **1c**.

REACTIONS WITH TRANSITION METAL COMPOUNDS

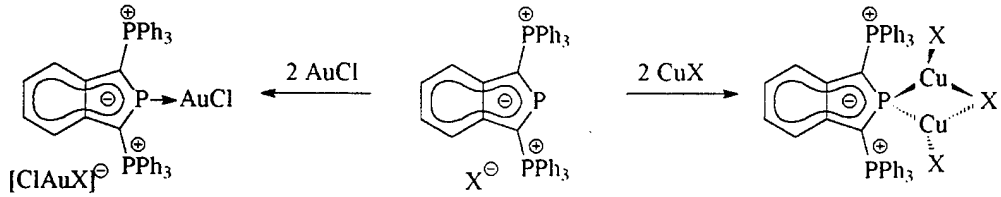
Regarding the ambident nature of the two coordinate phosphorus in **1**, **2**, we expected that these cations should react with transition metal nucleophiles with formation of neutral metallophosphenium compounds featuring a phosphorus metal bond. However, investigating the reactions of **1** and **2d,e** with the metal carbonylates **4** we found that not of the expected substitution products, but rather the ionic carbonyl metalates **5** were formed *via* metathetical anion exchange.[7] Inspection of the x-ray crystal structure of **5c**[7] suggested that the unexpected behaviour is related to the steric protection of the two coordinate phosphorus rather than its poor electrophilicity.



$LM(CO)_n$ = $Co(CO)_4$ (**a**). $CpMo(CO)_3$(**b**). $CpW(CO)_3$ (**c**)

In order to minimise any steric perturbations in reactions of bis(phosphonio)-isophosphindolium cations with electrophilic metal substrates, we investigated the reactivities of **1** towards compounds of the coinage metals.

Treatment of **1**[Cl] and **1**[CF_3SO_3] with AuCl yielded the phosphenium analogue complexes **6**. The end-on coordination of the cationic ligand to a two coordinate gold atom was derived from nmr data as well as an x-ray crystal structure analysis.[7] Reactions of **6** with Lewis-bases and with water, respectively, indicate that the cationic ligand is readily displaced from the metal, and that the π-electron system in the coordinated ligand is activated towards addition reactions.[7]

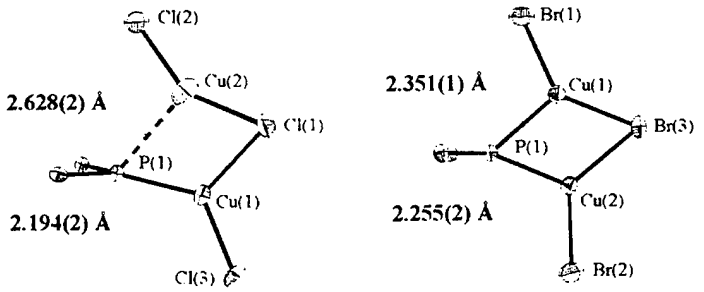


(X = Cl (**a**). Br (**b**)

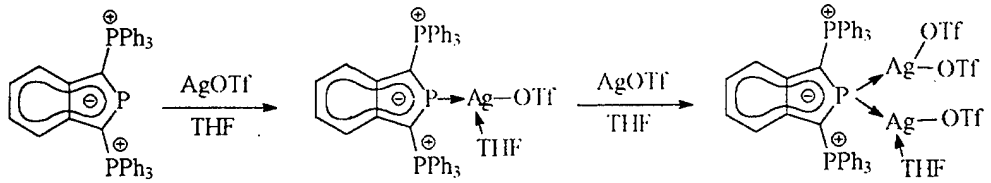
Reactions of **1**[Cl] and **1**[Br] with CuCl or CuBr, respectively, furnish the binuclear copper complexes **7a**[8],**b**. According to crystal structure determinations, the two metal atoms in each complex exhibit significant differences in their coordination spheres (Fig. 1) which can be related with the asymmetric bridging mode of the μ^2(P)-coordinated isophosphindolium ligand. The observed effects suggest that the Cu-P interactions do not constitute

electron precise 2-centre-2-electron (2c-2e) bonds as encountered in μ^2(P)-phospholide complexes[9], but should be rather described as electron deficient 3c-2e bonds in analogy to the bonding situation in μ^2-aryl copper compounds.[10] The differences in the P-Cu bond distances are in accord with the assumption that the Lewis basicity of the isophosphindole π-electron system is distinctly lower than that of the phosphorus lone pair.

Figure 1:
ORTEP-plots of the metal coordination spheres in the copper complexes **7a,b**.



Whereas **1** forms no complexes with silver halides due to their low solubility, both mononuclear (**8**) and binuclear (**9**) bis(phosphonio)-isophosphindolium silver complexes were obtained upon treatment of **1**[CF_3SO_3] with CF_3SO_3Ag, depending on the reaction conditions. Both products were isolated and characterised by spectroscopic methods and x-ray crystallography. In contrast to the situation in **7a,b**, the μ^2P-coordinated ligand in **9** forms a symmetric bridge, and the observed values for the P-Ag bond distances (2.41±0.02 Å) are more consistent with the presence of electron precise 2c-2e bonds.



1 $OTf^{\ominus}$ **8** $OTf^{\ominus}$ (OTF = SO_3CF_3) **9**

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REACTIVITY OF CATIONIC TRANSITION-METAL PHOSPHENIUM COMPLEXES

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Abstract Reactivity of cationic transition-metal phosphenium complexes has been investigated. Reaction of mer-$[(bpy)(CO)_3M\{PN(Me)CH_2CH_2NMe\}]^+$ (M = Cr, Mo, W) with X^-(X = Me, OEt) exhibits a nucleophilic attack at the phosphenium phosphorus, whereas that with L (L = phosphine, phosphite) shows CO/L substitution. Iron phosphenium complexes, $[Cp(CO)RFe\{PN(Me)CH_2CH_2NMe\}]^+$ undergoes a migratory insertion of the phosphenium ligand into the Fe-alkyl bond.

Key Words: Phosphenium complex, Transition metal, Nucleophilic attack, CO substitution, Migratory insertion.

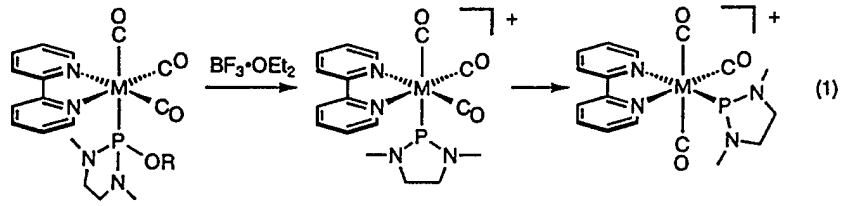
INTRODUCTION

A phosphenium cation described as PR_2^+ serves as a unique ligand toward a transition metal. It has both lone pair electrons and a vacant p orbital on the phosphorus atom, thus it can act as a σ-donor and also as a π-acceptor. Although many cationic transition-metal phosphenium complexes and some preparative methods have been reported so far, [1,2] information concerning their reactivity is much more sparse. In this paper, we report our results obtained so far concerning the reactivity of cationic phosphenium complexes.

PREPARATION OF CATIONIC PHOSPHENIUM COMPLEXES

Before discussing the reactivity of cationic phosphenium complexes, it may be pertinent to show the preparative method of cationic phosphenium complexes we employed.[3,4] Electrically neutral group 6 transition metal complexes with amino-substituted phosphite (**1**) react with a Lewis acid such as $BF_3{\cdot}OEt_2$ to give cationic phosphenium complexes (**2**) by the abstraction of an OR group as an anion (eq 1). The product has a facial geometry which gradually changes to its meridional form. The isomerization is completed for 1 day for Cr and Mo complexes, whereas the W complex does not

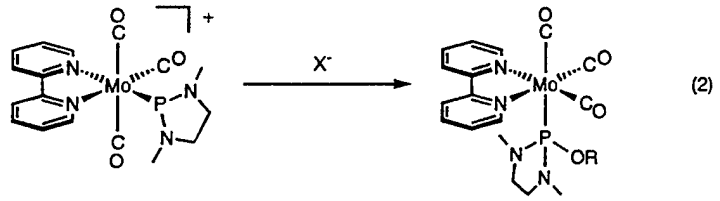
isomerize for several days at room temperature.



These reactions are clean and quantitative and the products are stable in solution at room temperature for several days but sensitive toward air. Several trials to isolate the product in the solid state were unsuccessful. Therefore, these phosphenium complexes were prepared in solution and subjected to further reactions without isolation.

REACTIVITY WITH R^-, OR^-, AND $HNEt_2$

A cationic phosphenium Mo complex (**mer-2-Mo**) reacted with LiMe and NaOEt to give **3-Mo** and **1a-Mo**, respectively (eq 2), while **1-Mo** did not react with LiMe or NaOEt.[3] Therefore, it was established that **mer-2-Mo** is susceptible to nucleophilic attack at the phosphorus atom.



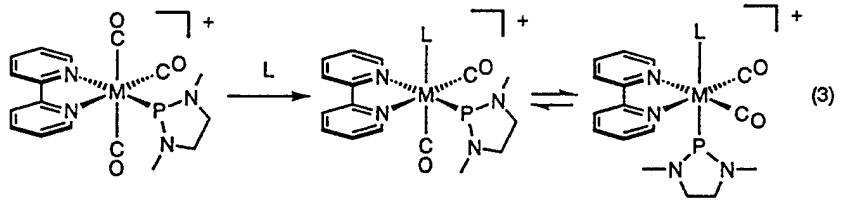
In the reaction with $HNEt_2$, **1b-Mo** containing an OMe group was unexpectedly obtained from **mer-2-Mo** and $HNEt_2$, both of which have no OMe group. **1b-Mo** may be formed from the reaction of **mer-2-Mo** with OMe^- which is released by the attack of $HNEt_2$ on the $BF_3(OMe)^-$ present.

It is known that cationic carbonyl complexes react with OR^- to give alkoxy carbonyl complexes.[5] **mer-2-Mo** can be regarded as a cationic carbonyl complex. In this case, nonetheless, OR^- and R^- selectively attack the phosphorus atom but not the carbonyl carbon.

REACTIVITY WITH TRIVALENT PHOSPHORUS COMPOUNDS

The reaction of **mer-2** with a trivalent phosphorus compound (L) in CH_2Cl_2 yielded a CO/L substituted product.[6] Two geometrical isomers were detected and it was found that

they were at equilibrium (eq 3).



(3)

mer-2 L = P(N-N)(OMe) cis-4 trans-4
L = P(N-N)(OEt) cis-5 trans-5
L = PPh_3 cis-6 trans-6
(N-N = $NMeCH_2CH_2NMe$)

In the reaction in eq 3, **cis-4** may be formed first. A phosphenium ligand is a strong π acceptor, so three CO ligands in **mer-2**, especially two CO ligands mutually trans are activated by it. Thus, one of the two CO ligands is readily replaced by L to give **cis-4**, which then isomerizes to **trans-4** to reach the equilibrium. It should be noted here that a non-phosphenium complex, **1**, does not undergo CO/L exchange reaction at room temperature.

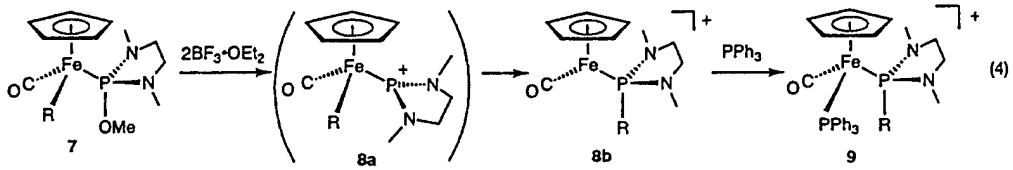
Bpy and L serve as a σ-donor and also as a weak π-acceptor, and the π-acidity is weaker for bpy than for L.[7] Therefore, the cis form where a phosphenium ligand is trans to bpy is electronically favored than the trans form where a phosphenium ligand is trans to phosphite. The J_{PW} values of **4-W** indicate that the phosphenium ligand is bonded more strongly to W for the cis form than for the trans form.

A cis/trans isomer ratio was 24/76 for **4-Mo** and 22/78 for **4-W**, whereas 0/100 for **4-Cr**. It is suggested that Cr, having a small radius than Mo or W is too small to accept the two lignads in the cis configuration. The P-P coupling constant for the Cr complex (91.6 Hz) was smaller than that for the Mo (274 Hz) or the W (268.6 Hz) complexes. It is suggested that the phosphite and/or the phosphenium may not approach closely to the small Cr to make a sufficient bond due to the steric repulsion. The ratio of 7/93 for **6-Mo** can be rationalized also by the steric effect. These equilibriums are on a critical balance, but basically it can be said that the cis form is electronically and the trans form is sterically favored.

REACTIVITY OF $Cp(CO)RFe\{PN(Me)CH_2CH_2NMe(OMe)\}$ WITH PPh_3

Piano stool iron complexes containing an alkyl group (Me, CH_2Ph) and diamino-substituted phosphite, **7**, reacted with $BF_3{\cdot}OEt_2$ then PPh_3 to give **9** (eq 4).[8] The reaction may proceed as follow. In the reaction of **7** with $BF_3{\cdot}OEt_2$, an OMe group on a phosphorus is abstracted by BF_3 as an anion to give a cationic iron phosphenium complex **8a**. Due to its high reactivity, **8a** can not be detected, and undergoes migratory

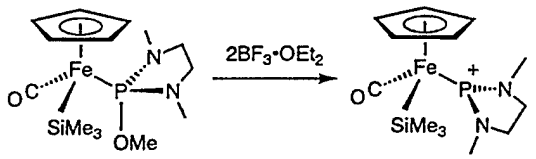
insertion of a phosphenium ligand into an Fe-alkyl bond (or alkyl migration form iron to phosphenium phosphorus) to give **8b** which is detectable in solution. **8b** is trapped by PPh_3 to give stable **9**.



(4)

Alkyl migration to CO ligand to give an acyl ligand on a transition metal is well known.[9] Complex **8a** has a terminal carbonyl ligand as well as a phosphenium ligand. It is thus notable that an alkyl group migrates exclusively to a phosphenium ligand in the present reaction.

The reaction of a silyl iron complex showed very significant results from the mechanistic aspect. The reaction of **10** with BF_3•OEt_2 in CH_2Cl_2 gave a homogeneous solution containing a cationic phosphenium iron complex with a silyl group (**11**) (eq 5).



(5)

Treatment of **11** with PPh_3 caused no reaction. No silyl migration to the phosphenium phosphorus may be due to a stronger Fe-silyl bond than Fe-alkyl bond. However, the detection of the phosphenium complex **11** supports the reaction sequence shown in eq 4.

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P_n-COMPLEX LIGANDS: an INTERIM REPORT

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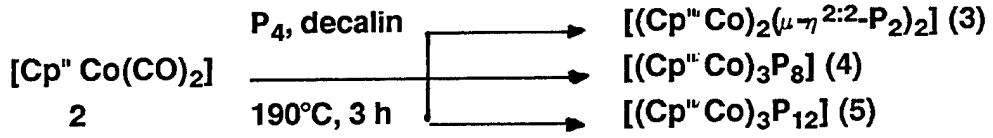
Abstract The thermal or photochemical reaction of white phosphorus, P_4, with mono- and dinuclear Cp substituted carbonyl metal complexes affords a wide variety of coordinatively stabilized P_n ligands. E.g.: P_1,P_2, acyclic and cyclic P_3, P_4 and P_5 as well as P_8(P_5-P_3) and P_{12}(P_5-P_7). Mechanistic aspects of P-P bond cleavage in white phosphorus are discussed.

Within the last decade we and others could show [1] that the formation of P_n ligands is strongly influenced by the substituent pattern of the Cp ligand on the transition metal.

In the case of ^{4}Cp (^{4}Cp = (i-Pr)$_4$C$_5$H) the hitherto unknown PO ligand could be stabilized in the trinuclear complex **1** [2].

[(^{4}CpNi)$_2$(μ_3-PO)$_2${W(CO)$_4$}] (1)

The rather bulky Cp$^{'''}$ ligand (Cp$^{'''}$ = 1,2,4-tBu$_3$C$_5$H$_2$), incorporated into [Cp$^{'''}$Co(CO)$_2$] (**2**), is necessary for the formation of **3**, **4**, and **5** on the cothermolysis of **2** and P_4 [3].

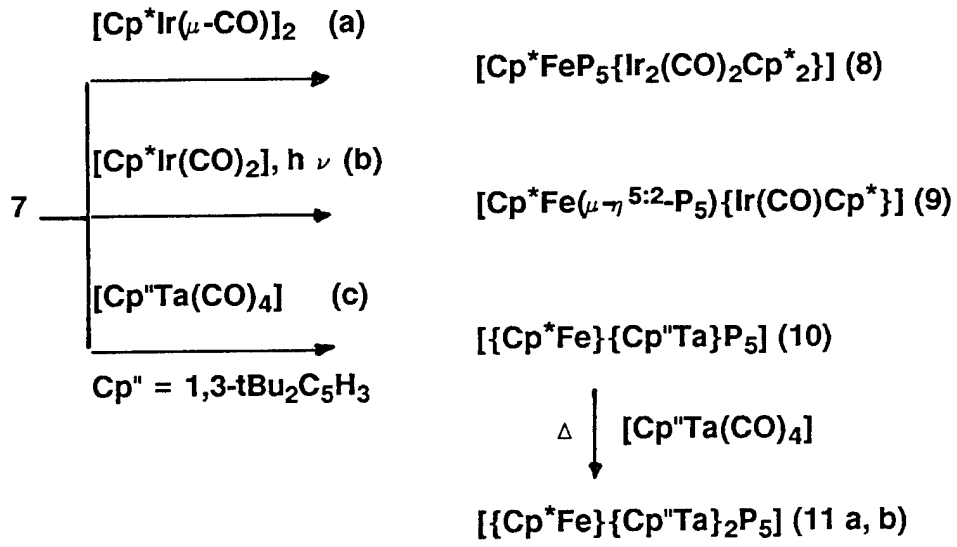


The P_8 and P_{12} skeletons in **4** and **5** consist of P_5-P_3 (open edged P_8 dihydrocalicene) and P_5-P_7 (P_7 norbornadiene and open edged P_5) building blocks. P_8, P_{10} and P_{12} can formally be derived [3] from Hittorf phosphorus.

Further coordination of **3** with $[W(CO)_5(thf)]$ affords with coupling of two P_2 units an acyclic P_4 ligand [4].

Starting with the sandwich complex $[Cp''Ni(\eta^3\text{-}P_3)]$ and $[Cp^*Co(CO)_2]$, $Cp^* = C_5Me_5$, besides known compounds also $[Cp''NiP_3Co_2(\mu\text{-}CO)Cp^*_2]$ (**6**) is formed, the $NiCo_2P_3$ skeleton of which forms a strongly distorted prismane [5].

Of special interest are the ligating properties of the sandwich complex $[Cp^*Fe(\eta^5\text{-}P_5)]$ (**7**) [6].



The spirocyclic complex **8** (equation (a)), which possibly is formed in a [2+1] cycloaddition, contains an intact cyclo-P_5 ligand with envelope conformation. The photochemical reaction of **7** with $[Cp^*Ir(CO)_2]_2$ gives **9** (equation (b)), where for the first time the μ-$\eta^{5:2}$-cyclo-P_5-coordination mode has been realized [6b]. According to equation (c) **10** is synthesized, a cluster with a TaP_5 Dewar-benzene skeleton capped by Cp^*Fe [6a]. Its further reaction with $[Cp''Ta(CO)_4]$ leads under cage enlargement to the cubane-like compounds **11 a, b**. One isomer consists of an FeP_5 chair with two Cp"Ta capes; the P_5 ligand of the other one is a trigonal pyramidal P_4 and a P_1 unit.

A new coordination type of P_2 as well as the novel ligands P_2S_2 and P_2Se_2 have been realized with the "naked" Cp ligand [7].

$$[CpFe(CO)_2]_2 \xrightarrow[190°C,\ 10\ min]{P_4} [(CpFe)_4(P_2)_2] \quad (12) \xrightarrow[grey]{4/_8S_8,\ Se} [(CpFe)_4(P_2X_2)_2] \quad (13,\ X = S,Se)$$

In **12** and **13** the Fe_4P_4 framework belongs to the class of triangulated dodecahedra.

Mechanistic inside in the cleavage of P_4 could be reached by the following reaction [8]:

$$[Cp''Fe(CO)_2]_2 \xrightarrow[THF,\ 25°C]{P_4,\ h\nu} [(Cp''Fe(CO)_2P)_2P_2] \ (14) + [(Cp''Fe(P_4)\text{-}Fe(CO)_2Cp'']\ (15)$$

$$[Cp''FeP_4\{Fe(CO)Cp''\}] \ (16) + [Cp''FeP_4FeCp''] \ (17)$$

The successive cleavage of one (complex **14** with P_4 butterfly), two (complex **15** with cyclo-P_4), and three (complexes **16**, a P_4 "ferrole", and **17** with trapezoidally arranged acyclic P_4) P-P bonds in P_4 (six P-P bonds), followed by stepwise CO elimination, affords compounds **14-17**.

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REACTIONS OF THIOESTERS OF PHOSPHORUS ACIDS WITH CATIONIC COMPLEXES OF MANGANESE

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Abstract The thioesters of P(III) acids react with $[Cp(CO)_2Mn(NO)]^+$ by substituting one CO-group with formation of a stable cationic products with a Mn-P bond. Fourier transform infrared spectroscopy and a special program were used for the real-time monitoring of the mechanistic path of the reaction of S-ethyl-N,N-tetraethyldiamidothiophosphite with $[Cp(CO)_2Mn(NO)]^- BF_4^+$. The formation of a few intermediates is described.

INTRODUCTION

The chemistry of thioesters of P(III) acids is one of the promtly developing areas of organophosphorus compounds. However, until now there are insufficient works on the investigation of reactions of the thioesters of P(III) acid derivatives with organometallic compounds, including cymantrene and its derivatives.

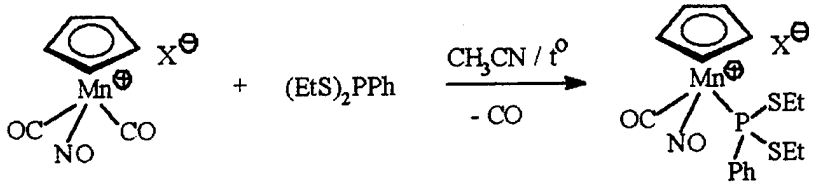
We have reported[1] on the synthesis of similar complexes by interaction of thioesters of P(III) acids with intermediate (1). In this case, stable free-radical complexes of the this type with a manganese-sulfur bond, were isolated together with complexes of manganese, containig thioderivatives of P(III) acids as ligands. Isoelectronic analogues of cymantrene, nitrosyl cationic complexes of manganese (2,3) in reactions with thioesters of P(III) acids have not been studied.

RESULTS AND CONCLUSIONS

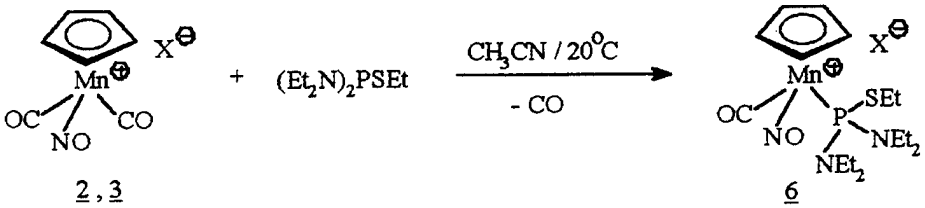
We have established, that triethyltrithiophosphite does not react with cationic complexes in solution of acetonitryle even at long heating with reflux.

If the number of electronegative alkylthio groups at phosphorus is reduced, the process of substitution of carbonyl on the phosphorus-containing ligands is

facilitated. Prolonged heating with reflux of dithiophosphonite with a cationic complex in solution of acetonitrile results in the formation of a new complex (4), containing dithiophosphonite as a ligand. The interaction of cationic complexes with thiophosphinite in the same conditions is proceeds much more readily. The reaction proceeds up to the end during 5 hours with the formation of a new complex. The introduction of strong electron-seeking amidogroups to a phosphorus atom makes it possible to synthesize appropriate complexes (6) at room temperature in 1 hour.



2, 3 4



2, 3 6

X = PF_6 (2), BF_4 (3)

All new complexes were isolated in the pure state. Their structure has been confirmed by methods of IR and NMR spectroscopy.

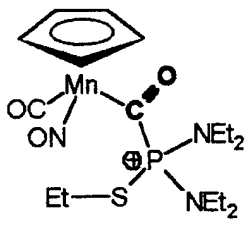
Analysis of the results has shown, that one of the factors, determining the rate of reaction of cationic complexes of manganese with the compounds of trivalent phosphorus, is the donor properties of phosphorus atom. The increase of the number of electronegative alkylthio groups reduces the rate of the subsititution of carbonyl. In the case of trithiophosphites the subsititution reaction actually does not take place. The introduction of electron-seeking amidogroups considerably accelerates the process of exchange of ligands. On the basis of these data a con-clusion can be drawn, that the rate of the reaction discussed decreases in the following series of the compounds of trivalent phosporus:

$(EtO)_3P > Ph_3P \sim (Et_2N)_2PSEt > Ph_2PSEt > PhP(SEt)_2 > (EtS)_3P \sim PCl_3$

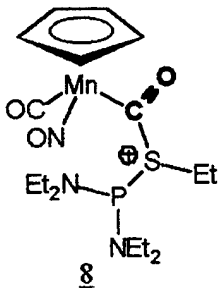
In order to elucidate the mechanism of the reaction, we monitored the reaction of complex (3) with S-ethyl-N,N-tetraethyldiamidothiophosphite using Fourier Transform Infrared spectroscopy[2].

Meanwhile time in spectral range (1900-1700 cm^{-1}), the appearance of a new absorption band at 1752 cm^{-1} due to the vibration ν(CO) is noted. The intensity of this band steadily decreases until it disappears completely after about 40 minu-tes. The appearence of this new vibration ν(CO) can be explained by the fact that, during the reaction, a new intermediate is formed.

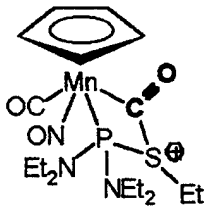
It is known[3] that, for cation (3) , the addition reaction of a suitable nucleophles to the carbon atom of the CO ligand is most specific. Taking into account the ambident nature of the P-S bond in the thioester of P(III) acid, it is possible to assume that the same type of reaction is attributable to the formation of either of the intermediates (7) or (8) in the reaction of a complex (3) with diamidothiophosphite.



7



8

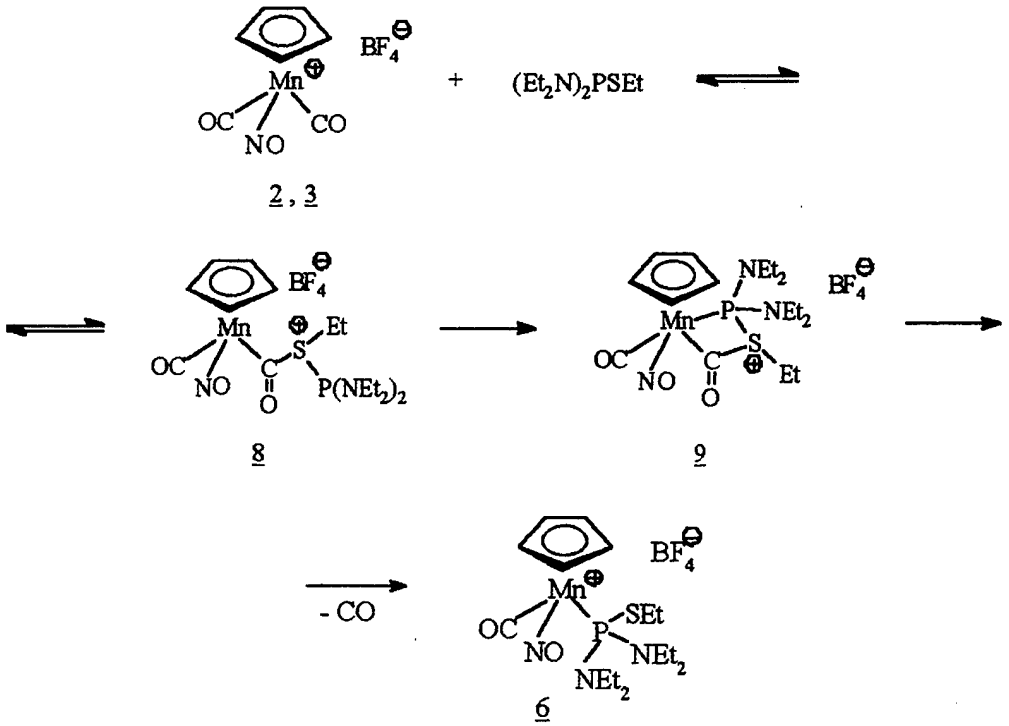


9

Perhaps both intermediates (7) and (8) are formed at the earlier stages of the reaction. It also seems reasonable to assume that compound (8) would be preferable as an intermediate product.

Besides, when analyzing the spectral map, it is seen that, while the 1752 cm^{-1} band decreases, the intensity of the absorption near 1776 cm^{-1} increases. This absorption band is related to the vibration of the carbonyl group of another intermediate (9) having a cyclic system, where the frequency of the ν(CO) is that of compound (8). Later, the alteration of the 1776 cm^{-1} band is masked by the beginning of growth of the 1799 cm^{-1} band related to the stretching mode ν(CO) of the final product.

On the basis of our results, and taking into account pertinent literature data, we assume that the reaction of the cationic complex (3) with the diamidothiophosphite proseeds as follows.



Thus, we have shown that the thioesters of P(III) acids react with cationic complexes of manganese by substituting one carbonyl and forming stable cationic products having a manganese-phosphorus bond. Our Fourier Transform Infrared investigation of the reaction of S-ethyl-N,N-tetraethyldiamidothiophosphite with the nitrosyl complex of manganese has made it possible for us to examine the spectral surface and spectral map approaches. We believe that we have established the formation of a few intermediates, and we are able to suggest a conceivable path for the reaction.

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DIFFERENT WAYS OF P_4 TRANSFORMATION IN THE COORDINATION SPHERE OF TRANSITION METALS

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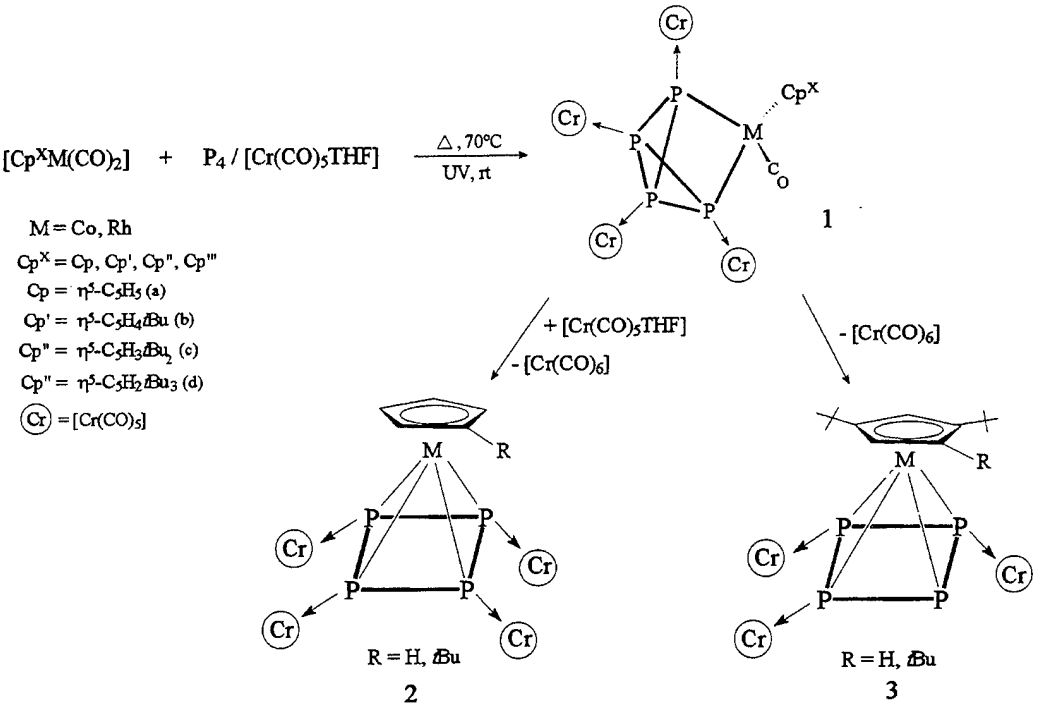
Abstract The transformation pathway of tetrahedral P_4 to the corresponding P_n ligands has been studied by the three-component-reaction are found to depend on the electron number of the complex fragments used. In the case of complexes forming fragments with an even number of valence electrons, a stepwise P-P bond cleavage is observed with a bicyclotetraphosphine intermediate to give a *cyclo*-P_4 containing product. Complexes with an odd number of valence electrons cause a P_1/P_3 fragmentation. A possible product of this reaction is a phosphido complex of the type $[L_nM{\equiv}P{\rightarrow}M'(CO)_5]$ (M' = Cr, W), which is self-stabilised by dimerisation. The phosphido complex $[(tBuO)_3W{\equiv}P{\rightarrow}M(CO)_5]$ (M = Cr, W) is formed via the reaction of $W_2(OtBu)_6$ with $RC{\equiv}P$ in the presence of the Lewis acids $[M(CO)_5THF]$.

INTRODUCTION

Recently we studied the reaction of white phosphorus with transition metal carbonyl complexes, where *cyclo*-P_4 containing complexes are obtained.[1] To study the transformation pathway of the P_4 tetrahedron within the coordination sphere of transition metals we have developed the concept of the three-component-reaction. By adding simple metal carbonyls such as $[Cr(CO)_5THF]$ to the reaction mixture of P_4 and the corresponding coordination compound, the lone pairs of the first formed P_n ligands are able to coordinate to the carbonyl complexes. Thus intermediates may be stabilised along the reaction pathway.

RESULTS AND DISCUSSION

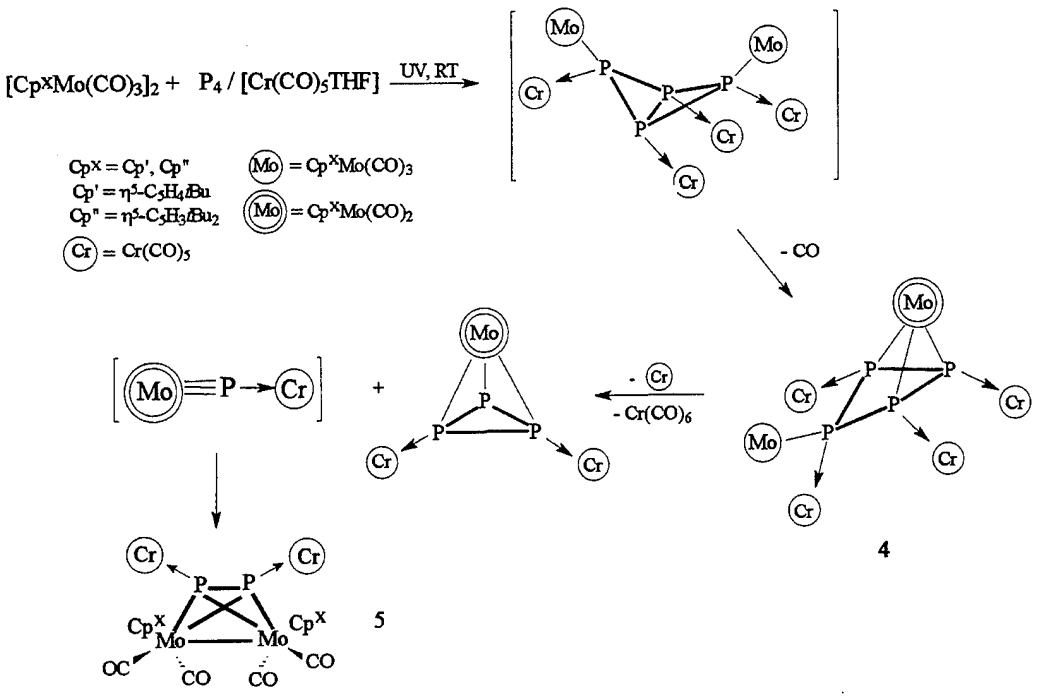
Coordination compounds forming fragments with an even number of valence electrons such as $[Cp^xM(CO)_2]$ (M = Co, Rh; $Cp^x = \eta^5\text{-}C_5H_{5-m}tBu_m$, m = 0, 1, 2, 3) react with P_4 in the presence of $[Cr(CO)_5THF]^{2\text{-}4}$ under either thermal or photochemical conditions to form the bicyclotetraphosphine derivatives 1 and the *cyclo*-P_4 ligand complexes 2 and 3. All compounds are stabilised by chromium pentacarbonyl moieties.



These results suggest the following reaction pathway: (i) First a P-P edge of the P_4 tetrahedron is opened by the metal complex making the lone pairs of all the phosphorus atoms in the newly formed tetraphosphabicyclobutane chemically active for coordination to $[Cr(CO)_5]$ groups thus forming complex 1. (ii) The attack of a second $[Cp^XM(CO)]$ fragment at a P-P edge is prevented by the $[Cr(CO)_5]$ groups and therefore CO abstraction from the coordinated metal complex triggers the opening of another P-P bond in 1 and the formation of complexes 2 and 3 with square planar *cyclo*-P_4 moieties. The substitution pattern of the *cyclo*-P_4 ring depends on the steric influence of the Cp^X ligands. In the case of the CpM or Cp'M complexes all four P atoms coordinate to $[Cr(CO)_5]$ groups. An additional tBu-group in the case of Cp"M complexes 3 results in only three of the phosphorus atoms bonding to a $[Cr(CO)_5]$ moiety. Adding a third *t*Bu-group also yields complexes of type 3, but in solution there is a strong tendency for conversion into species with two or one Cr-carbonyls

Our attempts to examine parallel reactions with $[Cp^*Ir(CO)_2]$ led to bicyclotetraphosphine derivatives where only three of the P atoms coordinate to Cr-carbonyls. In one of these bicyclotetraphosphines a CO molecule has inserted into an Ir-P bond.

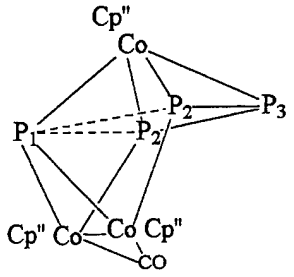
For coordination compounds forming fragments containing an odd number of valence electrons a P_1/P_3-fragmentation of the P_4 tetrahedron is observed. The scheme shown below gives an overview of preliminary results of the reaction of $[Cp^XMo(CO)_3]_2$ with P_4 in the presence of $[Cr(CO)_5THF]$.



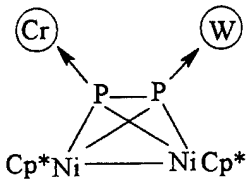
The reaction proceeds with the formation of a bicyclotetraphosphine intermediate anchored by two Mo complex fragments. One of the Mo units subsequently adopts a capping position. We have structural evidence for a fragmented species of 4, obtained after chromatographic workup. The P_3/P_1-fragmentation results in a *cyclo*-P_3-ligand compound and a complex where a terminal phosphido ligand coordinates to a $Cr(CO)_5$ group. Such species are not stable as monomers and a dimerisation readily occurs. The tetrahedral P_2Mo_2 complex 5 was structurally characterised.

Additional evidence for a P_1/P_3 fragmentation was obtained with the isolation of complex 6, formed by the two component reaction between $Cp"Co(CO)_2$ and P_4 under photochemical conditions.[5] Complex 6 shows a new type of a kite-like distorted planar P_4 ligand capped by a Cp"Co moiety. A $[(Cp"Co)_2(CO)]$ dimer coordinates to three of the phosphorus atoms. The most remarkable feature of the structure is the long P···P distance between P(1) and P(2) of 2.503 Å. EHMO calculations suggest that it can be considered as a weak P···P contact and is therefore on the borderline between a P-P bonding interaction and a Van der Waals contact.

Two other synthetic approaches to phosphido ligand complexes containing a metal phosphorus triple bond are also possible. The phosphinidenes $[\{M(CO)_5\}_2PCl]$ (M = Cr, W) react with $[Cp^*NiCO]^-$ to give Ni_2P_2-tetrahedral complexes. There are two indications of a phosphido complex as an intermediate.

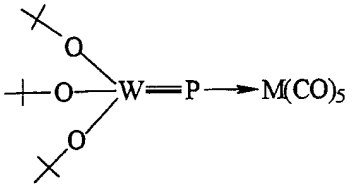


6



(M) = M(CO)5; M = Cr, W

7



M = Cr (a), W (b)

8

Firstly, the reaction of the phosphinidene with $[Cp^{X}Mo(CO)_3]^-$ leads to a compound where a CO molecule is inserted into a P-P bond. Secondly, the reaction of $[Cp^*NiCO]^-$ with an equimolar mixture of the phosphinidenes of chromium and tungsten reveals, in addition to the homonuclear chromium and tungsten complexes, a statistically mixed substituted tetrahedral compound 7.

Another approach to phosphido complexes was observed by the reaction of $[W_2(O^tBu)_6]$ with RC≡P in the presence of the Lewis acids $[M(CO)_5THF]$ (M = Cr, W).[6] The formation of the alkylidyne $[(^tBuO)_3W{\equiv}C^tBu]$ and the phosphido complexes 8a,b occurs. An additional reaction between the first formed phosphido complex and phosphaalkynes is not completely hindered and four membered ring compounds are also formed. Finally a 1,3-O^{t}Bu shift results to give phosphaalkoxy derivatives. By fractional crystallisation we were able to enrich a solution with the desired phosphido complexes 8a,b. The monomeric nature of these products is supported by two separate experiments.

ACKNOWLEDGMENT We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support. We are grateful to the Degussa AG for the gift of precious metal compounds.

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SPECTROSCOPIC AND X-RAY CRYSTALLOGRAPHIC STUDIES OF PENTAMERIC ETHYL CYCLOPOLYPHOSPHINE DERIVATIVES OF TRIOSMIUM CARBONYL CLUSTERS

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Abstract Reaction of pentaethylcyclophosphine, $(EtP)_5$, with triosmium cluster $[Os_3(CO)_{10}(NCMe)_2]$ in dichloromethane at room temperature afforded $[Os_3(CO)_{10}\{1,2\text{-}(EtP)_5\}]$ (**1**) with an unusual 1,2-chelation mode for the cyclophosphine. The same reactants at a higher temperature gave rise to $[Os_3(CO)_{10}\{1,3\text{-}(EtP)_5\}]$ (**2**). Treatment of the same ligand with triosmium cluster $[Os_3(CO)_{11}(NCMe)]$ yielded several new clusters $[Os_3(CO)_{11}(EtP)_5\}]$ (**3**), $[\{Os_3(CO)_{11}\}_2\{1,3\text{-}(EtP)_5\}]$ (**4**), $[\{Os_3(CO)_{11}\}_2\{1,,2\text{-}(EtP)_5\}]$ (**5**), $[Os_3(CO)_{10}\{1,2,3\text{-}(EtP)_5\}Os_3(CO)_{11}]$ (**6**) and $[Os_3(CO)_{10}\{1,2,4\text{-}(EtP)_5\}Os_3(CO)_{11}]$ (**7**).

Key words: cyclophosphine, cluster, osmium, phosphorus

INTRODUCTION

Studies on the reactions of homocyclic phosphines with a variety of metal carbonyls have shown that cyclophosphines can function as monodentate, bidentate, and tridentate ligands, respectively.[1] However, little attention has been paid recently to coordination chemistry with transition metal carbonyl clusters where cyclophosphines ligate intact or where phosphorus ring fission occurs to afford phosphido groups to stabilize formed clusters. We found that the reactions of the pentameric phosphine $(PhP)_5$ and the tetrameric phosphine $(CF_3P)_4$ with ruthenium or osmium carbonyl clusters gave rise to not only phosphido groups but also rare diphosphene fragments to build up several interesting cluster structures.[2,3] On the other hand, we found that the reactions of $(PhP)_5$ with the activated triosmium or

triruthenium carbonyl clusters give several cluster derivatives where the phosphorus ring structure remains intact.[4] Furthermore, the solution NMR data of these derivatives yielded a lot of useful information on the cyclophosphine structure in solution. As an in-depth extension of this investigation, we report here reactions of pentaethylcyclophosphine, $(EtP)_5$, with the activated triosmium carbonyl clusters $[Os_3(CO)_{10}(NCMe)_2]$ and $[Os_3(CO)_{11}(NCMe)]$.

RESULTS AND DISCUSSION

I Synthesis and Characterisation of 1 and 2 Reaction of $(EtP)_5$ with an equivalent amount of the activated triosmium cluster $[Os_3(CO)_{10}(NCMe)_2]$ in dichloromethane at room temperature afforded a 1,2-substituted product **1** (yield 17%). The reaction carried out at 80°C yielded the 1,3-substituted product **2** (yield 7%). The ^{31}P NMR spectrum of **1** shows an AA'BXX' pattern with two multiplets at δ 8.33 and 71.64 in the ratio of 3 : 2, respectively. The elemental analysis data was found to be consistent with the calculated values. The molecular structure of **1** was determined by a single-crystal X-ray diffraction study and is shown together with the atomic labelling scheme in Fig 1. The cyclophosphine, $(EtP)_5$, acts as a bidentate ligand, taking up equatorial sites of the osmium triangular plane and chelating across an Os-Os edge, through two P atoms in the 1,2-positions of the phosphorus ring. This is the first example in cyclophosphine chemistry where chelation occurs via the 1,2-positions in the cyclophosphorus ring. **1** possesses approximate m symmetry with the symmetry plane passing through Os(3), the mid-points of the Os(1)-Os(2) and P(1)-P(2) bonds, and P(4). It is also noteworthy that the P atoms bonded to Os atoms, P_1 and P_2, are in an almost fully eclipsed conformation. The ^{31}P NMR spectrum of **2** shows a perfect first-order pattern. The COSY-45 ^{31}P NMR spectrum of **2** (Fig. 2) shows that ^1J cross-peaks are seen at AD, AE, BC, BE and CD, while ^2J cross-peaks are observed at AB, AC, BD and ED. The molecular structure of **2** was determined by a single-crystal X-ray diffraction study and is shown together with the atomic labelling scheme in Fig 3. In this case, $(EtP)_5$ acts as a bidentate ligand, chelating via two equatorial sites of the osmium triangular plane through two P atoms in the 1,3-positions of the phosphorus ring. However, unlike the phenylcyclophosphine system, the expected inversion isomer of **2**, was not found in this case.

II Synthesis and Characterisation of 3 - 7 The reaction of $(EtP)_5$ with a two-fold molar amount of the activated triosmium cluster $[Os_3(CO)_{11}(NCMe)]$ in

dichloromethane at room temperature overnight afforded $[Os_3(CO)_{11}(EtP)_5]$ **3** (yield 35%), $[\{Os_3(CO)_{11}\}_2\{1,3\text{-}(EtP)_5\}]$ **4** (yield 35%), $[\{Os_3(CO)_{11}\}_2\{1,2\text{-}(EtP)_5\}]$ **5** (yield 19%), and a mixture (yield 2%) of $[Os_3(CO)_{10}\{1,2,3\text{-}(EtP)_5\}Os_3(CO)_{11}]$ **6** and $[Os_3(CO)_{10}\{1,2,4\text{-}(EtP)_5\}Os_3(CO)_{11}]$ **7**. The elemental analysis data of **3**, **4** and **5** were found to be consistent with calculated values. The IR data in the carbonyl region of **3** is similar to that of $[Os_3(CO)_{11}(PhP)_5]$. In the carbonyl region, the IR data of **4** is similar to that of $[\{Os_3(CO)_{11}\}_2\{1,3\text{-}(PhP)_5\}]$. The IR data in the carbonyl region of **5** is quite similar to that of **4**. The correlation of P atoms in **3**, **4** and **5** has been established by two-dimensional COSY-45 ^{31}P NMR spectroscopy. Although the one dimensional ^{31}P NMR spectrum of **5** looks very similar to that of **4**, obvious differences between the two clusters were detected in their two- dimensional COSY-45 NMR spectra. The molecular structure of **4** has been established by X-ray crystallography and is shown in Fig. 4 together with the atomic labelling scheme. The cyclopolyphosphine links through phosphorus atoms in the 1,3-positions to equatorial sites in the two triosmium triangles. The average length (2.215 Å) of P-P bonds in **4** is quite similar to that of free cyclopolyphosphines, but shorter than that (2.241Å) in $[\{Os_3(CO)_{11}\}_2\{1,3\text{-}(PhP)_5\}]$. The isomers, **6** and **7**, cannot be separated by TLC. Their ^{31}P NMR spectrum shows eight sets of signals containing ten phosphorus atoms in total. However, the ^{31}P NMR (COSY-45) spectrum shows that there are two five-membered rings, unconnected to each other. The electrospray ionization (ESI) mass spectrum of the mixture shows the molecular ion at m/z 2030 agreeing with $[Os_3(CO)_{10}\{1,2,3\text{-}(EtP)_5\}Os_3(CO)_{11}]$ **6** or $[Os_3(CO)_{10}\{1,2,4\text{-}(EtP)_5\}Os_3(CO)_{11}]$ **7**.

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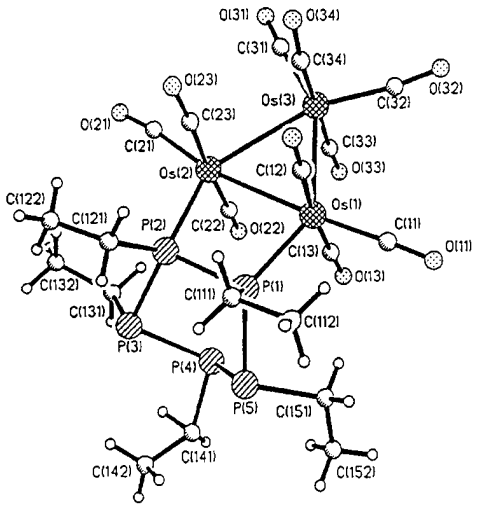


Fig. 1 Molecular structure of **1**

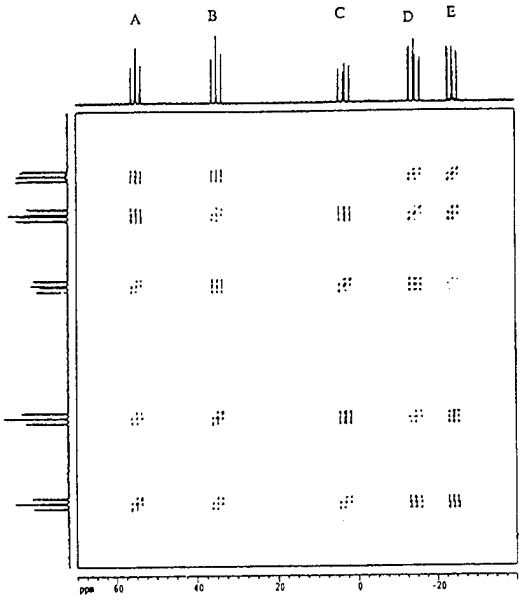


Fig. 2 ^{31}P NMR (COSY-45) spectrum of **2**

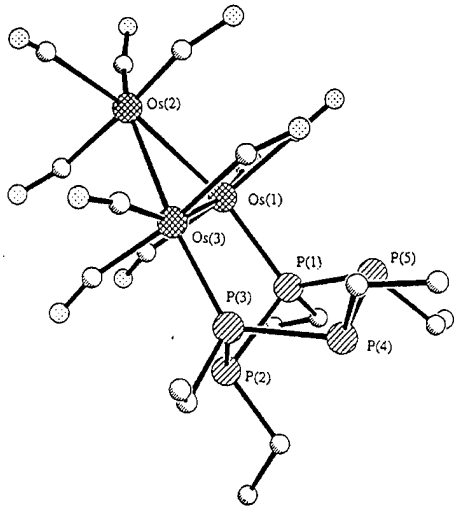


Fig. 3 Molecular structure of **2**

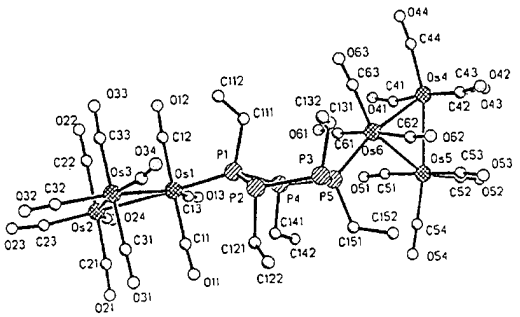


Fig. 4 Molecular structure of **4**

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η^8-CYCLOOCTATETRAENE METAL COMPLEXES, A NEW CLASS OF TEMPLATES FOR PHOSPHAALKYNE CYCLOOLIGOMERIZATIONS.

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STEFAN LEININGER,

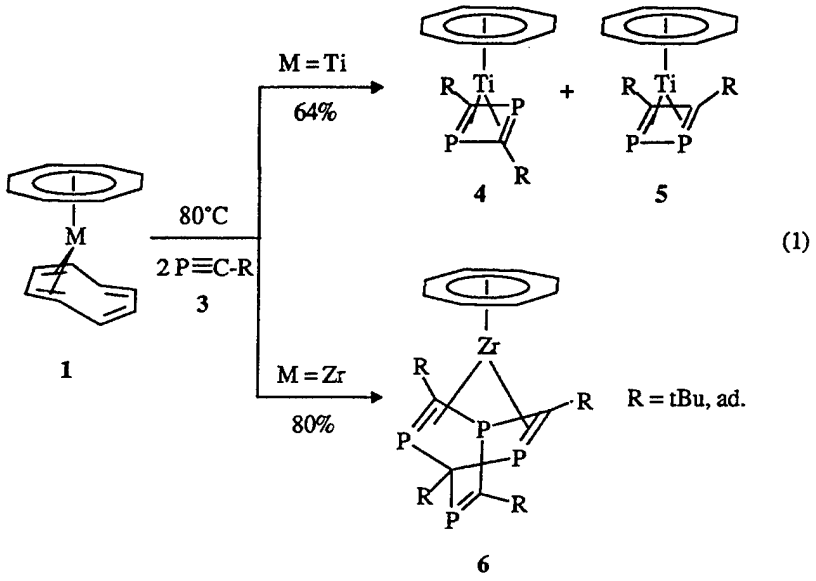
Fachbereich Chemie der Universität Kaiserslautern, Erwin-Schrödinger-Str., 67663 Kaiserslautern

Abstract For the first time selective cyclodi-, tri-, and tetramerization of phosphaalkynes are induced by an unique class of transition metal complexes by changing the reaction conditions.

The conveniently available η^8-cyclooctatetraene early transition metal derivatives (M = Ti, Zr, Hf) such as bis(cyclooctatetraene) titanium (**1a**) and zirconium (**1b**)[1] or (η^8-cyclooctatetraene) (η^4-butadiene) zirconium **2a** and -hafnium **2b**[2] are interesting starting materials for the cyclooligomerization of phosphaalkynes (**3**). With **1a** a mixture of the η^4-1,3-diphosphete- and η^4-1,2-diphosphete titanium complexes **4** and **5** are formed after prolonged heating of **1a** and **3** to 80°C in good yield[3]. Under the same conditions **1b** leads to the formation of a new tetramer complex of **3**, the 1,3,5,7-tetraphosphabarrelene zirconium complex **6**[4] (equ. 1).

From the η^4-butadiene hafnium complex **2b** the butadiene is displaced by a phosphaalkyne **3** under much milder conditions. Moreover it depends on the reaction temperature whether di-, tri- or tetramerization of **3** occurs (see equ. 2). Thus at -78°C a new

η^8-cyclooctatetraene hafnium complex **7** is formed which contains a cyclotrimer of **3** whose bonding situation is still unknown. Complex **7** is an intermediate of the cylotetramerization of **3** which occurs at room temperature to give the hafnium complex **8.**

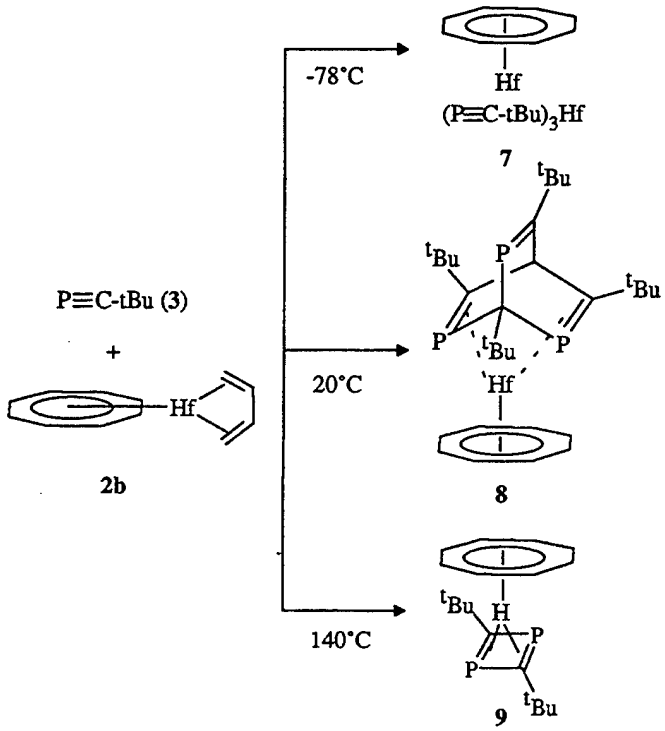


Surprisingly at higher temperature (ca. 140°C) the reaction between **2b** and **3** ends with a cyclodimerization of **3** exclusively to the 1,3-diphosphete hafnium complex **9.**

Comparable results are obtains using (η^8-1,4-bis(trimethylsilyl)cyclooctatetraene) (η^4-3-butadiene) hafnium **10** as starting material with one exceptions: the cyclotrimerization of **3** in the presence of **10**, which takes place at 0°C leads to another hafnium complex **11** in which the interaction between the cyclotrimer of **3** and the metal differs considerably from that in complex **7** (^{31}P- and ^{13}C-NMR). Presumable complex **11** contains a 7-hafna-1,3,5-diphosphanorbornadiene unit (equ. 3).

The organophosphorus part of the new hafnium complexes **7-9** and **11** is conveniently displaces by hexachloroethane in a redox reaction. In this way it was possible to synthesise for the first time 1,3,5-triphosphabenzene and 1,3,5-triphospha-Dewar-benzene derivatives **15** and **16.**

From complex **8** the recently synthesised 1,3,5,7-tetraphosphabarrelen **14** is liberated whereas complex **9** gives the undetectable 1,3-diphosphete **12** which cyclodimerise under these reaction condition to the known tetraphosphacuban **13** [5,6].



(2)

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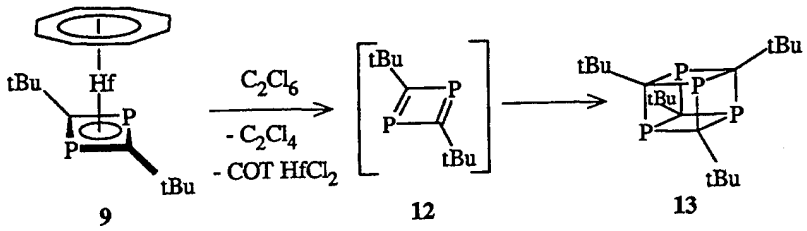
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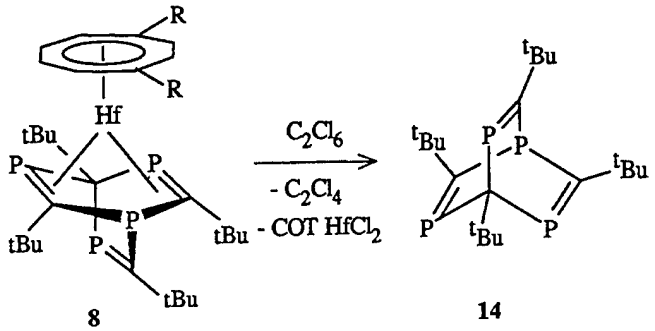
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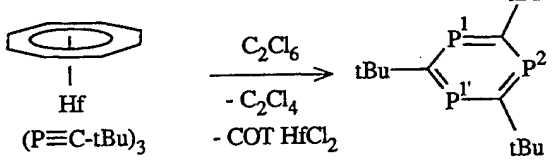
9 12 13



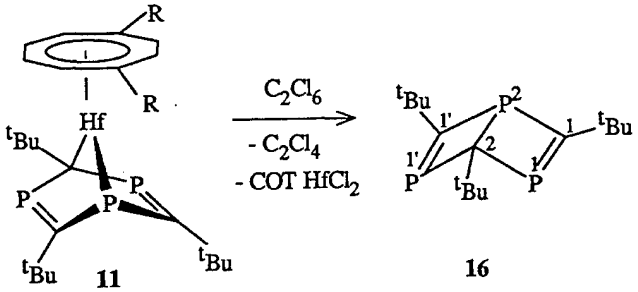
8
R = H
R = $SiMe_3$

14

(3)



7 15



11
R = $SiMe_3$

16

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RECENT RESULTS ON SYNTHESIS AND RING CLEAVAGE REACTIONS OF 2*H*-AZAPHOSPHIRENE DERIVATIVES

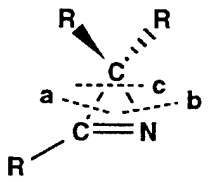
RAINER STREUBEL and ANNETTE OSTROWSKI
Institut für Anorganische und Analytische Chemie
der Technischen Universität Braunschweig
Postfach 3329, D-38023, Braunschweig, Germany

Abstract Reactions of [amino(aryl)carbene](pentacarbonyl)metal complexes with chlorophosphane derivatives under basic conditions yield 2*H*-azaphosphirene complex derivatives. Investigations of thermally induced ring-cleavage reactions of 2*H*-azaphosphirene tungsten derivatives in the presence of various trapping reagents are presented.

Keywords: phosphorus heterocycles, 2H-azaphosphirenes, carbene complexes, phosphanediyl complex.

Introduction

There are few known synthetic methods that give access to strained three-membered heterocycles containing a ring system with a C=N-moiety and a further heteroatom. These heterocycles are of interest because of their molecular structure and expected high reactivity. In contrast, the chemistry of 2*H*-azirenes has been investigated in detail, especially with respect to ring-opening reactions.[1] Several reaction pathways have been reported, including reactions that pro-



Scheme. Ring-opening reactions of 2*H*-azirenes.

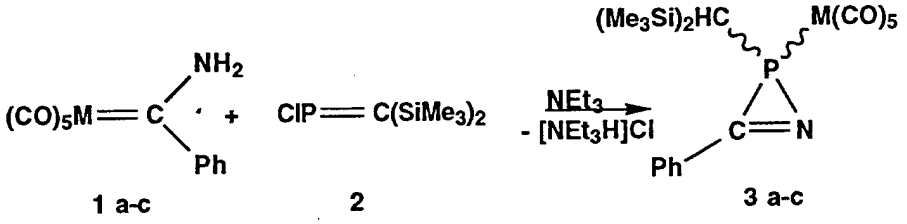
ceed by one- (a, b) or two-fold bond fission (c) (scheme).

The first synthesis of 2*H*-azaphosphirene tungsten complexes has been achieved by reaction of [amino(aryl)carbene](pentacarbonyl)-tungsten(0) complexes with [bis(trimethylsilyl)methylene]chlorophosphane under basic conditions.[2]

Results

Syntheses of 2*H*-azaphosphirene complexes

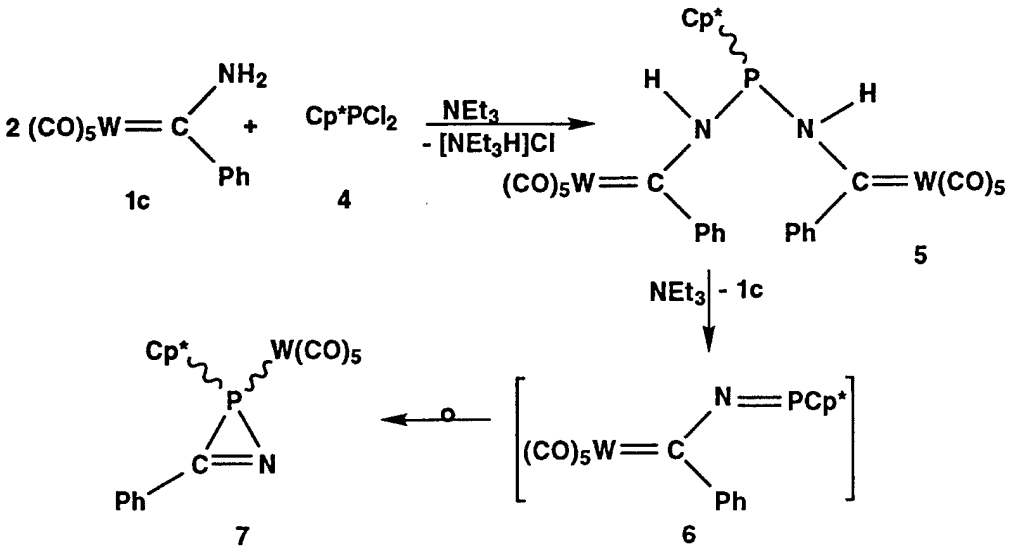
In order to exploit our synthetic approach to 2*H*-azaphosphirene complexes, we decided to investigate the reaction of amino(phenyl)carbene metal complexes (M = Cr, Mo, W) **1a-c** towards methylene(chloro)phosphane **2**. In the presence of triethylamine a clean reaction occurred, affording 2*H*-azaphosphirene metal complexes **3b,c** in good yields, whereas compound **3a** showed a slow decomposition yielding diphosphene complex derivatives even at ambient temperature.[3]



1 a-c 2 3 a-c

1a, 3a: M = Cr; 1b, 3b: M = Mo; 1c, 3c: M = W

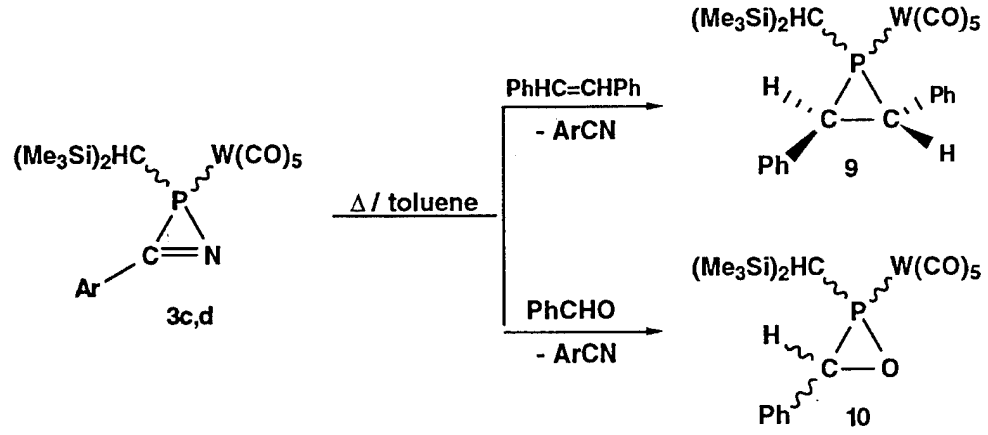
The employment of a *cis*-phosphane-substituted carbene tungsten complex showed that this rearrangement reaction proceeds stereospecifically with respect to the metal center.[3] A surprisingly selective base-induced condensation reaction of [amino(phenyl)carbene]-tungsten(0) derivative **1a** with the bulky alkyl(dichloro)phosphane derivative **4a** (R = Cp*) led to the 2*H*-azaphosphirene complex derivative **7** via the bisamino-substituted phosphane **4**.[3] As crucial reaction step a rearrangement of a transiently formed 2-aza-1-phospha-4-tungsta-1,3-butadiene derivative **6** to give **7** is proposed.



Investigations of thermally induced ring-opening of **3c,d**

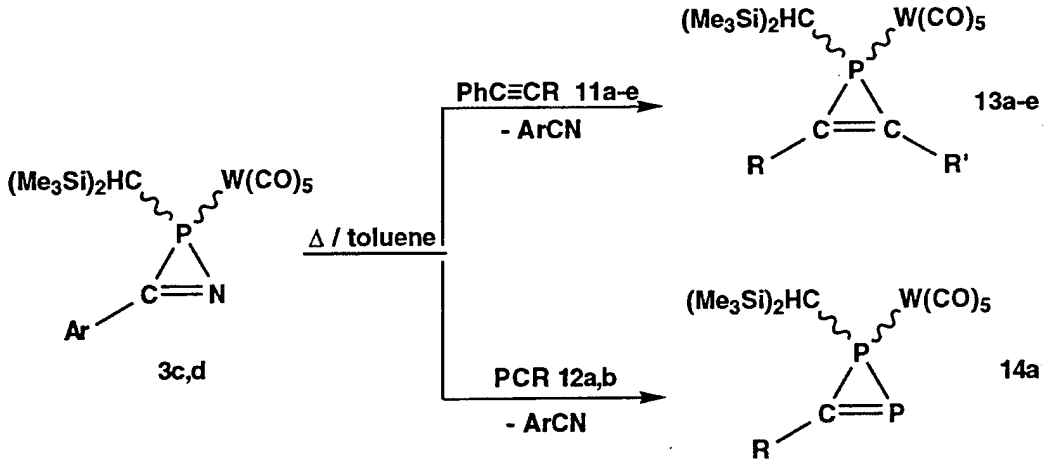
One of the most interesting aims in heterocyclic chemistry of small ring compounds is to explore their ring-opening behaviour.

The P-C-N ring system of the 2*H*-azaphosphirene tungsten complex **3d** possesses very narrow ring angles, pointing to a strained ring system.[2] As first investigations of the reactions of **3c,d** have shown, it displays a remarkably low stability in solution. Thermal decomposition of **3c,d** in toluene in the presence of *trans*-stilbene or benzaldehyde afforded the corresponding nitrile derivatives and the [2+1]-cycloaddition products **9**[3],**10**.[4] The nitrile derivatives have been identified by IR-spectroscopy. The formation of **9**,**10** can be rationalized by reaction of a transiently formed phosphanediyl complex with these multiple bond systems, nevertheless a short liv



ing phospha-analogue of a nitrile ylide - generated by ring-opening of **1c,d** - cannot be completely excluded. The X-ray structure analysis of **10**[4] reveals a widened P-C-O ring system in comparison to another oxaphosphirane complex.[5]

Further substantiation for the proposal of a phosphanediyl complex intermediate has been obtained using other trapping reagents. Thermal decomposition of **3c,d** in toluene in the presence of acetylene derivatives **11a-e** (**11a**: R,R' = Ph; **11b**: R = Ph, R' = H; **11c**: R = Ph, R'' = Me; **11d**: R = H, R' = OEt; **11e**: R,R' = CO_2Me) or phosphaalkynes **12a,b** (**a**: R = *i*Pr(Me_3Si)N; **b**: R = *t*Bu) afforded the corresponding 1*H*-phosphirene derivatives **13a,b**[4],**c-e**[6] and the 1*H*-diphosphirene complex **14a**[6]; in the case of **12b** a 1,2-dihydro-1,2,3-triphosphete complex[6] is the final product.



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CYANAMIDE SUBSTITUTED PHOSPHORUS COMPOUNDS

LOTHAR JÄGER

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Abstract Referring to the field of phosphorus chemistry the fragment N(CN) is discussed as pseudochalcogen.

INTRODUCTION

The general principle of element displacement [1], including the special case of the cyanogen displacement, allows the deduction of oxygen homologous functional groups. From this point of view the radicals N(CN) and $C(CN)_2$ can be considered as pseudochalcogens. Parallel to the well established pseudohalides a pseudochalconide concept was suggested by KÖHLER in 1970 [2,3] which is based on a multitude of formal identical reactions of (pseudo)chalcogen compounds like H_2Y, YH^- and Y^{2-} (Y = O, NCN, $C(CN)_2$ etc.).

The comparative investigation of water, formaldehyde and pseudochalcogen modified homologs H_2Y and $H_2C{=}Y$, respectively, by means of theoretical methods reveals similarities referring to electronic, thermochemical, and structural properties which allows a quantitative description of these relations [4].

NCN-MODIFICATION OF PHOSPHORUS COMPOUNDS

Phosphorus chemistry is a suitable field to demonstrate the pseudochalcogen character of the groups N(CN) and $C(CN)_2$. The ability to oxidize is one of the features of (pseudo)chalcogens. It is necessarry to emphasize that oxygen, ozone, nitrous oxide,

amineoxides and sulfoxides and on the other hand the N(CN) and $C(CN)_2$ homologs are able to oxidize phosphines and to transfer these pseudoelements in place of oxygen [3].

These types of reactions can be used to synthesize very different phosphorus compounds. We tried to prepare a homolog of P_4O_{10}. For that reason we oxidized P_4O_6 with cyanogen azide and isolated a nearly unsoluble, colourless solid which together with sodium hydroxide produces quantitatively monocyanamido monophosphate.

$$P_4O_6 + 4\,NNN\text{-}CN \rightarrow P_4O_6(NCN)_4 + 4\,N_2 \quad (1)$$

The oxidation of diorganophosphides with cyanogen azide, yielding bis(cyanamido)phosphinates $[R_2P(NCN)_2]^-$, is an other example of this type of reactions.

$$[Ph_2P]^- + NNN\text{-}CN \rightarrow [Ph_2P(NCN)_2]^- + 2\,N_2 \quad (2)$$

A second group of reactions can be summerized under the headline pseudochalcogenolysis relating to the parallel behaviour of water, hydroxide, oxide and the homologous N(CN) or $C(CN)_2$ representatives toward most different species of phosphorus. In this connection we were concerned with the cyanamidolysis of phosphorus halides, for instance $PSCl_3$, under different conditions. The cyanamidolysis of phosphorus oxo- and thiochloride in the presence of p-$Me_2NC_5H_5N$ produces donor stabilized halides of modified derivatives of the monometaphosphorus acid.

$$PYCl_3 + NaNHCN + 2\,B \rightarrow B{\rightarrow}P(Y)(NCN)Cl + NaCl + [HB]Cl \quad (3)$$

B = p-$Me_2NC_5H_5N$; Y = O, S

On the other hand $PSCl_3$ reacts with a lye of cyanamide in water to a mixture of different cyanamido thiophosphates. The ability of the hydrogen cyanamide ion to compete in the system hydroxide water was rather surprizing.

$$PSCl_3 \xrightarrow[-Cl^-,\,H_2O]{NHCN^-,\,OH^-} \begin{cases} [PO_2S(NCN)]^{3-} & 20\% \\ [POS(NCN)_2]^{3-} & 50\% \\ [PS(NCN)_3]^{3-} & 30\% \end{cases} \quad (4)$$

Under comparable conditions the P-S-P sequences of P_4S_{10} are cleaved by hydrogen cyanamide in water, and mixed cyanamido thio-monophosphates are isolated.

$P_4S_{10} + 12\ NaNHCN \rightarrow 2\ Na_3[PS_3NCN] + 2\ Na_3[PS_2(NCN)_2] + 6\ H_2NCN$ (5)

This kind of synthetic routes can be applied to gain any other phosphorus pseudochalconide derivatives as you like: phosphimates, phosphonates, phosphinates etc.

$Ph_2P(Y)Cl + NaNHCN + NaOH \rightarrow Na[Ph_2P(Y)NCN] + NaCl$ (6)
$Y = O, S$

Furthermore, the idea to build a group of pseudochalconide homologs parallel to any element chalcogenides can be transferred to other elements. Corresponding modified carbonates, nitrites, nitrates, sulfites, sulfates and related compounds are well known [3].

COORDINATION BEHAVIOUR OF CYANAMIDO ANIONS

In connection with the coordination behaviour we were interested in the charge distribution in these ambidentate ionic species. Both, structural and spectroscopical data reveal that the NCN group takes over a greater part of the ionic charge than each one of the oxygen or sulfur atoms. We assume that within the NCN group the ionic charge is concentrated on the nitrile N-atom. The charge on the amide N-atom and the angles NC=N-E (E = O_2N-, $R_2P(O)$-, $R_2P(S)$-, RSO_2-, NC-) seem to be a function of the character of the substituent E. However, the bonding angles within this row vary between 110 and 130° which has got consequences with regard to their coordination modes.

$>P(S)\text{-}NCN]^-$ $>P(O)\text{-}NCN]^-$ $\text{-}SO_2\text{-}NCN]^-$ $O_2N\text{-}NCN]^-$ $NC\text{-}NCN]^-$

For diphenyl-cyanamidothiophosphinate we obtained exclusively compounds with this ligand in a monodentate function. In agreement with the discussed relations the coordination is preferentially held on via the terminal N-position.

$$+ R_3ECl \rightarrow Ph_2P(S)\text{-}NCN\text{-}ER_3 \quad (7)$$

$$[Ph_2P(S)NCN]^- + Ni^{2+} + 4\ py \rightarrow [Ni\{NCNP(S)Ph_2\}_2py_4] \quad (8)$$

$$+ Cu^{2+} + 2\ py \rightarrow [Cu\{NCNP(S)Ph_2\}_2py_2] \quad (9)$$

$[Ph_2P(S)NCN]^-$ $+ Au^+ + PPh_3$ -> $[AuSP(NCN)Ph_2(PPh_3)]$ (10)

Exclusively toward selected soft central atoms, like gold(I), cyanamido thiophosphinate is coordinated through the sulfur atom [5-7]. Parallel to these observations cyanamidosulfonate coordinates monodentately through the nitrile N-atom. Additionally, coordination polymers with this ligand in a bidentate bridging position and with bonds to the terminal N- (equatorial) and to one of the O-atoms (axial) of a neighbouring sulfonyl group are also known [8,9]. Dicyanoamide almost preferentially functions bidentately. In each case, for the mono- or bidentate bridging ligand exclusively bonds through the terminal N-atoms are observed [10,11]. On the other hand cyanamidonitrate coordinates through the nitrile and the amide nitrogen atoms [12].

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BISPHOSPHANYLHYDRAZIDES AS NOVEL CHELATING PHOSPHINES IN TRANSITION METAL CHEMISTRY - SYNTHETIC AND CATALYTIC STUDIES

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Abstract: The synthesis of alkoxy- and aryloxy- functionalized bisphosphanyl hydrazides, $(RO)_2PN(Me)N(Me)P(OR)_2$, is described. Interaction of these ligands with transition metals, particularly rhodium(I), has been investigated. The steric effects around P^{III} centers have pronounced effects on the pathway of reactions of Rh(I) precursors. For example, the reactions of these ligands with $[RhCl(CO)_2]_2$ leads to the formation of carbonyl free, chlorobridged dinuclear complexes when the groups are relatively smaller (*e.g.*, CH_2CF_3, Ph), whereas mononuclear carbonyl-containing complexes are formed with bulky substituents (e.g., $C_6H_3Me_2$-*2,6*, $C_6H_3(OMe)_2$-*2,6*).

Key words: Bisphosphanyl Hydrazides, Rhodium Complexes, Bisphosphites, Catalysts.

INTRODUCTION

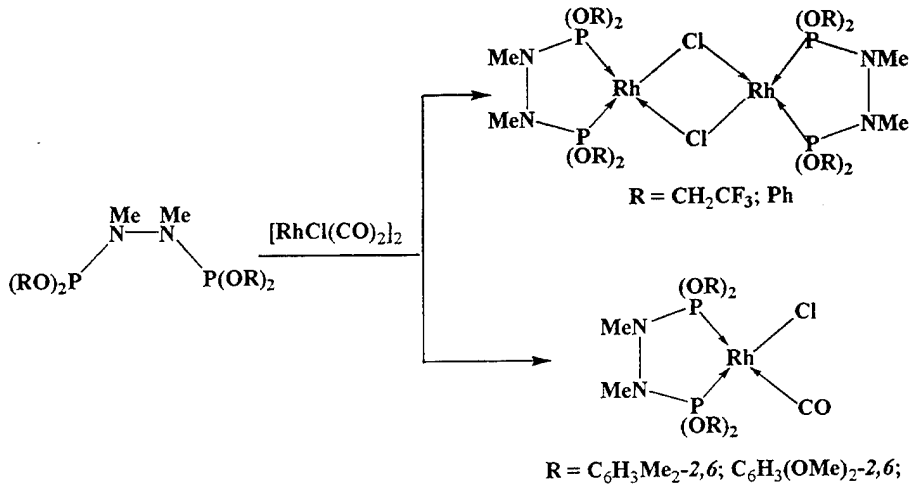
Since the early 80's the application of phosphites as ligands in the rhodium-based hydroformylation of olefins has been a field of active interest. The mediation of electronic and steric effects of oxygen substituents (of phosphites) on to the interacting Rh(I) center in the rhodium-phosphite-based hydroformylation reactions is of fundamental importance. Chelating phosphites may provide contrasting binding properties with Rh(I), wherein even if one of the phosphite-rhodium bond is reversibly broken (in the presence of a substrate molecule) the other P^{III}-Rh bond will provide access to a reactive intermediate. Therefore, effective catalysts my be generated from chelating bisphosphites if synthetic routes to such ligands are developed. Toward this objective, we have developed synthetic strategies to a new genertion of bisphosphites of the general structure: $(RO)_2PN(Me)N(Me)P(OR)_2$.[1-4] This paper reports the coordination chemistry of a new class of bisphosphites with Rh(I) precursors.

The alkoxy- and aryloxy-functionalized dinitrogen-bridged bisphosphanes $(RO)_2PN(Me)N(Me)P(OR)_2$ (R = Me, Et, CH_2CF_3, $CH_2CH{=}CH_2$, $(CH_2)_7CH_3$, $CH(CH_3)_2$, C_6H_5, C_6H_4Me-*p*, $C_6H_4(CH_2CH{=}CH_2$-*o*)) were obtained from the reactions of the corresponding alcohols or phenols with $Cl_2PN(Me)N(Me)PCl_2$ in the presence of Et_3N in 75-90% yields (Equation 1). These alkoxide and aryloxide derivatives are air-stable and are colorless viscous liquids. All the compounds were characterized by various spectroscopic and analytical methods. The ^{31}P NMR spectra of all the compounds consisted of single resonance(s) in the range between 137-148 ppm.

$$Cl_2PN(Me)N(Me)PCl_2 \xrightarrow[-4Et_3N.HCl]{4ROH/4Et_3N} (OR)_2PN(Me)N(Me)P(OR)_2 \quad (1)$$

R = Alkyl or Aryl

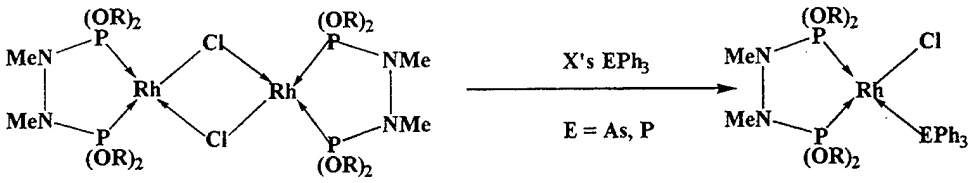
The reactions of bisphosphanylhydrazides $(RO)_2PN(Me)N(Me)P(OR)_2$ (R = CH_2CF_3, Ph) with $[RhCl(CO)_2]_2$ afford the chlorobridged Rhodium(I) dimers, $[RhCl\{(RO)_2PN(Me)\text{-}N(Me)P(OR)_2\}]_2$ in near quantitative yields (Scheme 1). The absence of bands due to ν(CO) in their IR spectra confirmed complete decarbonylation in these reactions. Observation of single resonances in the ^{31}P NMR spectra ($^1J_{RhP}$ = 287.0 Hz for R = CH_2CF_3; 296.5 Hz for R = Ph) indicated chelate structures with *cis* dispositions for P^{III} centers around Rh(I) as shown in Scheme 1. The chloride bridge in



SCHEME 1

these dimeric 16-electron species can be readily cleaved upon reactions with triaryl-phosphines or arsines (Scheme2) providing an efficient synthetic avenue for the mixed phosphine-bisphosphite complexes of Rh(I).

It is important to note that the integrity of the five-membered P-N-N-P-Rh rings in both the complexes were retained even when 4-10 fold excess of ER_3 (E = As or P) were used in these reactions. These mononuclear 16-electron species may be considered as 'hybrids' to the Wilkinson catalyst $[RhCl(PPh_3)_3]$.



SCHEME 2

Reactions outlined in Scheme 1 also demonstrate that the steric bulk on the phosphorus will change the course of reactions with $[RhCl(CO)_2]_2$. For example, the reactions of $(RO)_2PN(Me)N(Me)P(OR)_2$ (R = $C_6H_3Me_2$-*2,6* and $C_6H_3(OMe)_2$-*2,6*)) with $[RhCl(CO)_2]_2$ afford the mononuclear carbonyl complexes $[RhCl(CO)\{(RO)_2PN(Me)$-$N(Me)P(OR)_2\}]$ in near quantitative yields (Scheme 1). All these complexes were characterized by various spectroscopic and analytical methods. The structures of the dimeric and monomeric rhodium complexes were confirmed by X-ray crystallography (Figure 1).

The N-N bonds in the simple hydrazine and its derivatives tend to be unstable toward hydrolysis, metallation reactions and also in common orgnic solvents at elevated temperatures. In sharp contrast the bisphosphanyl hydrazides, especially the ones with the bulky substituents on the P^{III} centers, are stable in common organic solvents even at

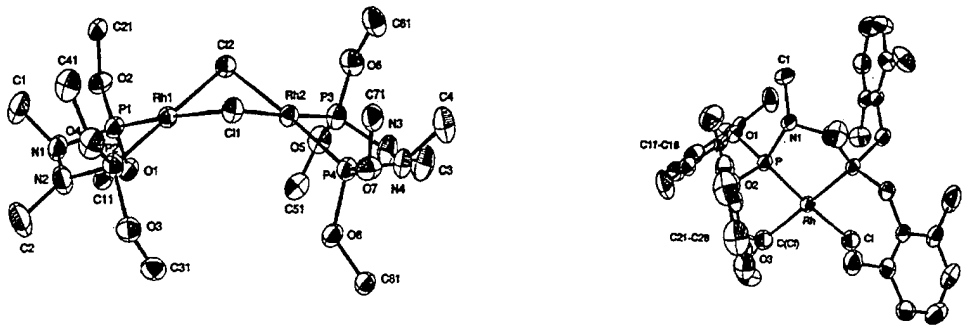


FIGURE 1

elevated tempertures (up to 140 °C). In addition the N-N bonds are inert toward reactions with various early and late transition metallic precursors. These observations suggest that the bisphosphanyl hydrazides will find applications as a new generation of bisphosphites for use in transition metal/organometallic chemistry.

Preliminary studies suggest that Rh(I) complexes of bisphosphites derived from bulky substituents ($(RO)_2PN(Me)N(Me)P(OR)_2$; R = $C_6H_3Me_2$-*2,6* and $C_6H_3(OMe)_2$-*2,6*)) catalyze the hydroformylation of propylene to *n* and *i* butanal with good selectivity and catalytic efficiency.

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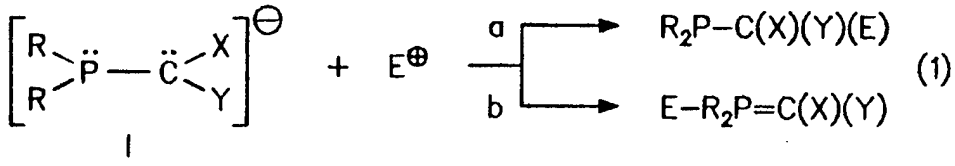
AMBIDENT PHOSPHINOMETHANIDE LIGANDS: FROM ROBUST COMPLEXES TO FRAGILE FRAMEWORKS

HANS. H. KARSCH*, ROLAND RICHTER and EVA WITT
Anorganisch-chemisches Institut, Technische Universität München, Lichtenbergstraße 4, D-85747 Garching, Germany

Abstract The ambidentate nature of phosphinomethanides leads to a broad variety of coordination modes to metal centers. For instance, high phosphine coordination numbers are achieved with diphosphinomethanide ligands. Furthermore, phosphinomethanides undergo readily rearrangements on reaction with electrophiles, leading to a manifold of new compounds with unexpected structural features, e.g. novel heterocycles. In addition, redox reactions with oxidative coupling of the phosphinomethanides are often encountered, which again lead to novel heterocyclic structures with group 15 element oxidants like PCl_3 or $AsCl_3$.

INTRODUCTION

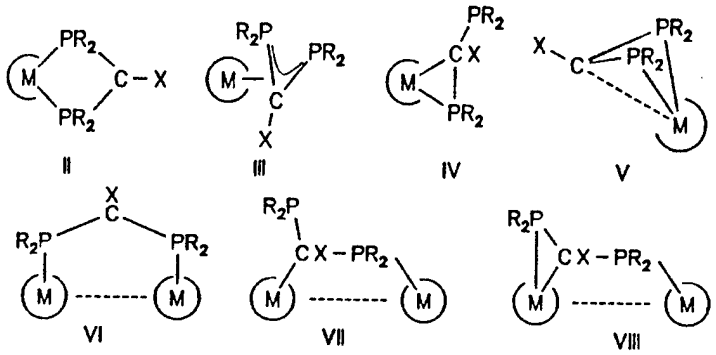
Whereas carbon commonly is regarded as the typical element of the second period in the periodic table, phosphorus can be regarded as representative for the heavier elements. A comparison of both elements with regard to their chemical properties should use a system, which comprises the same number of bonds and electrons for both elements. This requirement is met by phosphinomethanides I, where both elements are connected directly together, which has the additional advantage, that the reactivity can be evaluated with one single component. Both reaction at carbon as well as at phosphorus is possible and tunable by the appropriate choice of substituents R, X and Y (eq. 1).



I (1)

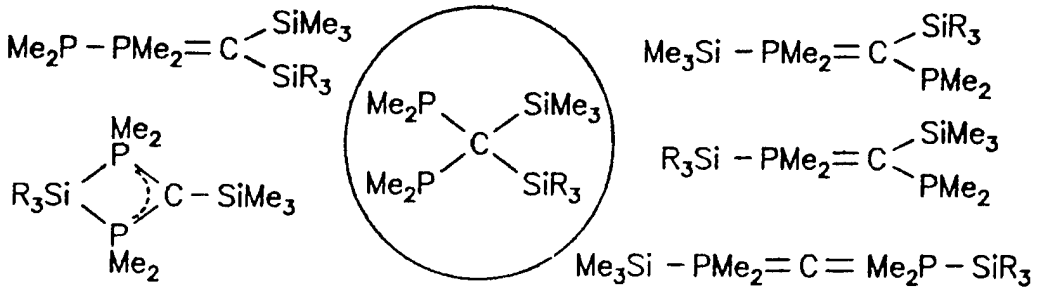
HIGH COORDINATION NUMBERS

Simple phosphinomethanides (X = Y = H) will react with most kind of electrophiles via carbon (a). With hetero-element substituents at carbon, ylide formation (b) is also possible. Thus, with diphosphinomethanides (Y = PR_2), complexes of s/p,d,f elements with high phosphine coordination numbers and with numerous kinds of coordination modes are accessible, e.g. II-VIII.



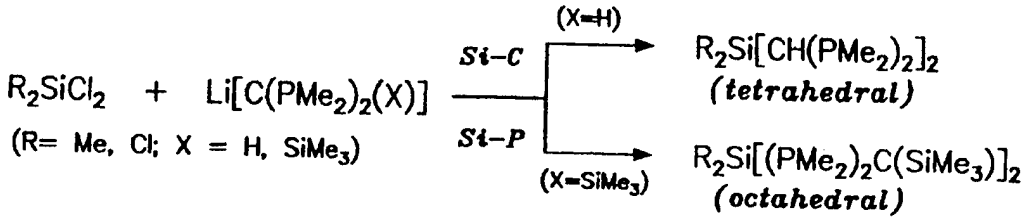
SKELETON REARRANGEMENTS/MONOFUNCTIONAL SYSTEMS

The coordination of heteroelement substituted phosphinomethanides to (formal) silicenium or phosphenium type of electrophiles depends on reaction conditions and substitution patterns. Quite frequently, the initially formed products are not stable and rearrange to thermodynamically more stable products. Thus combining $Li[C(PMe_2)_2(SiMe_3)]$ with R_3SiCl, potentially six different isomers are possible and - at least in part - indeed observed:



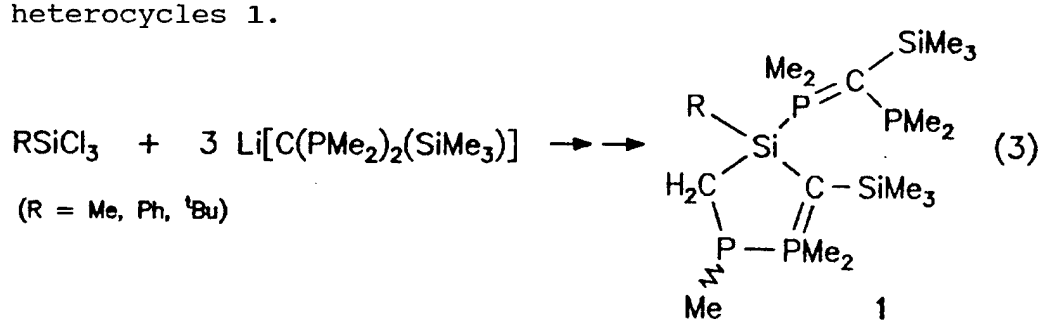
SKELETON REARRANGEMENTS/MULTIFUNCTIONAL SYSTEMS

The interaction of a silicon center with more than one phosphinomethanide ligand again will result in different kind of products (eq. 2):



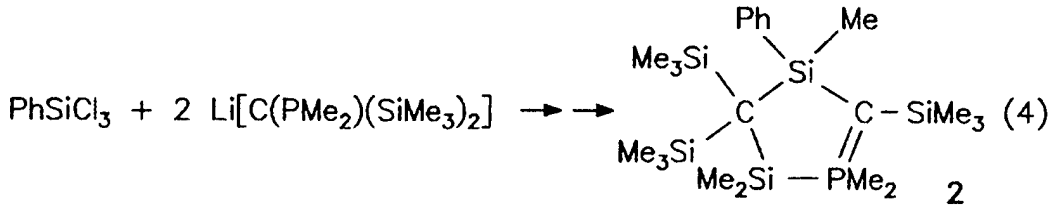
(2)

Rearrangement and additional metalation is observed in the case of eq. (3), resulting in the novel, fluctional heterocycles 1.



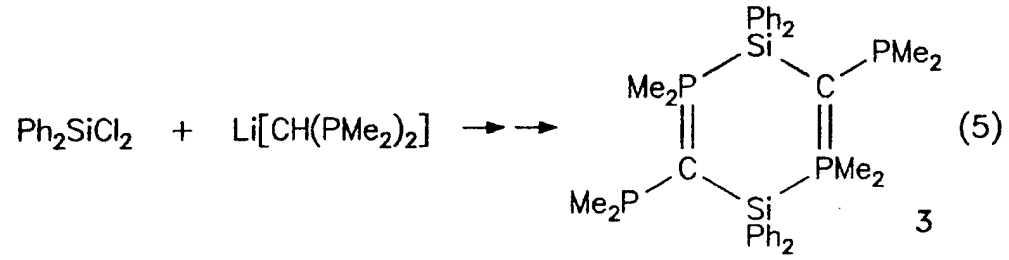
(3)

A methyl migration from one silicon to the other and chlorophosphine elimination are the key steps in the formation of the novel heterocycle 2, probably via a silene intermediate (eq. 4)



(4)

A silene intermediate also may be involved in the formation of the novel heterocycle 3 (eq. 5)

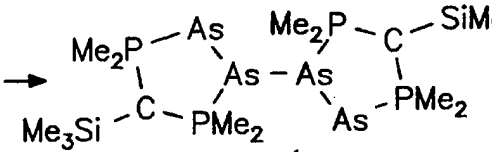


(5)

OXIDATIVE COUPLING OF PHOSPHINOMETHANIDES

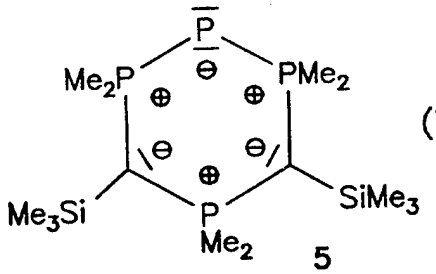
P-P, P-C and C-C coupling reactions are observed in the reaction of titanocene dichloride with lithium phosphinomethanides. Similar coupling reactions are also observed in the reactions with group 15 element halides.
Thus, for instance, the tetranuclear arsenic derivative **4** is obtained according to eq. (6).

$$AsCl_3 + 3\ Li[C(PMe_2)_2(SiMe_3)] \longrightarrow \quad \mathbf{4} \qquad (6)$$



With PCl_3, a variety of heterocycles with low coordinate phosphorus is obtained, e.g. according to eq. (7).

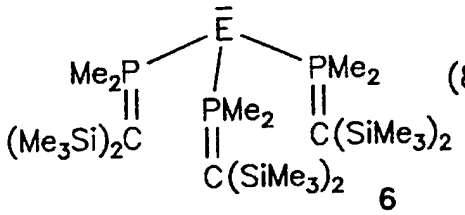
$$PCl_3 + 3\ Li[C(PMe_2)_2(SiMe_3)] \longrightarrow \quad \mathbf{5} \qquad (7)$$



The postulated intermediate, a trisylidic phosphine derivative can be characterized as well as its heavier congeners by slight changes in the substitution pattern eq.(8).

$$ECl_3 + 3\ Li[C(PMe_2)(SiMe_3)_2] \longrightarrow \quad \mathbf{6} \qquad (8)$$

(E = P, As, Sb)



Compounds, 1-6 have been characterized by NMR spectroscopy and X-ray diffraction.

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NOVEL COMPOUNDS FORMED FROM REACTIONS OF $[(\eta^5\text{-}Me_5C_5)MCl_2]_2$ (M = Ru, Rh) WITH VINYLDIPHENYLPHOSPHINE AND ALLYLDIPHENYLPHOSPHINE

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Abstract The complexes $[(\eta^5\text{-}Me_5C_5)Ru(R_3P)_2(NCCH_3)]^+ PF_6^-$, where R_3P is vinyldiphenylphosphine and allyldiphenylphosphine, readily dissociate CH_3CN to form η^3-phosphaallyl and η^3-homophosphaallyl complexes (**1** and **2**) respectively. While **1** is conformationally rigid in solution, **2** undergoes inversion by a dissociative process in solution. The analogous complex $[(\eta^5\text{-}Me_5C_5)Rh(Ph_2PCHCH_2)_2Cl]^+ PF_6^-$ undergoes a novel Michael type addition of the methyl CH bonds across the vinyl functionalities of the coordinated phosphine to produce chelating 1,2- and 1,3-*bis*(diphenylphosphinopropyl) trimethylcyclopentadienides (**3** and **4**) respectively. In contrast, with $Ph_2PCH_2CHCH_2$ the classical phosphine complex $[(\eta^5\text{-}Me_5C_5)Rh(Ph_2PCH_2CHCH_2)_2Cl]^+ PF_6^-$ (**5**) is formed. These new complexes have been characterized by a variety of NMR techniques and by single crystal X-ray crystallography.

Key Words phosphaallyl, NMR spectroscopy, X-ray crystallography, CH Michael additions.

We previously reported[1] that $[(\eta^5\text{-}C_5H_5)Ru(Ph_2PCHCH_2)_2(CH_3CN)]^+ PF_6^-$ reversibly dissociates CH_3CN to form the η^3-phosphaallyl complex $[(\eta^5\text{-}C_5H_5)Ru(\eta'\text{-}Ph_2PCHCH_2)\ (\eta^3\text{-}Ph_2PCHCH_2)]^+ PF_6^-$ and showed that the η^1-to-η^3 conversion is endothermic and entropy driven. Since $\eta^5\text{-}Me_5C_5^-$ is a better donor than $C_5H_5^-$, the metal in complexes of the former should be more electron rich than in complexes of the latter. An electron rich metal center would be expected to facilitate the η^1-to-η^3 conversion. Accordingly, the $\eta^5\text{-}Me_5C_5$

phosphaallyl complex was synthesized in high yield *via* reaction 1. That the η^3-phosphaallyl complex was formed in this

$$[(\eta^5\text{-}Me_5C_5)RuCl_2]_2 \xrightarrow[\text{i. Zn}\\ \text{ii. } 2Ph_2PCHCH_2\\ \text{iii. } NH_4PF_6]{CH_3CN} [(\eta^5\text{-}Me_5C_5)Ru(\eta^1\text{-}Ph_2PCHCH_2)(\eta^3Ph_2PCHCH_2)]PF_6 \quad (\mathbf{1}) \ (60\%) \qquad (1)$$

reaction rather than $[(\eta^5\text{-}Me_5C_5)Ru(Ph_2PCHCH_2)_2(CH_3CN)]^+ PF_6^-$ was established by $^{31}P\{^1H\}$ NMR spectroscopy and X-ray crystallography (Figure 1).

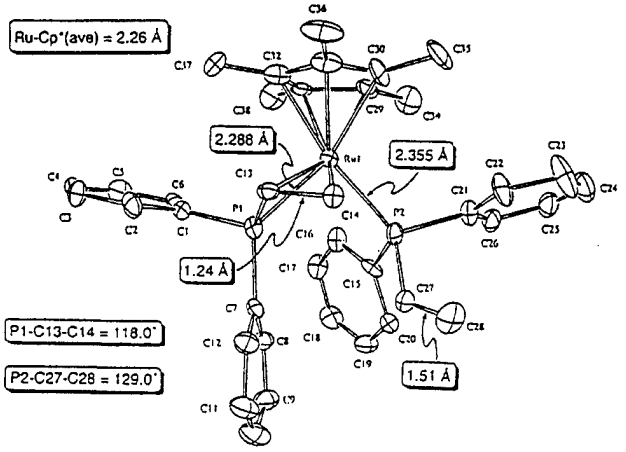
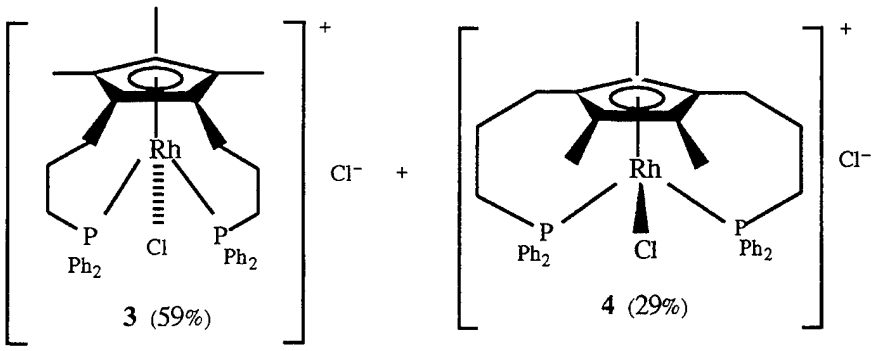


Figure 1. Structure of the cation of 1

The $^{31}P\{^1H\}$ NMR spectrum exhibited three resonances: δ - 145.0 (septet, $^1J(PF)$ = 7 12.7 Hz, PF_6^-), 12.9 (d, $^2J(PP)$ = 48.7 Hz, η^3 - Ph_2PCHCH_2), 43.3. (d, $^2J(PP)$ = 48.7 Hz, η^1 - Ph_2PCHCH_2) rather than the two expected for the CH_3CN adduct. Thus, the η^1-to-η^3 conversion is spontaneous even in CH_3CN solution. X-ray crystallography and ^1H NOE difference spectroscopy established that the phosphaallyl moiety adopts the *exo*- configuration in both the solid and solution states. Reaction **1** with $Ph_2PCH_2CHCH_2$ in place of Ph_2PCHCH_2 produced the η^3-homophosphaallyl analog $[(\eta^5\text{-}Me_5C_5)Ru(\eta^1\text{-}Ph_2PCH_2CHCH_2)$ $(\eta^3\text{-}Ph_2PCH_2CHCH_2)]^+ PF_6^-$ (**2**) in high yield. Compound (**2**) is dynamic in solution as shown by variable temperature $^{31}P\{^1H\}$ NMR spectroscopy.

Analogous reactions of $[(\eta^5\text{-}Me_5C_5)RhCl_2]_2$ with Ph_2PCHCH_2 proceed quite unexpectedly[2] (reaction 2).

$$[(\eta^5\text{-}Me_5C_5)RhCl_2]_2 + 2\,Ph_2PCHCH_2 \xrightarrow[\Delta]{C_6H_6} \qquad (2)$$



The structures of the two novel products of reaction 2 are shown in Figure 2.

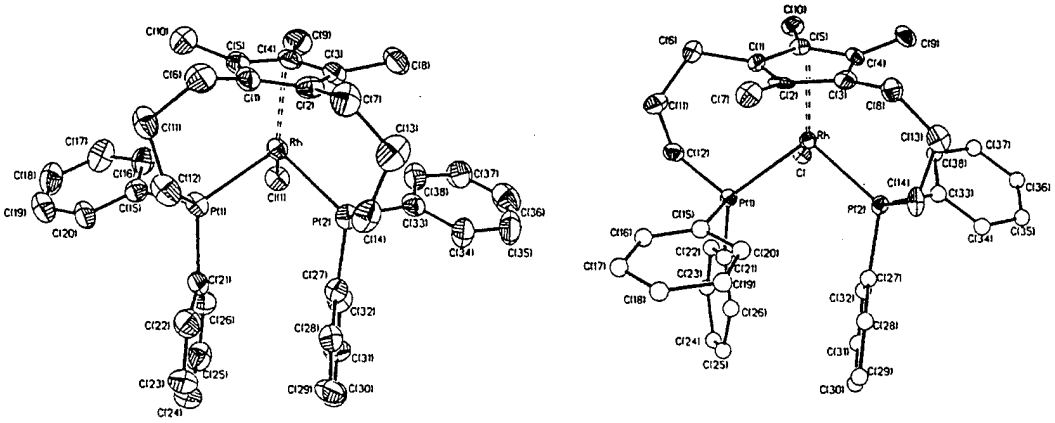


Figure 2. Structures of the cations of **3** (left) and **4** (right).

In contrast, reaction of $[(\eta^5\text{-}Me_5C_5)RhCl_2]_2$ with $Ph_2PCH_2CHCH_2$ and $NaPF_6$ gave the ligand substitution product $[(\eta^5\text{-}Me_5C_5)Rh(Ph_2PCH_2CHCH_2)_2Cl]^+ PF_6^-$ (**5**, Figure 3).

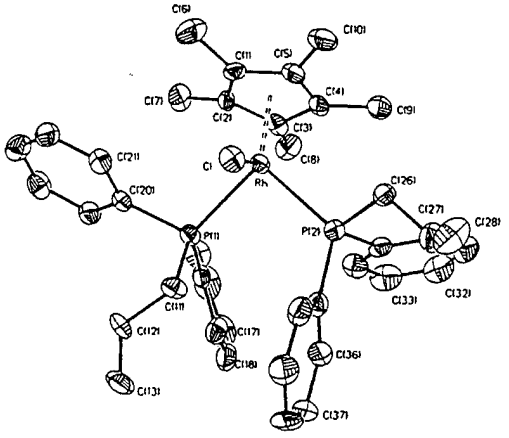


Figure 3. Structure of the cation of **5**.

ACKNOWLEDGEMENTS We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their financial support and Johnson Matthey, Aesar/Alfa for their generous loan of $RuCl_3 \bullet 3H_2O$ and $RhCl_3 \bullet 3H_2O$.

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η^6-PHOSPHININE- AND η^6-1,3-DIPHOSPHININE IRON COMPLEXES

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Abstract Efficient synthetic routes are described, leading to novel η^6-phosphinine- (**1**) and η^6-1,3-diphosphinine (**4, 5**) iron(0) complexes. **1** is a catalyst for pyridine formation by a [2+2+2]-cyclic addition reaction of nitriles and alkynes and **4** is a useful source of unsaturated free four and six membered organophosphorus rings.

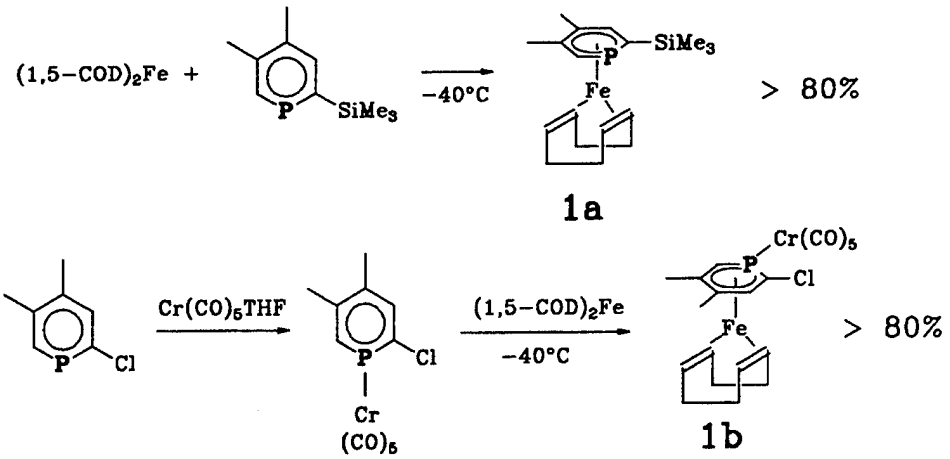
INTRODUCTION

14 valence electron fragment generating complexes are known for their catalytic potential. Prominent examples are (cyclopentadienyl)CoL_2 species, which are catalysts for the formation of substituted pyridine derivatives, [1] whereas recent work on Cp_2ML_n complexes (M = Ti, Zr, Hf; n = 1,2) lead to a real revolution on Ziegler-Natta type catalytic processes. [2] Arene iron complexes are isoelectronic to CpCo species. They exhibit the same principal reaction pattern, but significant milder reaction conditions are observed. This includes catalysis, however, turnover numbers are smaller normally. [3] To solve this problem, P-atoms as part of co-ordinated aromatic rings seem to be appropriate. In principal reactions of phosphaalkynes in the co-ordination sphere of transition metals lead to unsaturated organophosphorus ring ligands, but mainly four and five membered rings are formed. [4] This is true for reactive Fe(0) complexes as well. In contrast to alkynes, the cyclotrimerization is avoided, and two five membered rings are formed from five phosphaalkynes. [5] Only very recently, first proof has been found for a triphosphinine formed in the vicinity of a transition metal. [6]

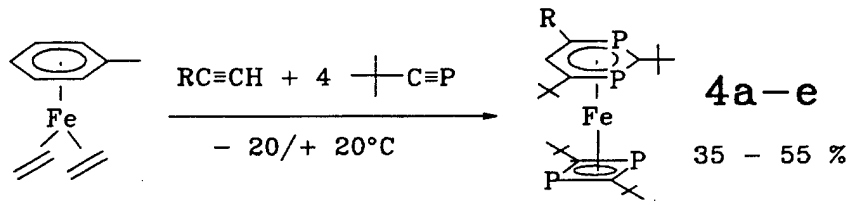
Results

In spite of the fact, that bis(1,5-cyclooctadiene)iron (COD_2Fe) [7] has never been used successfully for the preparation of arene(COD)Fe complexes by ligand exchange, we tried this route with phosphinine derivatives. The reaction produces excellent yields of (η^6-phosphinine)(COD)Fe derivatives **1**, if the lone pair of the phosphorus atom is

shielded by a big ortho substituent (TMS, **1a**), or if it is blocked by a σ-bonded transition metal fragment like $Cr(CO)_5$ (**1b**). Alternatively **1** can be made by three-component metal vapour reactions of $Fe_{(gas)}$, COD and the phosphinines, but the yields are somewhat lower. The molecular structure of **1a** has been proven by X-ray.

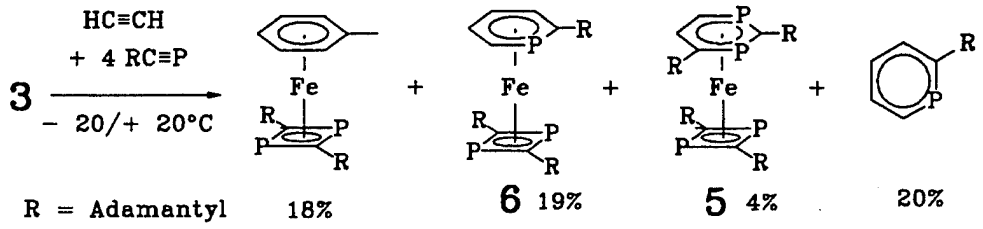


As di- or triphosphinines are not available yet, only $(CF_3)_4$-1,4-diphosphinine has been identified in solution so far, [8] a new synthetic approach to these aromatic heterocycles is necessary. We solved this synthetic problem by a [2+2+2] cocyclization of alkynes and phosphaalkynes. Compared to the so far unsuccessful cyclic trimerization of *tert*-butylphosphaethyne **2a** at most transition metal complexes, the inclusion of acetylene or terminal alkynes with small substituents into the process, leads to lesser sterical hindrance of transition states, yielding six membered rings. The reaction proceeds well with the highly reactive metal vapour product bis(ethylene)(toluene)iron **3** [9], yielding (η^6-1,3-diphosphinine)(1,3-diphosphete)iron complexes **4a-e** as the main product. Functional groups as parts of the alkyne substituents do not hinder the reaction. [10] If adamantylphosphaethyne **2b** is reacted with **3** and acetylene, the product spectrum changes significantly. The 1,3-diphosphinine complex **5** is only a side product in this case, while adamantylphosphinine complex **6** and free 2-adamantylphosphinine dominate the products. Thus still [2+2+2] cyclic addition reactions are the main route, however, two alkynes are united with one adamantylphosphaethyne only.

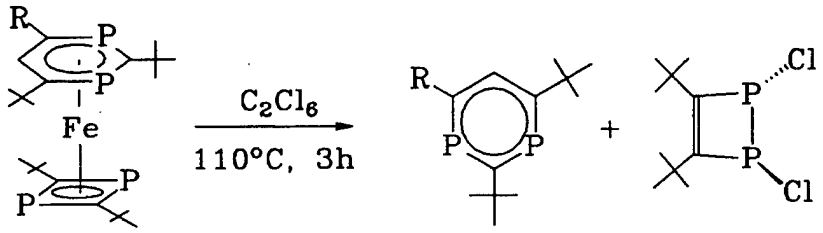


3

R = H, CH_2OH, CH_2OCH_3, $n-C_4H_9$, $CH_2OC(O)CH_3$



The formation of **4a-e** is strictly regiospecific. Exclusively 1,3-diphosphinines are formed and the substituent, introduced with the alkyne, ends up always neighbouring the P atom. All arene(cyclobutadiene)iron derivatives, including those containing up to four P-ring atoms instead of C-R fragments, are extremely stable, if compared with other arene iron complexes (air stable for some time, thermal decomposition beyond +300°C, no ligand substitution reaction), thus they are not useful as catalysts. To make use of the novel 1,3-diphosphinines in this sense, decomplexation is necessary. Oxidizing agents at elevated temperatures can be used for this purpose. $FeCl_3$ or CCl_4 deliberate the 1,3-diphosphinine ligands **7a,b** only, whereas C_2Cl_6 gives access to both free rings. However, the 1,4-diphosphete is oxidized partly and transformed into a *trans*-1,2-dichloro-1,2-phosphetene derivative **8** completely. All spectra recorded of **7a,b** so far, are in perfect agreement with viewing the free rings as stable π^6 heteroarenes. This structure has been proven for the co-ordinated rings. The formation of the rings in the co-ordination sphere of iron(0) and the 1,3 → 1,2-rearrangement of the four membered ring upon decomplexation cast interesting mechanistic questions.

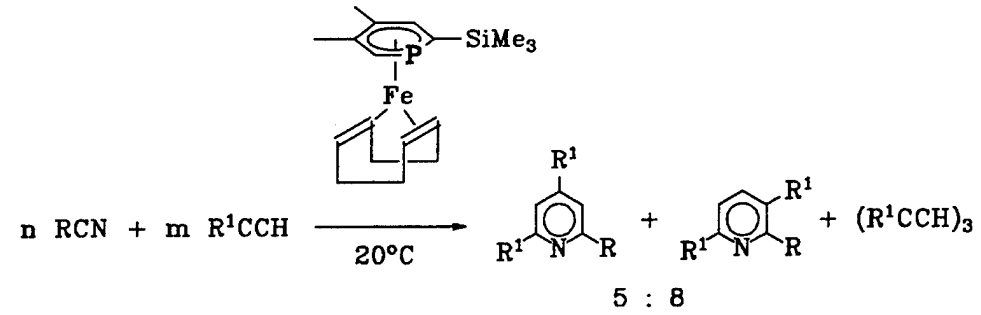


4a,e **7a,b** **8**

R = H, $CH_2OC(O)CH_3$

We are engaged in the moment in recomplexation experiments of **7a,b** with more promising coligands as 1,3-diphosphetes, aiming for potentially catalytic active complexes. The proposed benefit of phosphinine iron complexes as catalysts for pyridine formation was confirmed for **1a**. Conveniently it is active at room temperature, the optimal temperature for laboratory and industrial scale catalytic processes. As the turnover numbers (TON) and the chemoselectivity are still far away from technical requirements, more experiments are necessary to optimize the reaction. Complexes of **7** are promising, as the replacement of toluene by phosphinine ligands of the catalyst

prototype (arene)FeL_2 leads to a significant improvement. Therefore the introduction of a second P atom as part of the arene ligand of iron(0) is believed to have an additional positive effect on pyridine formation as well.



c(Cat.) = 5×10^{-4} mol/l $R^1 = CH_2OCH_3$

Chemoselectivity	Benzenes : Pyridines = 1.4 – 4
TON (max.)	Benzenes 470, Pyridines 160
Alkyne conversion	4 – 84%

Acknowledgements

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MONO-, BIS- AND TRIS-METALLATED PHOSPHORUS COMPOUNDS

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Abstract Some new organometallated phosphorus compounds can be derived from the isolobal analogy. With $CpFe(CO)_2$ = Fp = ferrio substituent as the coordinating complex fragment on the central phosphorus atom, the syntheses, reactivities and structures of mono-, di- and triferriophosphines, -phosphonium salts and -chalcogeno- or -alkylidenephosphoranes are reported.

INTRODUCTION

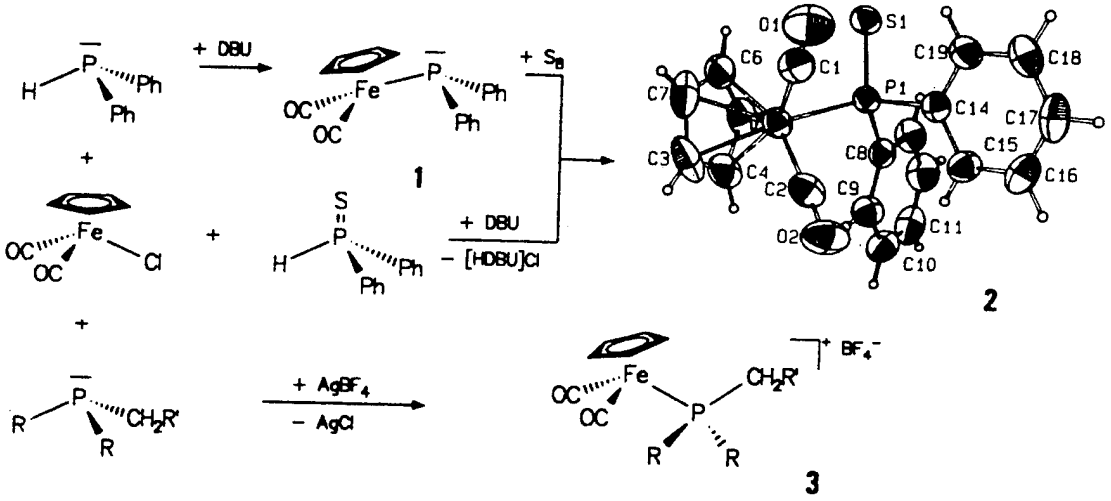
We are interested in the chemistry of organometallated phosphorus compounds which are isolobal to organic phosphorus compounds like phosphines, phosphonium salts and chalcogeno- or alkylidenephosphoranes. Previously we reported on some of our results which focused on open and closed diferriophosphonium salts and diferriothioxophosphoranes [1-7]

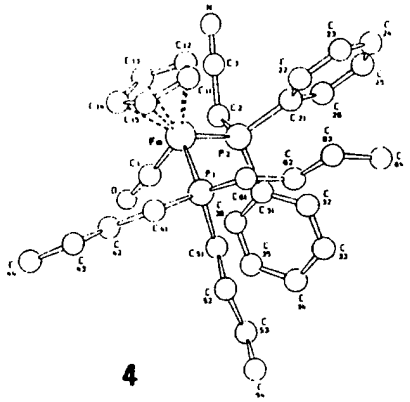
RESULTS AND DISCUSSION

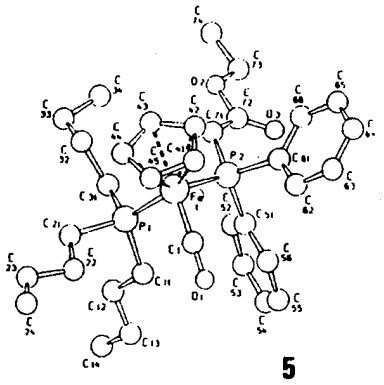
The monoferrio derivatives of phosphorus **1** - **3** are obtained from the reactions of $CpFe(CO)_2Cl$ with PPh_2H, $PPh_2(H)S$ or PPh_2R' as shown in scheme 1.

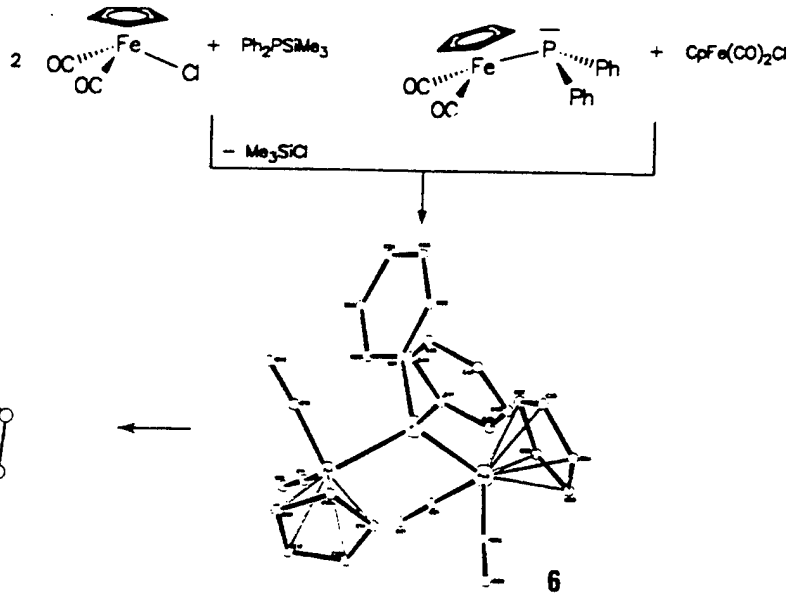
The α-deprotonation of **3** does not succeed because of a competing base reaction. The $^nBu_3P$-modified monoferriophosphonium salt **4**, however, can be deprotonated to give the corresponding alkylideneferriodiphenylphosphoranes **6** which are isolobal to the phosphorus ylides of the Wittig-type (scheme 2). And, indeed, they react with benzaldehyde to give alkenes [8].

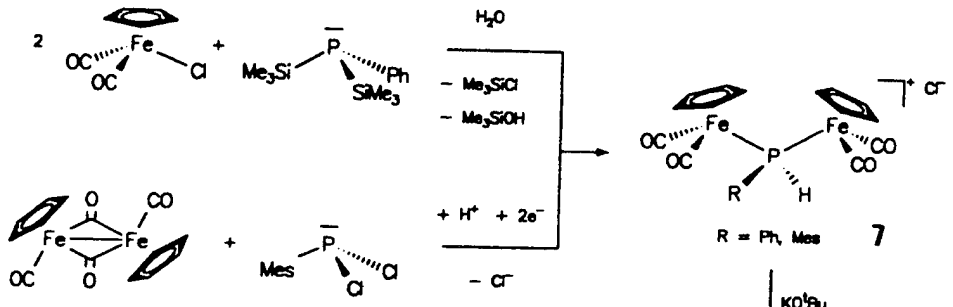
The diferriodiphenylphosphonium salt **7** arises from the reaction of $CpFe(CO)_2Cl$ with either **1** (1:1 molar) or with Ph_2PSiMe_3 (2:1 molar) shown in scheme 3. The *open* cation of **7** undergoes a photolytically induced CO elimination to give the *closed* diferriodiphenylphosphonium cation **7'**. Using the bissilylated phosphine

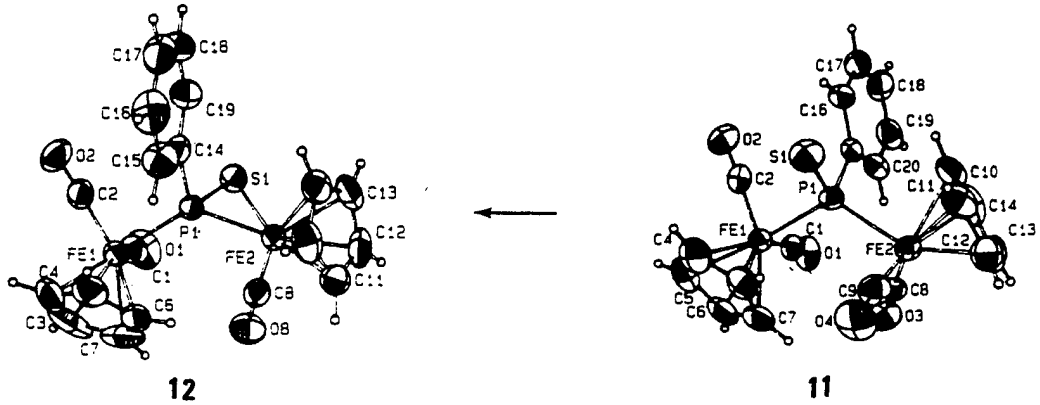

+ DBU
+ S_8
+ DBU
– [HDBU]Cl
+ $AgBF_4$
– AgCl
+ BF_4^-
1
2
3

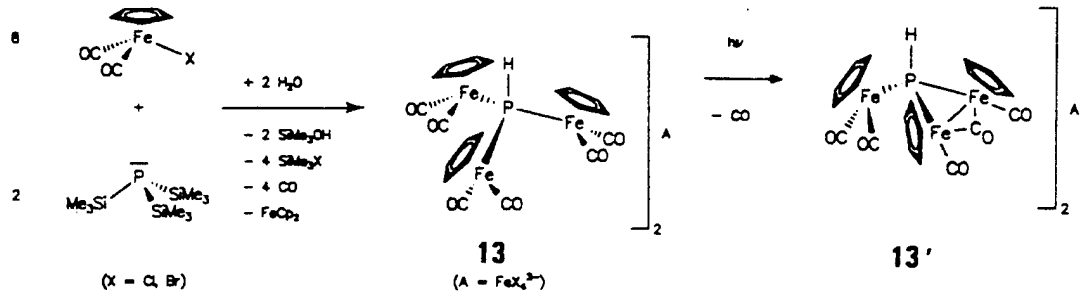

4

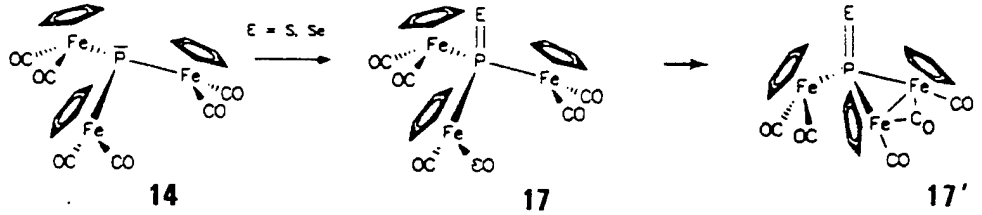

5


2
+ Ph_2PSiMe_3
+ $CpFe(CO)_2Cl$
– Me_3SiCl
6
6'


H2O
- Me3SiCl
- Me3SiOH
+ H+ + 2e-
- Cl-
R = Ph, Mes
7
KO tBu
8
RX
9
10
R' | CH3 | CH2SiMe3 | CH2Ph | CH2COOEt
X | I | Cl | Cl | Cl


12
11


+ 2 H2O
- 2 Me3SiOH
- 4 Me3SiX
- 4 CO
- FeCp2
(X = Cl, Br)
13
(A = FeX4 2-)
hν
- CO
13'


E = S, Se
14
17
17'

$PhP(SiMe_3)_2$ we obtain the PH-functionalized diferriophosphonium salt **8** which after deprotonation to the diferriophosphine **9** is realkylated to form the mixed diorganyldiferriophosphonium salts **10** (scheme 4). **10** can also be deprotonated in the α-position to give the alkylidenediferriophosphorane or, more accurately, the μ_2-phosphaalkene complex **11**, because it loses Fp_2.

The diferriophosphine **9** is very easily oxidized to give the corresponding *open* diferriochalcogenophosphorane **12**, where R-P=S acts as a 2 e donor to two 17 e complex fragments. The photolytic decarbonylation of **12** leads, after migration of the resulting $CpFeCO$ fragment to the P=S bond, to the heterocyclopropane sytem **13** (scheme 5) where R-P=S now acts as a 4 e donor.

The trismetallated PH-functionalized triferriophosphonium salt **14** is obtained by the 8 : 2 stoichiometric reaction of $CpFe(CO)_2Cl$ and $P(SiMe_3)_3$ in the presence of water. The X-ray structure analysis shows that the FeP_3-skeleton in **14** is nearly flattened. The open form of **14** loses one CO-ligand to give the closed triferriophosphonium cation **14'** (scheme 6).

Both compounds **14, 14'** can be deprotonated to give the open and closed triferriophosphines **15, 15'** which can be transformed by quaternization to the corresponding PR- and PCl-triferriophosphonium salts **16, 16'** or by oxidation to the chalcogenotriferriophosphoranes **17, 17'** (scheme 7).

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REACTIONS OF THIOL DERIVATIVES OF ACIDS OF TRIVALENT PHOSHORUS WITH TRANSITION METAL HALIDES.

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Abstract Reactions of thiol derivatives of acids of trivalent phosphorus ($(RS)_3P$ $RSP(NR_2)_2$, $(RS)_2PCl$) with transition metal halides (Cu(I), Cu (II), Ag(I), Pd (II), Pt (II)) have been investigated.

Key words trialkyltrithiophosphite, transition metal halides, complex, coordination

Compounds containing a P-S -bond are of great interest in terms of their coordination chemistry.[1] The presence of two donor atoms in a ligand and their ability to form a bond with transition metals with one or both centers of the ambident system provides wide possibilities of obtaining new phosphorus-sulfur containing metal complexes and studying their structure and properties.

Our investigations began with the reaction of trialkyltrithiophosphites with copper (I) and copper(II) halides.[2] We have studied the reactions of triethyl, -n-propyl-, -i-propyl-, -phenyltrithiophosphite with CuCl, CuBr, CuI and have established, that in all cases the interactions result in the formation of complexes of the 1:1 ratio with the metal.

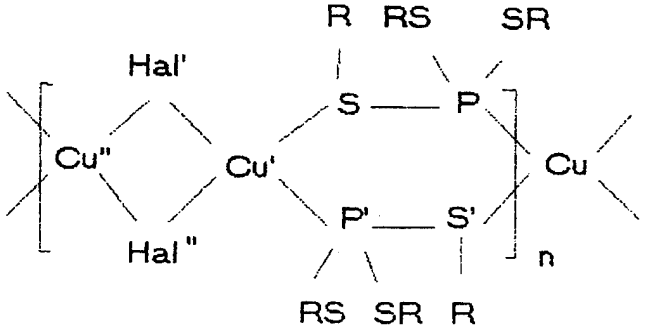


FIGURE 1. $(RS)_3P$·CuHal, where R=C_2H_5; Hal=Cl, Br, J.

With X-ray data it was established, that triethyl- and triphenyltrithiophosphites react with the copper(I) halides with the formation of crystalline complexes, in which the copper atoms are bonded to the phosphorus atom of one trithiophosphite fragment and the sulfur atom of another fragment. They form regular polymer chains with alternating 4- and 6- membered cycles(I).

Such a kind of coordination with both atoms of the ambident >P-S- system in a series of derivatives of P(III) acids is novel, as other derivatives of the P(III)- atom (amides, esters of P(III)) coordinate only with the participation of the phosphorus atom.

It is of interest, that the bulkier substituted triisopropyltrithiophosphite forms complexes coordinated with copper(I) bromide only with the phosphorus atom of the thiophosphite. The structure of the product has been established by X-ray data. It should be noted that one molecule of acetonitrile was drawn into the coordination sphere of copper when the complex was recrystallized from CH_3CN.

It is of interest to compare the X-ray data for the molecules of complexes of triethyl- and triphenyltrithiophosphites with CuCl (Table 1). Firstly, the CuCl and CuCl' bonds are essentially different in their length in the alkyl-complex.

TABLE 1. Some bond lengths for complexes of $CuCl{\cdot}P(SEt)_3$, $CuCl{\cdot}P(SPh)_3$ and $P(SPh)_3$ according to X-ray analysis data.

bond	$CuCl{\cdot}P(SPh)_3$	$CuCl{\cdot}P(SEt)_3$	$P(SPh)_3$
Cu-P	2.243(2)	2.208(1)	———
Cu'-S_3	2.344(2)	2.392(1)	———
Cu-Cl	2.323(2)	2.373(1)	———
Cu-Cl'	2.335(2)	2.312(1)	———
P-S_1	2.117(2)	2.074(2)	2.127(0)
P-S_2	2.103(2)	2.086(2)	2.127(0)
P-S_3	2.174(2)	2.128(2)	2.127(0)

Secondly, it is observed lengthening of the Cu-P bond on the transition from the alkyl to the phenyl complex (0.035Å) and the shorten of the S-Cu bond in the phenyl containing complex on (0.048Å). All the above shows that the interaction between the metal atom and the sulfur atom of one of the thiols groups of the ligand becomes stronger. On the other hand it leads to the lengthening of the P-S bond, the sulfur atom of which is bonded with the copper atom, when compared with triphenyltrithiophosphite and complexes with trialkylltrithiophosphites.

If we proceed from the crystal state to the solution , one can observe, that this tendency is preserved in the NMR ^{31}P data of trithiophosphites. If we compare the value of the displacement of ligand shift in the complexes of triphenyltrithiophosphite with the free triphenyltrithiophosphite, we can see, that the value of this displacement is very small (<5ppm) (Table 2).

Table 2. Changes in chemical shifts of ^{31}P NMR spectra for complexes of transition metals of a number of trithiophosphites ($\Delta\delta^{31}P = \delta^{31}P$ complex - $\delta^{31}P$ ligand).

SUBSTANCE	$\delta^{31}P$, ppm	$\Delta\delta^{31}P$, ppm
$CuCl \cdot P(SEt)_3$	104	12
$CuBr \cdot P(SEt)_3$	99	17
$CuCl \cdot P(SPh)_3$	130	2
$CuBr \cdot P(SPh)_3$	128	4
$CuBr \cdot P(S\ n\text{-}Pr)_3$	92	26
$CuBr \cdot P(S\ i\text{-}Pr)_3$	96	22
$P(SPh)_3$	132	—
$P(SEt)_3$	116	—
$P(S\ n\text{-}Pr)_3$	118	—
$P(S\ i\text{-}Pr)_3$	117	—

Meanwhile the value of displacement of the shift for the complexes of triethyltrithiophosphite exceeds 10 ppm, for the pure phosphorus coordinated complexes these values are about 20 ppm.

For the determination of the influence of the oxidation state of the metal on the direction of interaction the reactions of triethyltrithiophosphite with $CuCl_2$ and $CuBr_2$ have been studied. The reactions proceed as complicated redox processes with the formation of the complex of thiophosphite with copper (I) halide, which are coordinated on both centers of the >P-S- ambident system, cited above; dithiochlorophosphite or bromphosphite, tetrathiophosphite and disulfide.

$$2CuHal_2 \xrightarrow{P(SEt)3} 2CuHal + Hal_2$$

$$2CuHal + 2P(SEt)_3 \longrightarrow 2CuHal \cdot P(SEt)_3$$

$$Hal_2 + P(SEt)_3 \longrightarrow HalP(SEt)_2 + [EtSHal]$$

$$P(SEt)_3 + [EtSHal] \xrightarrow{Hal=Cl} HalP(SEt)_2 + EtSSEt$$

$$P(SEt)_3 + [EtSHal] \xrightarrow{Hal=Br} S{=}P(SEt)_3 + [EtHal]$$

It is of interest to note, that the increase in nucleophility of the phosphorus atom by introducing of the amido groups into the molecule of thiophosphite also results in a complex with the metal being coordinated to the phosphorus atom.

Diethyldithiochlorphosphite also react with CuCl in accordance with NMR ^{31}P data with the formation of a complex with the coordination of a phosphorus atom.. However this substance is unstable and destroyes in a solution with the formation of the complex of tryethyltrithiophosphite with CuCl and ethylthiodichlorphosphite.

Besides copper (I,II) halides we attempt to investigate the reactions of tryalkyltrithiophosphite with AgCl, AgBr, $PdCl_2$, K_2PtCl_4. But it appeared, that the reaction with AgCl in the same conditions doesn't take place. In the case of $PdCl_2$ by NMR ^{31}P the formation of an intermediate complex was observed (δ=110.9 ppm) but it is unstable and disintegrate with the formation of diethyldithiochlorophosphite and diethyldisulfide.

In the case of K_2PtCl_4 by NMR ^{31}P the formation of phosphorus coordinated complex, of $PtCl_2 \cdot 2P(SEt)_3$ was observed (δ=82.5 ppm, $J_{P\text{-}Pt}$=4140 Hz), This complex we have also obtained by the reaction of $(EtS)_3P$ with $PtCl_2 \cdot TOD$ (tetraoctadehalin).

Very interesting results have been obtained by us in the reactions of complexes of trithiophosphite with CuCl and CuBr with the proton containing compounds (EtOH, Et_2NH).

Pure trithiophosphite does not react with absolute ethyl alcohol neither at room temperature nor when boiled during several days. Meanwhile the complex has begun the reaction with the absolute ethanol at room temperature. The product of this reaction is diethylphosphoric acid.

The reaction of trithiophosphite with diethylamine does not take place at all. However if instead of thiophosphite in this reaction we take the thiophosphite complex with copper (I) halide the substitution reaction at the phosphorus (III) atom proceeds readily with the substitution of the thiogroups by amido groups. In accordance with the NMR ^{31}P data complex copper(I)halides with triamidophosphite and phosphorus containing compound with P-H bond are formed.

These first results demonstrate that with complexes we can conduct reactions which in ordinary conditions do not take place at all and we can pass over to other derivatives of phosphorus acids without sulfur atoms.

ACKNOWLEDGEMENTS

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PHOSPHORUS AND ZIRCONIUM: A FRUITFUL RENDEZ-VOUS

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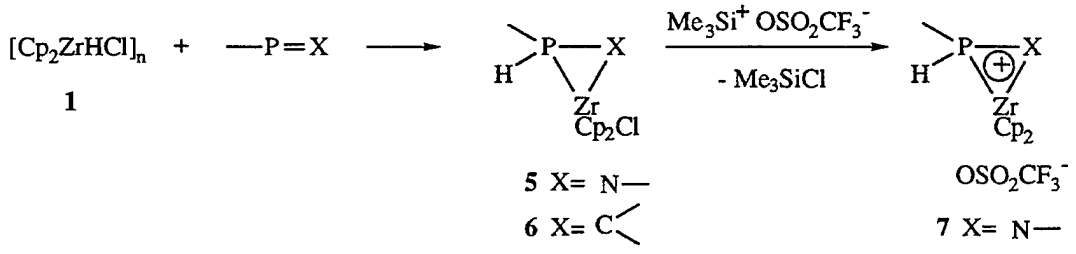
Abstract Zirconium reagents such as $[Cp_2ZrHCl]_n$, Cp_2ZrMe_2, $[Cp_2Zr]$ ... were found to be useful tools for the regio and diastereospecific synthesis of diphosphines including optically active diphosphines as well as for the generation of masked iminophosphide anions, metalated phosphorus containing macrocycles, phosphirane zirconacyclopentadienes or zirconacyclopropenes.

INTRODUCTION

Zirconium derivatives were found to be useful tools in organic and organometallic syntheses.[1] In contrast a few reactions were concerned with the interactions between main group elements, and more precisely phosphorus compounds with zirconium species. We describe here our efforts to develop new methodologies of synthesis of linear or cyclic, neutral or cationic phosphorus derivatives from easily available zirconium compounds such as $[Cp_2ZrHCl]_n$ **1**, Cp_2ZrMe_2 **2**, $[Cp_2Zr]$ **3** or Cp_2ZrCl_2 **4**.

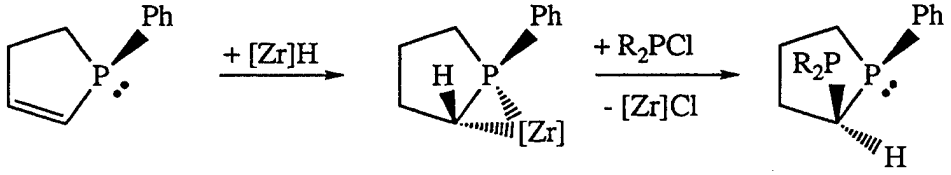
Reactions from $[Cp_2ZrHCl]_n$ 1

Addition of **1** to various phosphaimines or phosphaalkenes led to the metalated three membered ring **5** (X = N-) or **6** (X = C <). Abstraction of chlorine allowed the synthesis of the first cyclic zirconium phosphorus cations **7** (Scheme 1).[2]



Scheme 1

A regio and diastereospecific way to new diphosphines can be proposed from hydrozirconation of dihydrophosphole Ph-P-CH=CH-CH_2-CH_2 **8** followed by treatment of the resulting unexpected α-zirconated phopholane Ph-P-CH($ZrCp_2Cl$)$(CH_2)_2CH_2$ **9** with various chlorophosphines.[3] Such a methodology can be applied to the synthesis of an optically active diphosphine **10** (Scheme 2) and allowed to point out an unprecedented inversion of configuration at carbon in the electrophilic cleavage of the carbon-zirconium (IV) bond.[4]



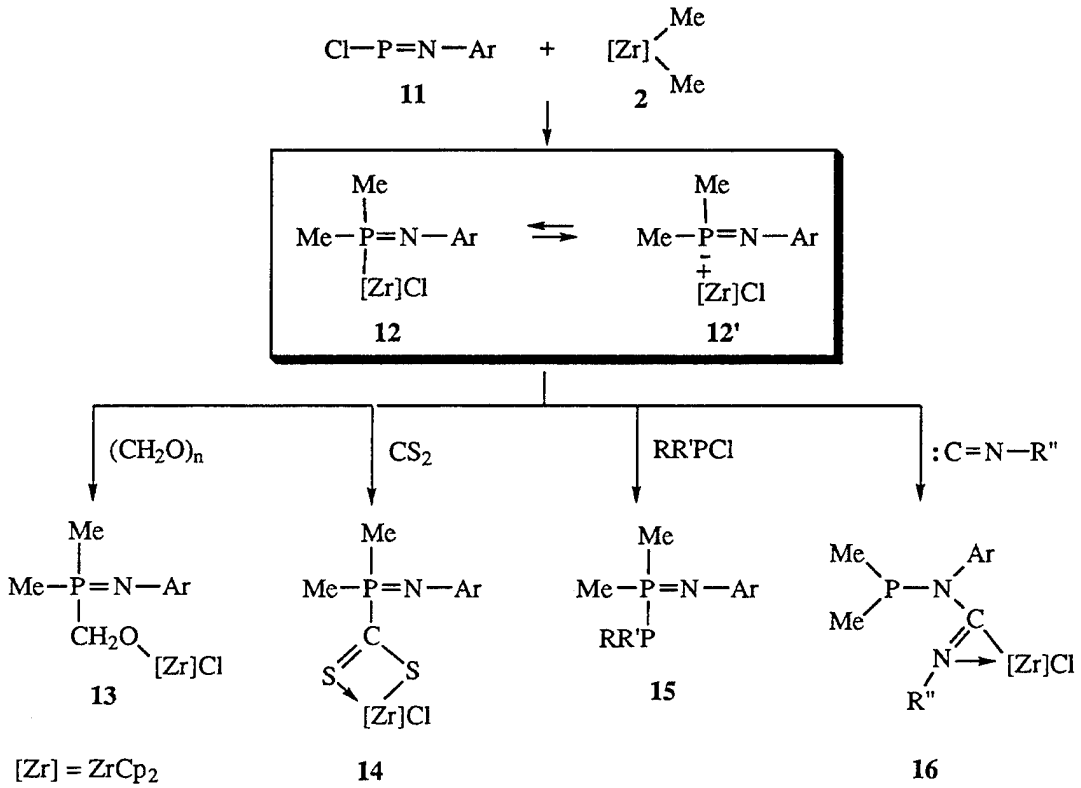
(R_p)-**8** (R_p)-**9** (S_p)-**10**

[Zr]= $ZrCp_2Cl$

Scheme 2

Reactions from Cp_2ZrMe_2 2

Treatment of the chlorophosphaimine **11** with **2** led to the iminozirconiophosphorane **12**, the first P-metalated iminophosphorane. This compound can be considered as a masked iminophosphide anion **12'** which has presented a versatile behaviour. Insertion reactions into the Zr-P bond, formal insertion into the N-Zr bond and reactions at phosphorus are illustrated in Scheme 3.[5]

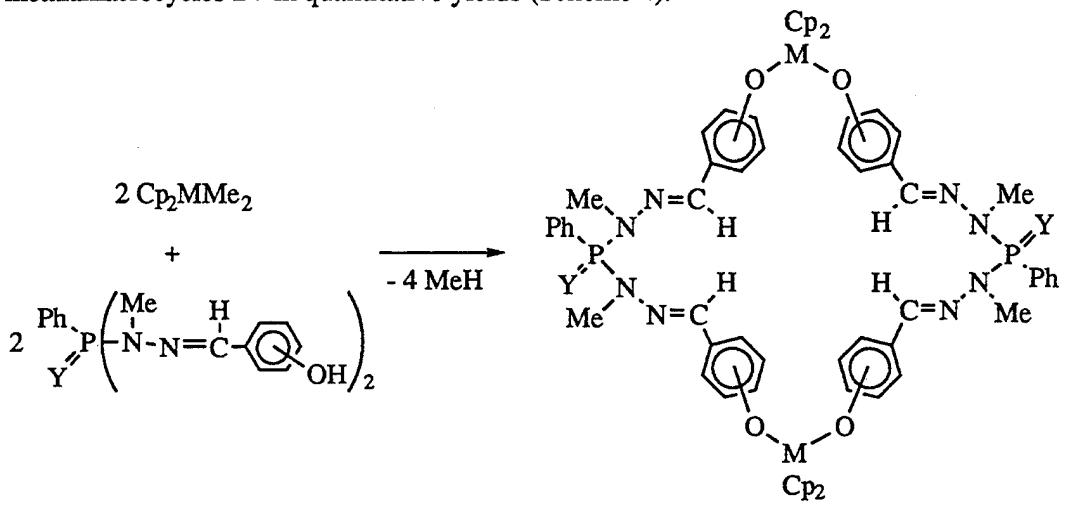


[Zr] = $ZrCp_2$

Ar = 2,4,6-^{t}Bu$_3$C$_6$H$_2$

Scheme 3

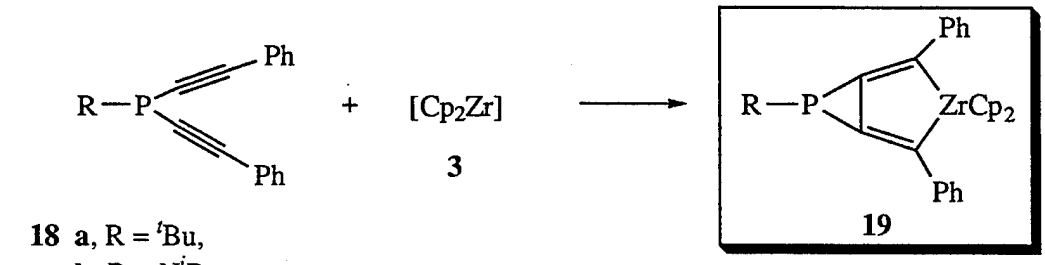
Cp_2MMe_2 (M= Zr, Ti) can be reacted with phosphodihydrazones to give metalamacrocycles **17** in quantitative yields (Scheme 4).[6]



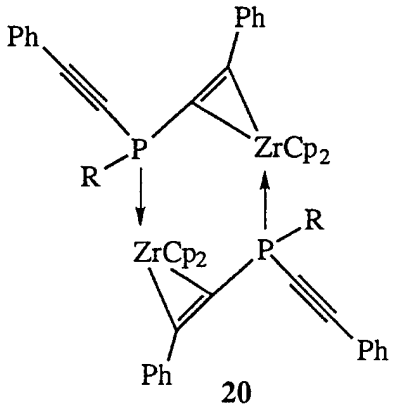
Scheme 4 **17** M= Zr, Ti

Reactions from $[Cp_2Zr]$ 3

A clean synthesis of metalated cyclic derivatives such as phosphirane-zirconacyclopentadienes **19** can be proposed from the addition of diacetylenic phosphines **18** to **3**. These bicyclic systems reacted as zirconacyclopropenes **20** towards a variety of reagents (H_2O, HCl, $PhPCl_2$, PCl_3, etc...) (Scheme 5) . The zirconacyclopropene **20c** was isolated and fully characterized.



18 **a**, R = ^{t}Bu,
b, R = N^{i}Pr$_2$
c, R = 2,4,6-^{t}Bu$_3$C$_6$H$_2$



20

Scheme 5

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1-AMINO-1-ARYLMETHYL PHOSPHONIC ACID DERIVATIVES. SYNTHESES, CHARACTERIZATION AND COMPLEXING PROPERTIES

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Abstract. In this paper we shall review the salient aspects concerning the syntheses, characterization and complexing properties of variously substituted mono- and bis-amino-phosphonates.

INTRODUCTION

α-Aminophosphonic acids,bioisosters of natural aminoacids, serve for inhibiting enzyme activity,[1] bacterical growth[2] and in agrochemistry as antifungal agents,[3] herbicides[4] and plant regulators. In addition, α-aminophosphonic acids and their mono-alkyl esters are of interest also in hydrometallurgy in order to extract metals[5] and in diagnostic medicine as screening agents, once complexed with lanthanides and actinedes.[6,7] Therefore considering the interest and the wide applications of such compounds we decided to synthesize a great variety of mono- and bis-α-aminophosphonic acid dialkylesters, as well as some of their mono-esters, as described in the text.

RESULTS AND DISCUSSION

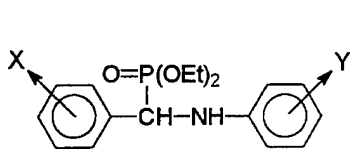
Mono-amino-phosphonic acid derivatives.

α-Aminophosphonic acid dialkyl esters were prepared by addition in neat or in solvents (polar or apolar) of dialkylphosphite to the Schiff base precursors.

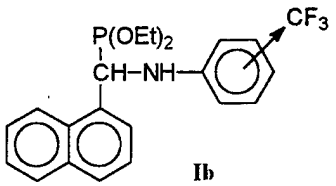
According to this procedure we prepared in good yields α-aminophosphonic dialkyl esters **Ia-If**, where the X and Y substituents range from H, halogens, trifluoromethyl groups, methoxy and carbomethoxy moieties, phenylazo, to free carboxylic groups.

In the ^{1}H-NMR spectra the most diagnostic signals are observed in the phosphorus alkoxy and in the methyne regions; in fact, the diethyl esters give rise to *two* distinct

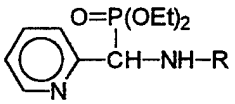
triplets at *ca.* 1.1÷1.3 ppm for the methyl groups and a complex multiplet for the methylene protons; the dimethyl esters show *two* distinct doublets (J_{HP} ≅10.5 Hz) for the OCH_3 protons at ca. 3.1÷3.8 ppm. This pattern is due to the close proximity of the stereocenter N-C-P and the chemical shift difference between the two triplets or the two doublets is very sensitive to the moiety attached to the methyne carbon bearing the phosphonate group. The methyne hydrogen of the -CH-P(O)$(OR)_2$ group appears as a sharp doublet (J_{HP} *ca.* 22÷24 Hz) or as a quartett of an ABX pattern, due to the additional coupling with the NH proton. Interesting enough, in phosphonates **Ia**, **Ie**, **If**, bearing a carboxy or carbomethoxy group in the ortho position, the NH proton resonates below 8.00 ppm experiencing a dramatically down-field shielding effect due to the formation of a hydrogen bond between the NH and the ortho carbonyl oxygen, via a six-membered cyclic structure.



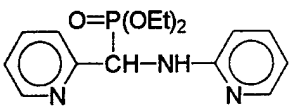
Ia



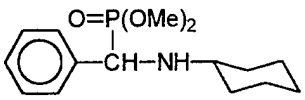
Ib



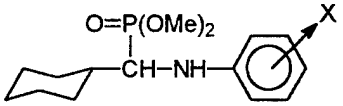
Ic



Id



Ie



If

The geometry adopted in the solid state by derivative **Ia** (X = Y = H) was investigated by X-ray diffraction techniques[8,9] and the experimental geometry was compared with that one obtained by using Molecular Modelling methods.[10] The results of our quantum mechanical structural analysis are in good agreement with the conformations obtained from X-ray diffraction studies and from ^{1}H-NMR spectra.

Since our amino-phosphonates **Ia** - **If** exist in two enantiomeric forms we developped a direct and efficient enantioselective resolution of some phosphonates **Ia** - **If** using commercially available HPLC chiral columns.[11,12] A great variety of racemic N-arylamino-1-arylmethyl phosphonic acid diethyl esters with various fluorinated substituents in one or both aryl rings (**Ia**, X = H; 3,4-F_2; 4-OCF_3; Y = H; 2-CF_3; 2OCF_3; 2-F; 3-F; 4-F; 3-CF_3; 4-CF_3; 3,4-F_2) have been resolved by using this technique.[12]

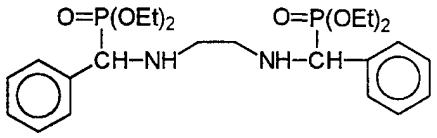
Amino-phosphonic acid diethyl esters containing the pyridine moiety (formulas **Ic** and **Id**) were also synthesized[13] with the aim of enhancing the complexation properties

towards lanthanides in order to use such compounds in diagnostic medicine, NMR imaging techniques and in agrochemistry. Indeed, alkaline hydrolysis of derivatives **Ic** and **Id** gave the corresponding monoethyl esters phosphonates, which are very versatile complexing agents for transition metals.[14]

In order to enhance the hydrophilicity and the complexing properties towards II° group elements we introduced in our amino-phosphonates one or more carboxylic groups (**Ia**, **Ie**, **If**, X = Y = COOH). Furthermore, the presence of such functionalities should facilitate enantiomer resolution both by HPLC methods or by conventional chemical techniques and will allow the synthesis of disparate derivatives (amides, amines, nitriles) and of definite polycondensates bearing the amino-phosphono functionality.

Bis-α-amino-phosphonates.

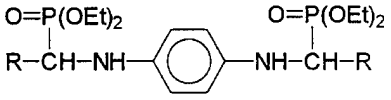
Addition of dialkylphosphite to bis-imines led us to obtain a variety of amino aryl-methyl-diphosphonate alkyl esters in good yields.[15] All compounds, whose structures are exemplified by formulas **IIa-c** and **III**, are crystalline solids and were characterized by ^{1}H- and ^{31}P-NMR and by MS-FAB techniques, which reveal the presence of peaks or fragmentation patterns very useful and diagnostic for constitutional assignments.[15]



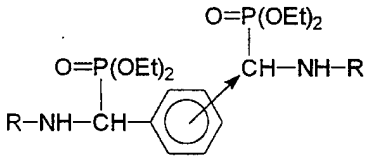
IIa



IIb



IIc



III

In the ^{1}H-NMR the presence of only one set of signals observed in all compounds for the methyne and ethoxy groups indicates that only one of the two possible diastereomers (the *meso* or the *racemic*) is formed stereospecifically in our addition reactions.[15]

This observation was further confirmed analyzing the ^{31}P-NMR spectra in which only one sharp phosphorus signal is observed in the majority of our samples.

Indeed, X-ray diffraction analyses clearly indicate that **IIa** has a *meso* configuration and the solid-state molecular conformation possesses a fully elongated trans-planar **Ci** structure along the P-C-N-C-C-N-P skeleton.[16]

The MS-FAB technique indicates that a protonated ion $[M + H]^+$ was observed in high intensity for all compounds, and the $[M + H - HPO(OEt)_2]^+$ ion or the $[M + H - (2 \times HPO(OEt)_2)]^+$ ion constitute the base peak.

Compounds of type **IIa** and **III** were hydrolysed to the corresponding mono-etsers, in alkaline solution.[17] Characterization of these mono-esters by MS-FAB technique can be performed only using the negative ion mode. All compounds examined show a pseudo-molecular ion $[M - Na]^-$ with very high intensity and peaks due to the cluster ions $[nM - Na]^-$, where n = 1, 2, 3. The presence of the ion $[2M - Na]^-$, is very diagnostic for determining the molecular masses of the salt molecules.[17]

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COORDINATION CHEMISTRY OF DITHIOIMIDOPHOSPHINATES.

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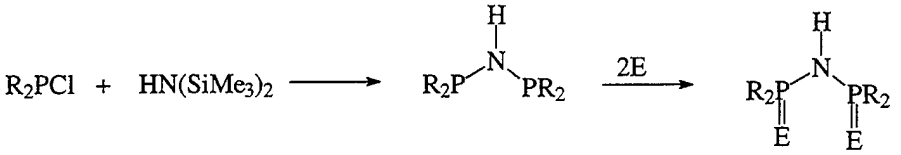
Abstract The preparation of $^{i}Pr_2P(S)NHP(S)^{i}Pr_2$ and its reaction to form simple chelate complexes $M(^{i}Pr_2P(S)NP(S)^{i}Pr_2)_2$ (M = Pd, Pt) is described. The neutral starting material forms H-bonded chains in the solid state whilst there are dramatic differences in ring geometry on changing M from Pd to Pt.

INTRODUCTION

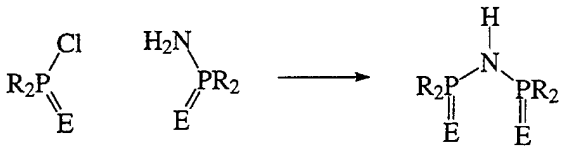
The coordination chemistry of $R_2P(E)NHP(E)R_2$ and $[R_2P(E)NP(E)R_2]^-$ (E= O, S, Se) is of interest for a number of reasons. These ligands represent inorganic analogues of the more extensively studied β-diketonates, they are readily deprotonated to form stable six-membered inorganic rings which have potentially interesting bonding properties (π-bonding involving d-orbitals may have a role) and they have the potential to behave as metal selective ligands as a result of the extensive range of chalcogenides and R groups which may be introduced. There have been several studies on systems with R = Ph and E = S [1,2] and some work on R = Me, E = S.[3,4] Here we report on our investigations into the sulfur compounds were R = ^{i}Pr.

RESULTS AND DISCUSSION

$R_2P(E)NHP(E)R_2$ may be prepared by a variety of routes. Simple condensation of the phosphine halide with $HN(SiMe_3)_2$ followed by oxidation with the appropriate chalcogen is appropriate for the synthesis of symmetric systems (eqn 1) whilst asymmetric compounds can be obtained by condensation of amine and chloro species (eqn 2). For the preparation of $^{i}Pr_2P(S)NHP(S)^{i}Pr_2$ **1** we chose the former method and obtained a 60 % yield of the pure compound (δ ^{31}P-{^{1}H} = 91.2 ppm).



eqn. 1



eqn. 2

The X-ray structure of **1** reveals that the P=S groups are disposed approximately *gauche* with respect to the P....P vector . The P-N distances are 1.678(3) and 1.681(3) Å whilst the P-S distances are 1.943(1) and 1.951(1) Å and the P-N-P angle is 132.0(2)°. The molecules pack (Figure 1) to form chains *via* P-S...H-N hydrogen

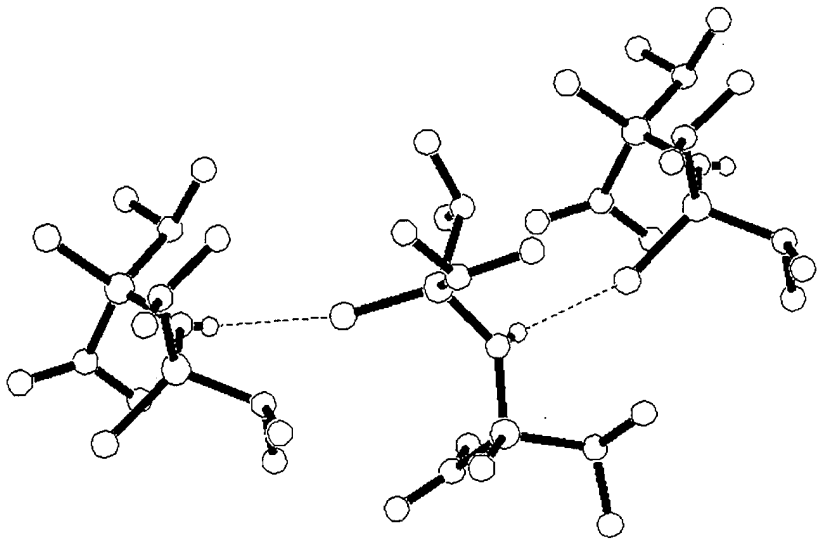


FIGURE 1 P-S...H-N Hydrogen bonding in $^{i}Pr_2P(S)NHP(S)^{i}Pr_2$

bonds (S...N 3.58, H...S 2.97 Å. Reaction of **1** with simple metal halides yields ML_2 complexes with deprotonation at the central nitrogen. Here, we highlight two examples which illustrate the ring geometries which we have observed to date. Thus, the palladium complex $Pd(^{i}Pr_2P(S)NP(S)^{i}Pr_2)_2$ **2** is essentially square planar about the metal with P-S bondlengths of 2.023(2) and 2.030(2) Å and P-N bondlengths of

1.598(4) and 1.588(4) Å ie., the P-S bonds lengthen and the P-N bonds shorten upon deprotonation/complexation which is compatable with a more delocalised structure in the complex. As can be seen from Figure 2 the PdS_2P_2N rings in **2** are distinctly

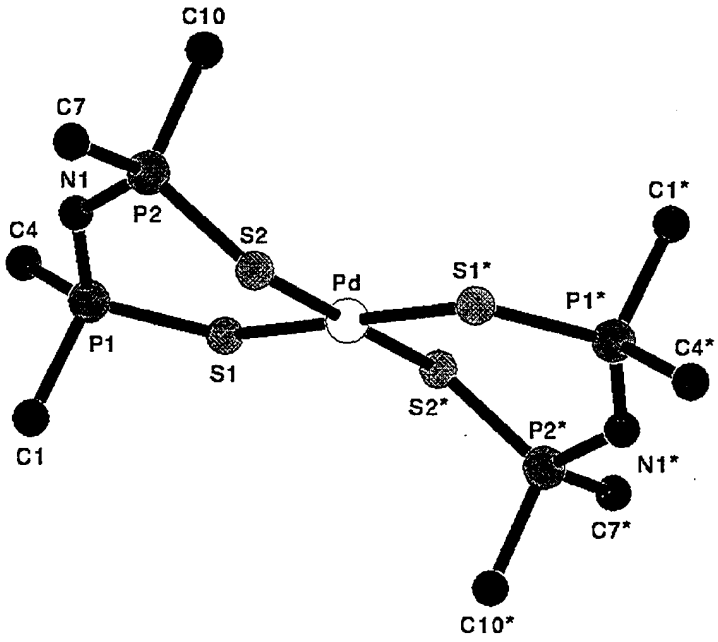


FIGURE 2 The X-Ray structure of $Pd(^iPr_2P(S)NP(S)^iPr_2)_2$ **2**

puckered in what might be described as a distorted boat conformation. Remarkably, the platinum complex $Pt(^iPr_2P(S)NP(S)^iPr_2)_2$ **3** has a substantially different ring geometry. The platinum centre is a approximately square planar whilst the P-S bondlengths (2.034(2) and 2.038(1) Å) and P-N bondlengths (1.586(4) and 1.575(4) Å) are not significantly different from those in **2** but the ring conformation changes to give a close to planar S_2P_2N fragment. The P-N-P angle does not differ markedly in **2** and **3** (130.2(2) and 135.0(2)° respectively) but the M-S-P angles are significantly reduced in **3** (104.07(5) and 99.62(7) in **3** cf. 114.04(6) and 108.62(6) in **2**) and this must imply the use of different orbitals for the coordination to the metal centres.

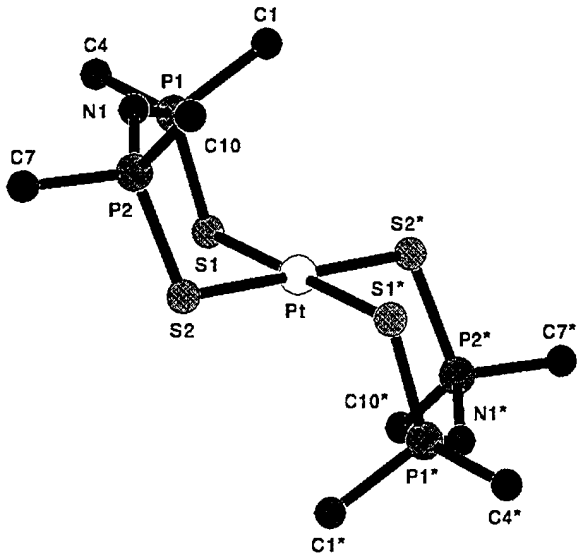


FIGURE 3 The X-Ray structure of $Pt(^{i}Pr_2P(S)NP(S)^{i}Pr_2)_2$ **3**

We have observed the puckered, boat, conformation in the tetrahedral zinc, cadmium and nickel complexes and it would appear that the more symmetric structure is the unusual case. Further studies are in progress.

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DEVELOPMENT OF AN 'ALL ORGANIC' PHOSPHORUS BASED CORROSION INHIBITOR.

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Abstract Albright and Wilson has developed a water soluble environmentally acceptable corrosion inhibitor, BRICORR288. Unlike current treatments for corrosion it does not contain chromium or zinc. Development of this organophosphorus corrosion inhibitor is described; both the process chemistry of manufacture and activity are discussed. BRICORR288 is manufactured by the aqueous radical reaction of phosphorous acid with maleic acid and is a telomeric mixture of phosphono succinic acid and 1-phosphono butane-1,2,3,4-tetracarboxylic acid. The general utility of the process chemistry is discussed with respect to the facile large scale manufacture of other water soluble phosphonates. BRICORR288 is now being manufactured on a multi tonne scale for sales in the UK and Europe.

INTRODUCTION

Corrosion is a serious problem, in the UK alone it accounts for the loss of £1000Ms each year as a result of direct damage and down time in industry. Treatments currently available to control corrosion often use materials which are now considered unacceptable. Chromium and zinc containing formulations in particular are used; they are toxic to marine life and persistent in the environment. In response to these pressures Albright and Wilson has developed an environmentally acceptable inhibitor system (BRICORR288) based on a water soluble phosphonate. Unlike currently available organophosphorus corrosion inhibitors it is stable to oxidation by bleach (currently used as a biocide in industrial cooling systems). The process for manufacture of BRICORR288 has minimal environmental impact; it has no by-products and uses a water solvent.

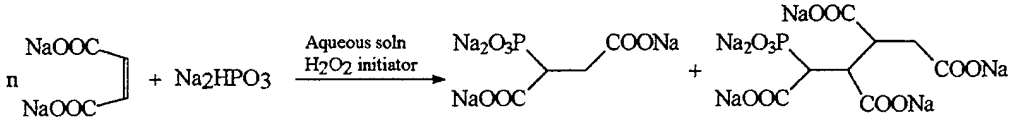
DISCUSSION

Choice of Compound

Any new potential corrosion inhibitor has to meet many criteria. These are:

(i) Good environmental profile in terms of toxicity, aquatic toxicity, environmental biodegradability and process chemistry / raw materials
(ii) Cost effective
(iii) Stable to oxidising biocides (e.g. bleach is commonly used in cooling systems)
(iv) Compatible with other water treatment agents (for formulation)
(v) Active over a wide range of water chemistry

Many phosphonates are used in water treatment. The main products are hydroxy phosphonoacetic acid[1], aminomethylene phosphonates[2],1-hydroxyethane-1,1-bis phosphonic acid[3], and 2-Phosphono butane-1,2,4-tricarboxylic acid. Over a period of two years we evaluated over 80 phosphonates in standard water conditions (60ppm active dose, 120ppm Ca, pH 7.5 at 20°C). Nearly half of the 20 'best' gave excellent corrosion inhibition (<2mils/yr); the final choice was not just based on activity but also on cost effectiveness, environmental profile of the process chemistry and chlorine stability. BRICORR288 is made by patented Albright and Wilson Technology:

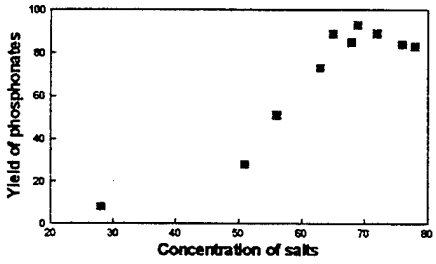


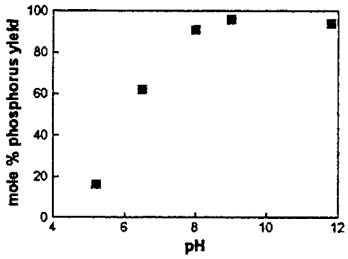
It is a telomeric mixture of phosphonosuccinic acid and 1-phosphonobutane-1,2, 3,4-tetracarboxylic acid made by the reaction of maleic acid with phosphorous acid. Variations have been made in the composition of BRICORR288. It has been discovered that an approximately 1:1 ratio of n=1 to n=2 gives optimum performance as a corrosion inhibitor. Details of this work will not be described here. No polymaleate is formed and oxidation to phosphate is <3%.

Choice of Process Chemistry

Raw material costs and disposal of by-products are vital considerations when designing a new process. The process must match the high environmental standards of the product. The chosen route uses phosphorous acid, this is a common feature in the manufacture of water treatment chemicals. In three of the above water treatment

compounds phosphorous acid is used as the source of phosphorus[1,2,3]. All three of these compounds decompose in the presence of bleach. [2-phosphonobutane-1,2,4- tricarbox--ylic acid uses a base catalysed addition of dialkyl phosphite to dialkyl maleate in the first stage[4] of manufacture]. BRICORR288 chemistry uses phosphorous acid in a radical process. Radical addition of alkyl phosphites[5], or half phosphites[6] to olefins in the manu--facture of organophosphorus products is very well known in industrial applications. The direct radical addition of phosphorous acid to olefins in an organic solvents, e.g. dioxane, using organic radical initiators (e.g. alkyl peroxides or azo-bis initiators) has also been reported[7]. BRICORR288 process chemistry enables direct reaction of water soluble olefins in water solvent using hydrogen peroxide as the initiator for the radical chemistry [8,9]. As such the chemistry does not use toxic solvents, such as dioxane, has no initiator by-products to contaminate the product and therefore meets the required characteristics.





BRICORR288 Chemistry[9]

This chemistry is very sensitive to pH and concentration. The optimum concentration is 65% - this represents about 10 moles of water per mole of phosphorus; at a greater concentration the yield drops because the reaction mixture becomes too thick to mix effectively. Clearly radical transfer and termination processes dominate at lower concentrations. The pH must be above 6-7 to obtain a good yield. The pK_2 of phosphorous acid is 6.5. Although it is not valid to compare the optimum pH for reaction (at 110°C, 65% solids) with the pK_2 in dilute solution at 25°C, it seems reasonable to postulate that it is the radical dianion which is required for this chemistry. In the ^{31}P and ^{13}C nmr spectra of BRICORR288 it is clear that only two of the expected four diastereomers of the n=2 compound are formed. Clearly there is some preferred stereochemical orientation in formation of the C-C bond.

Activity as a Corrosion Inhibitor

Typical operating conditions are 10ppm of Ca as $CaCO_3$, 10-30ppm of inhibitor, pH 5.5-9.0 and max. of 600-900ppm chloride. Corrosion inhibition with BRICORR288 requires the presence of calcium; also, metal that has been treated with BRICORR288 has a surface film in which we have detected calcium, phosphorus and carbon, by surface analysis. Corrosion is an electrochemical process and for the above reasons we believe that BRICORR288 acts at the cathodic sites on the metal. At these sites oxygen and water are being converted to hydroxide ions; the surface pH can be 10.5 - 11[10], whereas the bulk water pH may be 5-7. This local high pH is believed to result in the deposition of a calcium salt of BRICORR288; this would stop corrosion by blocking the flow of water and oxygen to the metal surface. At anodic corrosion sites on the metal, rust (as mixed iron oxides) is being produced; it is not clear to what extent BRICORR288 modifies the metal surface and the iron oxide / hydroxide being formed at anodic sites.

Conclusions / Summary

BRICORR288 is now being manufactured by Albright and Wilson and sold into the European Market. It has an excellent environmental profile:

Ecological / toxicological information: *Toxicity*: Rat oral LD50 > 5000mg/Kg, Rat dermal LD50 > 2000mg/Kg, Ames test negative: *Aquatic toxicity*: 96h LC50 rainbow trout >100mg/L, 48h EC50 Daphnia magna>100mg/L, EC50 (30min and 3h) >1000mg/L (activated sewage sludge respiration inhibition assay). *Process*: Environmentally acceptable, No toxic by-products.

Activity :*Chlorine stable* - 5% BRICORR288 and 5% Cl_2 as bleach stable for >1week at 70°C, *Water soluble* - compatible with other water treatment agents, *Cost effective* 10-30ppm active dose and *Ease of use* -supplied as a solution in water .

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BI- AND TRIDENTATE ORGANOPHOSPHORUS COMPOUNDS FOR EXTRACTION AND COMPLEXATION OF METAL IONS

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Abstract. Studies of structure-reactivity relations were carried out in solvent extraction and coordination chemistry of metal ions M^{z+} {Na(I), Mg(II), Ca(II), Sr(II), Ba(II), Ln(III) (Sc, Y, La...Lu), Hf(IV), Fe(II), Co(II), Ni(II), Pd(II), Cu(II), Ag(I), Au(III), Zn(II), Cd(II), Hg(II), Tl(I), Pb(II), and Bi(III)} with 38 bi- and tridentate μ-imido organophosphorus compounds with oxygen and sulfur donor atoms. These compounds are Brønsted acids, HA, and form chelate complexes MA_z in most cases. Different modes of coordination are observed. The extraction of metal ions depends not on only on the set of donor atoms, and the acidity and dimerization constant of the organophosphorus compound. In some cases steric effects are dominant. It was also observed an important influence of the diluent.

Key words: μ-Imido-diphosphates; μ-imido-thiodiphosphates; μ-imido-dithiodiphosphates, di-μ-imido-triphosphates, N-thiophosphoryl thioureas; solvent extraction; coordination chemistry.

INTRODUCTION

Starting with the tetraphenyl μ-imido-diphosphate **1a** [1-3] it has been shown, that μ-imido-diphosphates are effective reagents for complexation and liquid-liquid extraction of metal ions. The following compounds:
$(RO)_2P(X)$-NH-$P(Y)(OR^1)_2$ (X,Y = O: **1a-e**, **1g-h**; X = O, Y = S: **2a-d**; X,Y = S: **3a**, **3b**, **3d-f**; R,R^1= Ph: **a**; R,R^1= 2-Me-Ph: **b**; R,R^1= 3-Me-Ph: **c**; R,R^1= 4-Me-Ph: **d**; R = 4-Me-Ph, R^1= Ph: **e**; R = Ph, R^1= 2-Me-Ph: **f**; R,R^1= Oc: **g**; R,R^1= Hex: **h**), $(PhO)_2P(O)$-NH-P(O)(OPh)OH **4**, $(RO)_2P(O)$-NH-$P(O)(OR)NH_2$ **5**, $(RO)_2P(X)$--NH-P(X)(OR)-NH-$P(X)(OR^1)_2$ (X = O: **6a**, **6c**, **6e**; X = S: **7a**), $Ph_2P(S)$-NH-$P(S)Ph_2$ **8**, $(PhO)_2(S)$-NH-$C(CH_3)$=CH-CN **9**, $(PhO)_2P(S)$-NH-C(S)-NR^2R^3 **10i-u** (R^2= R^3= Et: **i**, *n*-Pr: **k**, *i*-Pr: **l**, *n*-Bu: **m**, *i*-Bu: **n**, *cyc*-Hex: **o**, Oc: **p**, Ph: **q**; R^2= Me, R^3= Ph: **r**; R^2= H, R^3= *t*-Bu: **s**, R^2= H, *n*-Hep: **t**, R^2= H, 4-Me-Ph: **u**)

were synthesized and tested to extend systematic studies of structure - reactivity relations in solvent extraction of Na(I), Mg(II), Ca(II), Sr(II), Ba(II), Ln(III) (Sc, Y, La...Lu), Hf(IV), Fe(II), Co(II), Ni(II), Pd(II), Cu(II), Ag(I), Au(III), Zn(II), Cd(II), Hg(II), Tl(I), Pb(II), and Bi(III).

RESULTS AND DISCUSSION

All these μ-imido compounds are Brønsted acids, HA or H_2A. Some acidity exponents pK_a were determined by potentiometric titration in ethylenglycole monomethylether/ water (4:1). The pK_a values are 2.4, 2.7, 2.8, 2.6, 2.8, 3.0, 3.0, 3.2, (2.2 and 10.8), 4.4, (2.4 and 9.4), and 9.9 for **1a**, **1b**, **1d**, **1e**, **2a**, **2b**, **2c**, **3a**, **3e**, **4**, **5**, **6e**, and **9**, respectively. The acidity of **1 - 6** increases with rising electronegativity of the substituents. Sulfur donor atoms decrease the acidity.

The tetraaryl esters of the derivatives of the μ-imido-diphosphoric acid form dimers via hydrogen bonds as shown by X-ray crystal structure analysis of **1a** [4] , **1b**, **2b**, **2c**, **2d** [5], and **3a** [6]. Dimers are also formed in nonpolar diluents. The dimerization constants K_{dim} were determined in benzene for some compounds (log K_{dim}: 3.3(3), 4.6(5), 2.8(5), 2.2(3) for **1a**, **1b**, **1d**, and **2a**, respectively). No dimerization was found for **3a** in benzene.

Most of the compounds **1-10** form neutral chelate complexes according to equation (1) and (2) by extraction of metal ions from aqueous solution.

$$M^{z+}_{(aq)} + z\,HA_{(org)} \rightleftharpoons MA_{z(org)} + z\,H^{+}_{(aq)} \quad (1)$$

$$M^{z+}_{(aq)} + z/2\,HA_{2(org)} \rightleftharpoons MA_{z(org)} + z\,H^{+}_{(aq)} \quad (2)$$

The mode of coordination is different. While Yb^{3+} is surrounded by six oxygen atoms in form of a slightly distorted octahedron in the complex with **1a** [7], Pd^{2+} and Ni^{2+} are coordinated via 4 sulfur atoms in a square planar complex with **3a** [6], and **10k** [8], respectively. Six-membered chelate rings are formed in both complexes. Four-membered chelate rings are observed in the square planar complex of Pd^{2+} with **2a**. However the coordination of the metal ion occurs via sulfur and nitrogen atoms [9]. Monovalent cations show an interesting self-organization effect. Oligomers with an inorganic nucleus (FIGURE 1) and an organic shell are formed. A three-nuclear copper(I) complex is yielded in the reaction of **10** with copper(II) [10]. Sodium forms with **1a** a six-nuclear complex in the crystal [11] as well as in benzene.

The slope analysis of the dependence of distribution ratios D on the concentration of HA in the organic phase and mineral acid in the aqueous phase shows that complexes MA_z are formed in the organic phase with Na(I), Mg(II), Ca(II), Sr(II), Ba(II), Ln(III) (Sc, Y, La...Lu), Fe(II), Co(II), Ni(II), Pd(II), Cu(II), Zn(II), Cd(II), Hg(II), Tl(I), Pb(II), and Bi(III). Silver yielded AgA(HA)[13].

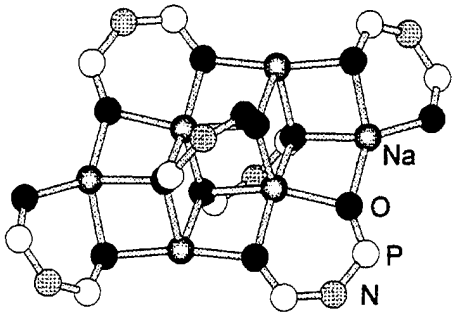


FIGURE 1 Nucleus of $\{Na[(C_6H_5O)_2PO]_2N\}_6$

The HSAB concept is reflected very well in the extraction of different metal ions in dependence on the set of donor atoms of the extractant. The strength of extraction of e.g. Ag(I) (see FIGURE 2) and Hg(II) decreases with the set of donor atoms SS > OS> OO. The corresponding sequences are OS > OO > SS, and OO >> OS > SS for Zn(II) and typical hard metal ions (e.g. rare earths, alkaline earth metals), respectively. For a given set the D values rises as a rule with increasing acidity of HA The highest strength of extraction was observed for silver. It is extracted quantitatively (log D > 4) from 1.0 M HNO_3 with **8**, even if the concentration of HA in the organic phase is only 10^{-7} M. D values decrease in the sequence of extractants **8** >> **3a** > **3e** > **10n** > **10r** >> **2b** > **2a** > **2d** >> **1b** > **6e**> **1a**. Steric hinderance results in different sequences of extractants for smaller and bigger metal ions (e.g.**1a** > **1d** > **6e** > **1b** > **2d** > **2c** > **2b** > **2a** > **3a** for Sc(III) and **6e** ≈ **4** > **5** > **1a** > **1d**>> **1b**> **3a** > **2c** > **3e** > **2a** for Ce(III). The small Sc^{3+} is not able to coordinate all the nine oxygen donor atoms of **6e**.) Distribution

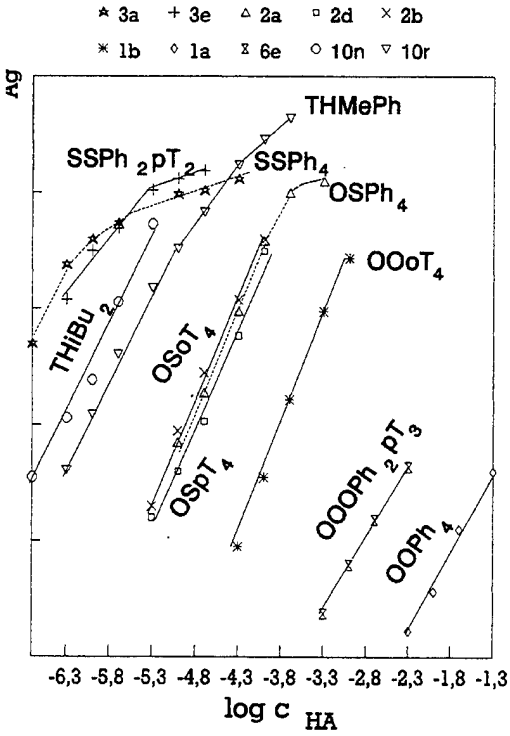


FIGURE 2 Log D of silver at 1 M HNO_3 vs. initial extractant molarity in benzene ($c_{Ag} = 6 \times 10^{-8}$ M)

ratios of rare earth ions drop as well as separation factors in the sequence **1a** > **1g** > **1h**.

The kind of the organic diluent has also a remarkable strong influence on the strength of extraction of e.g. Sc(III), Tm(III), and Eu(III) with **1a** or **10a** [14]. D values of e.g. Yb^{3+} drop under given conditions by four orders of magnitude using methyl-*iso*-butyl-ketone instead of benzene as a diluent for **1a**.

The results of this paper have shown, that the extraction behaviour of an organophosphorus compound depends on a lot of factors. Some of them are well understood. But it needs further investigations to obtain a more realistic picture for an aimed design of an extractant.

ACKNOWLEDGEMENTS

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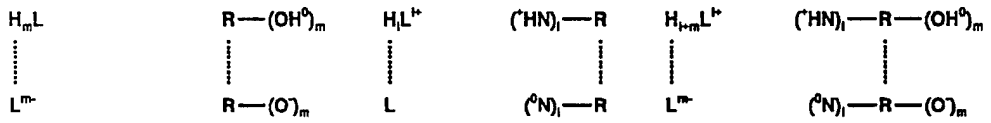
PROTONATION AND METAL COMPLEX FORMATION OF PHOSPHORUS CONTAINING ACIDS AND BASES

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Biorelevant acylphosphonic acids, phosphonocarboxylic acids, aminophosphonic acids and corresponding phosphinic acids give rise to interesting protonation and metal complex formation equilibria. Macroscopic stability constants are obtained by high precision PC-guided titration followed by iterative data evaluation. Additional informations on dynamically averaged structures of species involved in macroscopic equilibria, e. g. ion specific chemical shifts and coupling constants, are accessible via NMR-controlled titrations.

To understand these phenomena we will classify some model systems into 3 classes as shown below:

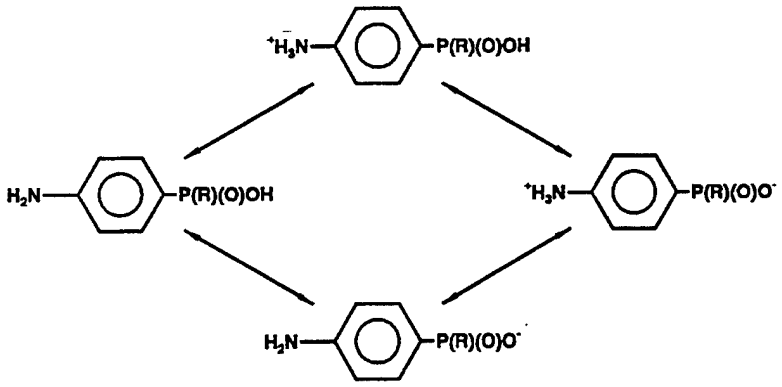
No.	Compound	Acid Type
1	$CH_3C(O)OH$	1 HL
2	$(CH_3)_2P(O)OH$	1 HL
3	$CH_3P(O)(OH)_2$	1 H_2L
4	$HO(O)(CH_3)PCH_2CH_2C(O)OH$	1 H_2L
5	$(HO)_2(O)PCH_2CH_2C(O)OH$	1 H_3L
6	NH_4^+	2 HL^+
7	$^+H_3NCH_2CH_2NH_3^+$	2 H_2L^{2+}
8	$^+H_2(CH_2CH_3)NCH_2P(CH_3)(O)OH$	3 H_2L^+
9	$^+H_3NCH(C_2H_5)P(O)(OH)_2$	3 H_3L^+
10	$^+H_3NCH_2CH_2P(O)(OH)_2$	3 H_3L^+
11	$^+H_3NC_6H_4P(O)(OH)_2$	3 H_3L^+



Type 1 **Type 2** **Type 3**

The protolytic equilibria of those acids involve the following species: Type 1: neutral acids ↔ anionic bases, Type 2: cationic acids ↔ neutral bases, Type 3: cationic acids ↔ anionic bases. Parallel observations of pH and NMR spectra of proto-

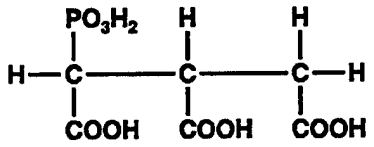
ves pH=f(V_b) or pH=f(τ), and the two-dimensionally correlated diagrams δ=f(V_b), δ=f(τ), δ=f(pH) obtained as stacked or contour plots. Technical details to hardware and software setup for NMR controlled titrations are given in [1]. Since the potentiometric measurement using a glass electrode and the NMR method as well is slow with respect to proton transfer in protolytic equilibria in general only the macroscopic dissociation constants are obtained from NMR controlled titrations. This is discussed together with underlying theory for model systems given in Table 1 above. For certain limiting conditions microscopic dissociation constants are accessible This is shown for compounds No. **4**, **8** and **9**. Recent interests are directed towards microscopic aspects of protolytic equilibria, e. g. such as:



Since the biological activities of these organophosphorus compounds and related structures will be influenced by the population of individual species shown in both schemes above it is imperative to inspect the microscopic equilibria by suitable methods. In addition to NMR techniques in favourable cases UV/VIS-controlled titrations (PHOTO_T) may lead to microscopic stability constants[2].

The formation of metal complexes is observed. Practical examples will involve aminophosphonic acids, e. g. Ciliatin **10**, and acylphosphonates obtained from the E. Breuer group in Jerusalem and FOSCARNET from K. Kellner, Halle.

Other practical applications of NMR controlled titrations are involved with the identification of reaction mixtures. As a typical problem from industrial chemistry[3] the five-basic 1-phosphono-propane-1,2,3-tricarboxylic acid is used:



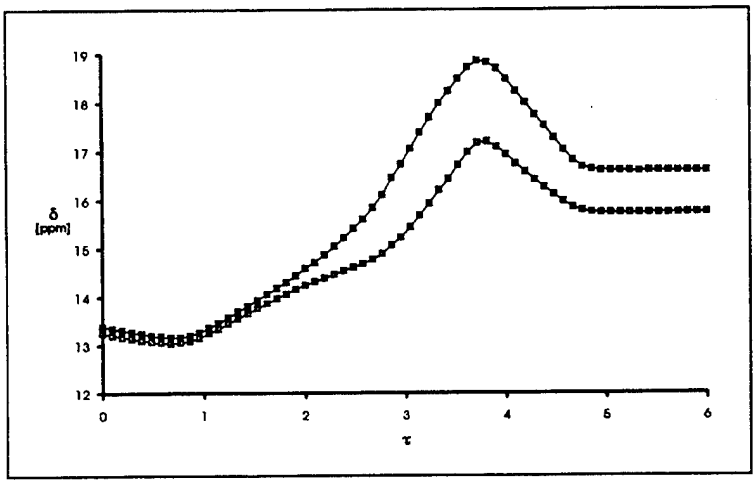


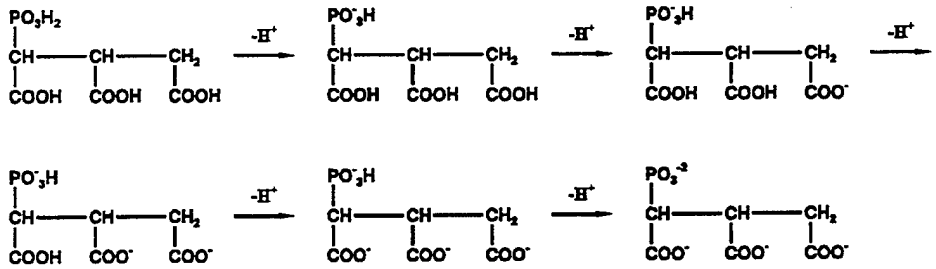
Figure 1: 81 MHz $^{31}P\{1H\}$-NMR controlled titration of H_5PPTC vs. NaOH. x-axis: degree of titration τ, x-min = 0, x-max = 6; y-axis: chemical shift δp [ppm], y-min = 12, y-max = 19.

Since carbon atoms C1 and C2 in PPTC are chiral, two specific forms (threo and erythro) are expected. Figure 1 clearly shows 2 phosphorus signals, but a stereospecific assignment is possible only by involvement of high resolution ^{1}H- and ^{13}C-NMR studies [2]. Analysis of data from NMR controlled titration yielded dissociation constants and ion specific chemical shifts for each form separately.

Parameter	Form 1	Form 2	Parameter	Form 1	Form 2
pK_S1:	1.36	1.18	$\delta p(H_5L)$:	15.99	16.88
pK_S2:	3.71	3.21	$\delta p(H_4L^-)$:	12.93	12.83
pK_S3:	4.95	4.26	$\delta pH_3L^{-2})$:	14.09	13.39
pK_S4:	6.55	6.77	$\delta p(H_2L^{-3})$:	15.76	14.61
pK_S5:	9.47	9.34	$\delta p(HL^{-4})$:	19.04	17.41
			$\delta p(L^{-5})$:	16.58	15.74

Table 2: Dissociation constants and ion specific chemical shifts δp [ppm] for the two epimeric forms of PPTC.

The most likely deprotonation sequence of PPTC is described in the following scheme:



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PROTONATION AND COMPLEXATION CONSTANTS OF PHOSPHONIC ACIDS WITH CATIONS OF ENVIRONMENTAL INTEREST

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Abstract Protonation and complexation constants of two phosphonic acids : nitrilotris(methylenephosphonic acid) (AMP) and 1-hydroxyethane-1,1'-diphosphonic acid (HEDP) were determined with different cations of environmental interest (Ca) and heavy metals (Cu(II), Zn, Ni, Cd, Pb). These equilibrium constants were calculated with the PKAS and BEST computer programs, with special attention to the uncertainty on the calculated values. Conditional complexation constants of AMP and HEDP with Cu(II) and Ca(II) were determined by ionometry. The insoluble HEDP complexes with Pb(II) and Cd(II) were identified and the corresponding solubility products determined.

Key Words : AMP, HEDP, heavy metals, calcium, complexation, protometry, ionometry.

INTRODUCTION

In this study, we determined protonation and complexation constants for two phosphonic acids : nitrilotris(methylenephosphonic acid) (AMP) and 1-hydroxyethane-1,1'-diphosphonic acid (HEDP) with different cations. These two phosphonic acids are used in detergents as builders, because of their complexing properties, especially the complexation with calcium and heavy metal cations.

The aim of this work is to study the potential mobilization of cations in river sediments. To calculate the cation speciation, the protonation and complexation constants of compounds present in water, such as AMP or HEDP, must be available. The cations studied here are those usually encountered in natural waters (Ca, Zn) and anthropogenic heavy metals (Cu(II), Ni, Cd, Pb).

The complexing properties of HEDP and AMP with many of these cations have already been studied, but there are quite large differences between these results. We determined these equilibrium constants with special attention to the uncertainty on the calculated values.

MATERIALS AND METHODS

AMP and HEDP were Fluka products, pure grade. Metal salts (nitrate) were pure grade compounds, the cation salt solutions were standardized with EDTA.

The equilibrium constants were calculated from the data obtained by potentiometric titrations performed at 25° C in 0.1 $mol.L^{-1}$ KNO_3 solution under a purified nitrogen stream.

pH titrations were carried out with a Metrohm automatic titrator model 716-DMS. The combined glass electrode was calibrated by titration with hydrochloric acid and sodium hydroxide solutions. The Martell and Motekaitis [1] computer programs were used to analyze the pH-metric data.

An Orion ionometer model 940SE was used with calcium and copper selective electrodes in the ionometric experiences. The ionometric titration data was exploited using the Buffle, Ruzic, and Scatchard methods [2].

DETERMINATION OF EQUILIBRIUM CONSTANTS

Protometry

The determination of the equilibrium constants needs to take into consideration different data :

* experimental data as concentrations, volumes, pH,
* theoretical data as water ionic product, activity coefficients.

The uncertainty of each one of these parameters leads to the uncertainty of the equilibrium constants.

Protonation constants These constants have been determined by using the PKAS computer program [1]. Differences between our results and those found in the literature [3] are small.

Complexation constants These constants have been determined by using the BEST program [1]. To determine these constants, one needs to take into account the parameters quoted above, but also the complexed cation species which may interfere. Speciation diagrams were used (SPE program [1]) to determine which hydroxide species could be neglected and at which pH value we can stop the exploitation, still considering all the phosphonic complex species. It appears that hydroxide species do not interfere with AMP, while the hydroxide/cation complexes cannot be neglected with HEDP.

The AMP complexation constants are close to those found in the literature [3] but there is a quite large difference in the case of HEDP complexation constants. Moreover, a better concordance between calculated and experimental pH values was obtained with AMP in comparison to HEDP.

Hydroxide/cation complexes interference complicates the determination of the complexation constants, particularly for HEDP, and surely is the cause of the difficulties to obtain a good concordance. The existence of other complexes, such as hydroxide/phosphonate/cation ternary complexes which could also interfere, might be an other possible reason for the difficulties to refine calculated pH to experimental pH.

Affinity with the different cations The equilibrium constants values and the titration curves point out the following order :

AMP : Cu (II) > Zn > Pb > > Cd > Ni >> Ca

HEDP : Cu (II) > Zn > > Cd > Ni > Ca

The affinity order for all the cations is the same for AMP and HEDP. The AMP complexing properties for each cation are higher than those of HEDP, particularly with copper and zinc (difference of six log units).

Uncertainty Each experiment was performed in triplicates and was reproduced three times. The standard deviation $\sigma(n-1)$ was calculated on all the results : the uncertainty is lower for the AMP equilibrium constants than for HEDP.

The complexation constants values for species present at higher pH are difficult to estimate accurately because of the interferences from hydroxide/cation complexes. In general it is difficult to assess data for the species representing less than 18 % on the speciation diagrams.

Ionometry

These experiments allowed to determine conditional complexation constants at a given pH. Calcium and copper ion selective electrodes were used at pH 3 and 5. Hydroxide precipitation problems did not allow to work at higher pH values.

These data were analyzed using the Buffle, Ruzic, and Scatchard methods [2]. There is quite good concordance between the results obtained with the three methods, and a good reproducibility of the results. These values confirm those obtained by protometry. AMP is more complexing than HEDP for both cations. Copper is better complexed than calcium for each phosphonate.

Carbonates

All the potentiometric experiments for Ca with HEDP or AMP were carried out under normal atmosphere. No difference was observed in comparison with those performed under nitrogen atmosphere. Under a normal atmospheric CO_2 partial pressure, carbonates do not interfere and the phosphonic acids behavior was not modified.

SPECIATION DIAGRAMS

We are interested in determining which are the dominating species in the pH range of natural waters (5 to 9), considering phosphonic acid and cation concentrations in our experimental conditions (2.10^{-3} mol.L^{-1}), and phosphonate concentrations closer to those found in natural waters (2.10^{-7} mol.L^{-1}), always keeping a phosphonate/cation ratio L/M = 1/1. Speciation diagrams for cations which have a comparable affinity with a phosphonate (Cu, Zn and Pb ; Ni and Cd) have the same type of dominating species.

At the experimental concentration, ML is the dominating species in any case and MHL is also significant in the case of AMP. At lower concentration, the dominating species are the same for AMP whereas free metal and ML are the dominating species for HEDP.

INSOLUBLE COMPLEXES

Precipitates of HEDP with Cd and Pb were characterized [4]. Polarography experiments confirmed by electronic microscopy examinations showed that the insoluble complex stoichiometries are : CH_3-C(OH)$(PO_3)_2Pb_2$ and CH_3-C(OH)$[PO_2(OH)]_2$Cd.

A kinetic study shows that the HEDP-Pb complex solubility is 5.10^{-7} mol.L^{-1} (after 8 days) whereas the HEDP-Cd complex solubility is $4.8.10^{-4}$ mol.L^{-1} (after 15 days).

CONCLUSION

This study points out that AMP, brought by domestic detergents, will contribute to the mobilization of cations in river sediments more than HEDP.

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COMPLEXES OF AMINOALKYLPHOSPHONIC ACIDS AND PHOSPHONODIPEPTIDES WITH Pt(II) AND Pd(II)

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Abstract Complexing properties of aminomethylenephosphonic acid and dipeptides glycyl-aminomethylenephosphonic acid and both diastereoisomers of (*S*)-methionyl-1-aminoethylphosphonic acid with Pt(II) and Pd(II) were investigated pH-metrically at 25 °C and at ionic strength of 0.1 mol dm^{-3} (KNO_3). The stability constants calculated indicate formation of the complexes with a metal : ligand molar ratio of 1 : 1 and 1 : 2. The differences found for diastereoisomers are much higher than for systems with common dipeptides. Distribution of all species found by potentiometry were confirmed by ^{31}P and ^{1}H NMR titrations.

INTRODUCTION

Aminoalkylphosphonic acids and their dipeptides with terminal aminoalkylphosphonic acid have obtained much interest due to biological activity and coordination ability. The coordination ability of the acid was intensively investigated and even a few papers were focused on the phosphonodipeptides [1]. Except NMR study of coordination ability of the aminoalkylphosphonic acid with Pt(II) and Pd(II) [2], all papers have been focused on the hard transition metals.

The aim of the present paper was to determine the stability formation constants of aminomethylenephosphonic acid (Amp), glycyl-aminomethylenephosphonic acid (GlyAmp) and *S,S* and *S,R* diastereoisomers of (*S*)-methionyl-1-aminoethylphosphonic acid (MetAmp).

RESULT AND DISCUSSION

The stability formation constants determined in the systems $[PdCl_4]^{2-}$ or $[PtCl_4]^{2-}$ - Amp or phosphonodipeptide are listed in Table I. The stability formation constants of Pt(II) and Pd(II) chlorocomplexes were taken from ref. [3] .

Distribution diagrams of Amp with Pt(II) and Pd(II) are shown in Fig. 1. From the distribution diagrams and from Table I, it is evident, that both the metals form complexes with metal : Amp molar ratio = 1:1 and 1:2. Pd(II) starts to form the protonated 1:1 complexes below pH = 2 and consequently, after deprotonation of phosphonic group the non-protonated species. The 1:2 complexes were determined as the major species in this system. I addition to the hydroxo complexes found in alkali region, a dimeric hydroxo-complexes were determined at about pH 4.

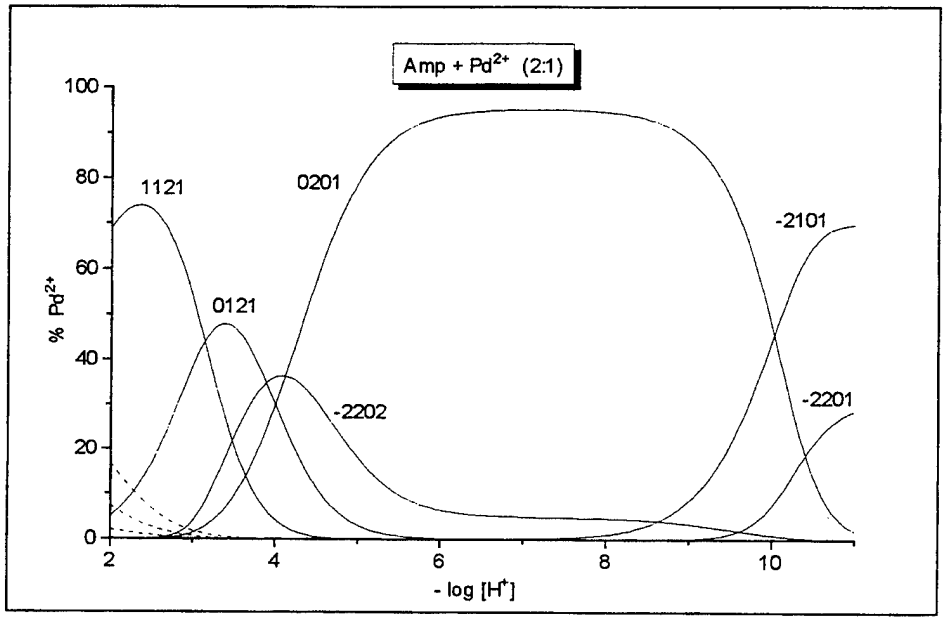
TABLE I. Stability formation constants (log β_{pqrss})

$H^+ L^{2-} Cl^- Pd^{2+}$	Amp	GlyAmp	SS-MetAep	SR-MetAep
1 1 2 1	24.66(1)	24.48(9)	-	-
0 1 1 1	21.52(1)	-	-	-
0 1 1 1	-	21.35(6)	-	-
-1 1 1 1	-	17.35(7)	-	-
-2 1 0 1	4.93(3)	9.70(7)	-	-
-3 1 0 1	-	0.48(7)	-	-
-2 2 0 2	30.51(5)	-	-	-
2 2 0 1	-	-	35.35(2)	35.01(2)
1 2 0 1	-	-	29.14(3)	28.71(3)
0 2 0 1	27.70(2)	27.50(6)	21.99(3)	21.54(3)
-1 2 0 1	-	-	12.88(5)	12.85(4)
-2 2 0 1	6.89(6)	12.11(7)	2.85(5)	2.67(4)
-4 2 0 1	-	-8.2(1)	-	-

$H^+ L^{2-} Cl^- Pt^{2+}$	Amp	GlyAmp	SS-MetAep	SR-MetAep
1 1 2 1	22.67(9)	23.14(3)	-	-
0 1 2 1	19.55(1)	-	-	-
0 1 1 1	-	17.72(2)	-	-
-1 1 1 1	-	11.93(2)	-	-
-2 1 0 1	0.70(5)	2.00(4)	-	-
-3 1 0 1	-9.9(1)	-7.90(6)	-	-
-2 0 2 2	-	-	-	-
2 2 0 1	-	-	37.27(3)	36.56(2)
1 2 0 1	-	-	30.99(4)	30.16(3)
0 2 0 1	22.28(2)	-	23.70(4)	22.92(3)
-1 2 0 1	-	-	15.21(5)	14.23(4)
-2 2 0 1	3.40(5)	3.9(1)	5.74(5)	4.65(4)
-4 2 0 1	-	-15.8(1)	-	-

Chloro-complexes of Pt(II) are more stable than the Pd(II) analogous species and therefore, a formation of Pt(II) complexes with Amp starts at higher pH range. Two dominant species 0121 and 0201 were found in this system. As well as in the Pd(II)

system, in the Pt(II) system the hydroxo-complexes were also determined. Comparison of Amp-Pd(II) system with the system Amp-Pt(II) we can see that Pd(II) prefers 1:2 complexes and Pt(II) 1:1 complexes, probably due to higher stability of the chloro-complexes.



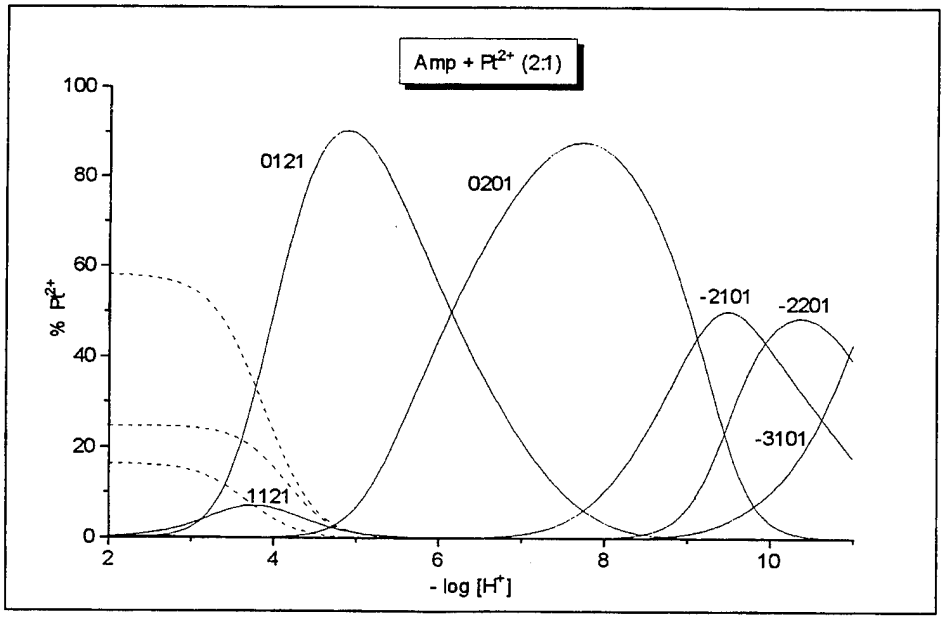


FIGURE 1 Distribution diagrams of Pd(II) and Pt(II) with Amp.
(- - - represents $[MCl_{4-n}(H_2O)_n]^{n+2-}$ species)

GlyAmp $H_2NCH_2C(O)NHCH_2PO_3H_2$ is a tridentate ligand. The ligand can be coordinated to a metal through amine, peptide-amide and phosphonic groups. This way of coordination was found in both Pd(II) and Pt(II) systems. The same tendency at formation of 1:1 and 1:2 complexes as in Amp series was observed in the GlyAmp systems. In the alkali-region, several types of hydroxocomplexes were determined. Both diastereoisomers of MetAep $CH_3SCH_2CH_2CH(NH_2)C(O)NHCH(CH_3)PO_3H_2$ form only 1:2 complexes and are coordinated to the both metals through sulfur and amino groups in acid and neutral region of pH. In alkali region the coordination through amine and peptide-amide groups were confirmed.

Complexes of Pd(II) and Pt(II) are kinetically stable and, thus, a presence of these species determined potentiometrically could be confirmed by ^{31}P and ^{1}H NMR titrations. The NMR titrations were done at concentration 0.15 $mol.dm^{-3}$, *e.g.* the concentration was 15 times higher than for the potentiometry titrations. In spite of that, the NMR titrations confirmed the potentiometrically found species and their distribution in acidic and neutral region of pH. At higher pH than 9, the same species were observed, however, their distribution was different. If the potentiometric titration was done at the same concentration as the NMR titrations, we found very good agreement of both used method.

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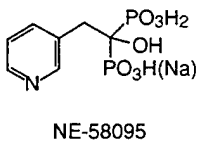
Elucidation of a Pharmacophore for the Bisphosphonate Mechanism of Bone Antiresorptive Activity

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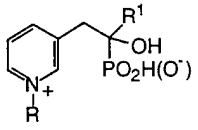
Abstract Our recent discoveries in the field of phosphonate bone antiresorptive agents include analogs of the pyridine containing bisphosphonate NE-58095 (Risedronate) such as the pyridinium bisphosphonate NE-10575, the pyridine phosphonocarboxylate NE-10790, and the pyridine phosphonophosphinate NE-10864. We believe these analogs differ at key recognition sites in the putative cellular pharmacophore and thus offer important structure-activity learnings.

INTRODUCTION

The structure-activity relationships of the bisphosphonate series of bone antiresorptive agents continue to be intriguing to the medicinal chemist. The work of several laboratories has now demonstrated the importance of basic nitrogen moieties in the design of potent drugs.[1] For example, we have studied the pyridyl class of bisphosphonates, such as Risedronate (NE-58095), in preclinical models,[2] and as a useful agent in the clinic for the treatment of osteoporosis.[3] We have also previously reported new modifications at the P-C-P moiety, which is known to be the primary chemical function responsible for bone affinity. Coupled with the growing biochemical evidence indicating cellular involvement, these structure-activity relationships suggest the bisphosphonate (BP) antiresorptive mechanism *in vivo* involves both bone targeting and a subsequent specific cellular recognition event.[4]



NE-58095



R = H, $R^1 = PO_3H_2$, NE-58019
R = CH_3, $R^1 = PO_3H_2$, NE-10575
R = H, $R^1 = CO_2H$, NE-10790
R = H, $R^1 = PO_2H(CH_3)$, NE-10864

FIGURE 1. Risedronate and Several Key Phosphonate Derivatives.

RESULTS AND DISCUSSION

Understanding the Nature of the BP-Nitrogen Pharmacophore

We have been interested in better characterizing the key elements of the putative BP cellular pharmacophore. For example, what type of interaction is occurring at the nitrogen binding site? Previous evidence suggested that a basic nitrogen was required for high potency in these molecules. Recently, we hypothesized that the protonated form of nitrogen was optimal in the pharmacophore (i.e.,

NE-58019). Thus, it could be interacting in an electropositive form through a coulombic attraction to an electronegative binding site. Therefore, a quaternized nitrogen functionality such as a pyridinium species should be an effective or improved moiety at the nitrogen site on the bisphosphonate molecule. To test this hypothesis, NE-10575 (Figure 1), the methyl pyridinium analog of NE-58095 was synthesized.

NE-10575 was synthesized through standard aqueous methylation conditions from Risedronate and methyl iodide.[5] and evaluated in the growing rat or Schenk Model.[2] Since the potency observed for NE-10575 (lowest effective dose (LED) = 0.0001 mg P/kg) was similar to that of Risedronate (0.0003) this rationale for the design of a potent new bisphosphonate was a success. In fact, since NE-10575 also demonstrated reduced bone affinity *in vitro* vs. Risedronate (NE-58095), we may have designed an analog with significantly improved cellular activity.

From this initial finding in the pyridyl series, we initiated the synthesis of several pyridinium analogs derived from a range of known pyridyl bisphosphonates with varying potency. We reasoned that if a structure-activity correlation existed, it would be likely that the pyridinium series was deriving its antiresorptive potency from the same cellular mechanism by utilizing the same nitrogen binding interaction as the pyridyl series. Figure 2 lists the series studied to initiate this comparison, with the corresponding antiresorptive potency reported in parentheses (LED in mg P/kg).

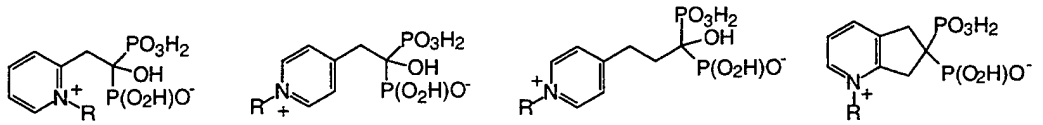


FIGURE 2. Lowest Effective Doses for a Variety of Substituted Pyridinium Bisphosphonic acids.

As demonstrated in Figure 2, potent pyridine containing BP's maintained high levels of potency when converted to the corresponding pyridinium analogs. This also included tolerance of more bulky, longer chain pyridinium species, such as NE-10447. Also, the two pyridinium examples derived from low potency BP's, NE-10335 and NE-10295, led to correspondingly low potency pyridinium analogs. Thus, this preliminary evidence suggests the pyridinium series is in fact involving the same antiresorptive mechanism as the parent pyridyl series.

Recent Analysis of the P-C-P moiety

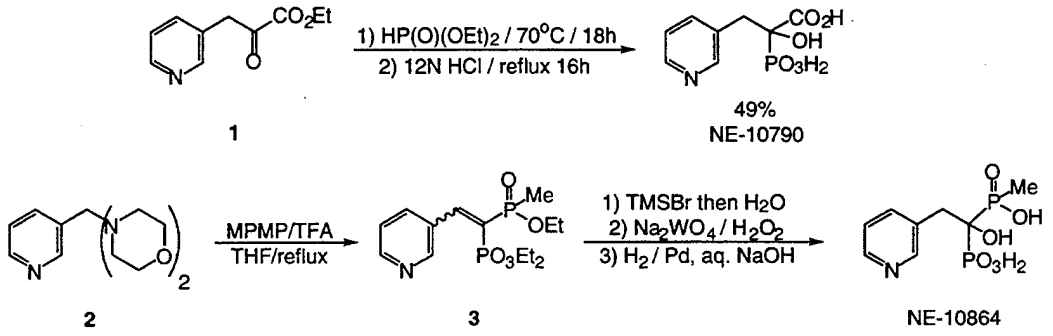
We have also studied, in more depth, the SAR of the P-C-P moiety of the bisphosphonates.[6] In recent years, with the evolution of more potent analogs, this moiety has been associated with the physicochemical mechanisms of accumulation of drug on the bone (hydroxyapatite) surface.[7] Based on new *in vitro* evidence, we now believe the phosphonate moieties of bisphosphonates have more than just a targeting function.[8,9]

Two new classes of phosphonate analogs with lower affinities for hydroxyapatite than bisphosphonates have been designed and studied. These are the pyridylethane hydroxy-phosphonocarboxylate (PC) and pyridylethane hydroxyphosphonomethylphosphinate, (PAP) analogs of Risedronate, NE-10790 and NE-10864, respectively (Figure 1).

The synthesis of NE-10790 was initiated with the condensation of pyridine 3-carboxaldehyde and N,N-dimethylglycine ethyl ester to give the α-ketoester reported (**1**) by Horner and Reuth[10] in suitable yield. Reaction of **1** with 4.5 equivalents of diethylphosphite at 70°C for 18 hours afforded the phosphonocarboxylate triethyl ester as an impure, viscous syrup in 78% yield. Acid hydrolysis in boiling concentrated HCl overnight led to a 49% yield (from **1**) of 2-hydroxy-2-phosphono-3-(3-pyridinyl)propanoic acid (NE-10790).

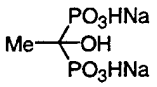
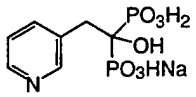
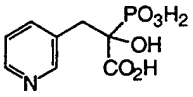
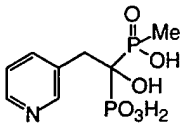
The synthesis of NE-10864 was began with the interesting acid mediated condensation of pyridylaminal **2** with methylenephosphonomethylphosphinic acid triethyl ester (MPMP) in 41% yield.[11] Vinyl bisphosphonate **3** was converted to the desired NE-10864 in the 3 step hydrolysis (99%), epoxidation (52%), and hydrogenation (61%) sequence shown in Scheme 1.

SCHEME 1



In our previous studies in the fetal rat long bone *in vitro* antiresorptive assay,[8] the potency of earlier low affinity, PAPs were devoid of any activity in these organ culture models at concentrations up to 5 mM. The phosphonocarboxylate (NE-10790) analog of Risedronate also displayed low bone affinity, but its antiresorptive activity was similar to that of an early generation bisphosphonate, etidronate, with an IC_{50} of around 50 μM. The PAP analog of Risedronate, NE-10864, which represents the first member of this class reported with a central geminal P-C-P carbon OH substituent was found to have bone affinity similar to or slightly higher than that of NE-10790. Although it is now the first PAP to demonstrate some antiresorptive activity *in vitro,* its activity (200 μM) is reduced compared to the corresponding PC, NE-10790 (Table 1). Thus, molecules differing in the structure of the phosphonate moiety, but with similar affinities for hydroxyapatite, and with the same nitrogen containing side chains, demonstrated markedly different antiresorptive effects. These findings provide additional evidence that the phosphonate moiety, beyond determining the affinity of the molecule for mineral surfaces, plays a key role in the pharmacophore of the cellular mechanism(s) of the bisphosphonate class of compounds.

TABLE 1. Antiresorptive Activity (*in vivo*-entry 1, *in vitro*-entry 2) of Bisphosphonates and Low Affinity Phosphonates.

				
	Etidronate BP	**Risedronate BP (NE-58095)**	**NE-10790 PC**	**NE-10864 PAP**
LED (mg P/kg)[1]	**1.0**	**0.0003**	**1.5**	**-**
IC_{50} (10^{-6}M)[7]	**30-50**	**3.5**	**50**	**200**

CONCLUSION

The alkylated/quaternized pyridinium analogs of Risedronate and other pyridine containing bisphosphonates have been discovered to be potent antiresorptive agents *in vivo*. Preliminary studies indicate a correlation between the structure-activity relationships of the pyridine and pyridinium bisphosphonates suggesting that these new analogs inhibit bone resorption through similar cellular mechanisms. The P-C-P moiety, in addition to its role as a bone targeting function, also appears to be important in the molecular mechanism by which bisphosphonates affect cell function.

ACKNOWLEDGMENTS

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NOVEL BISPHOSPHONATES FOR CALCIUM-RELATED DISORDERS

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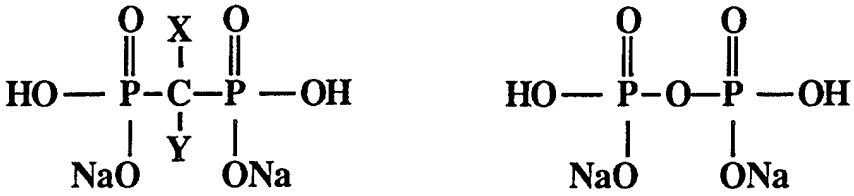
Abstract Bisphosphonates are drugs used clinically in various calcium-related disorders such as Paget's disease, hypercalcemia of malignancy, and tumor osteolysis and are undergoing clinical trials for osteoporosis. From the results obtained in various clinical studies using conventional bisphosphonates, it appears that there is a need for compounds with a greater margin between the inhibition of bone resorption and the inhibition of mineralization, without an accompanying increase in toxicity, and at the same time, improved oral bioavailability without gastrointestinal side effects. One research strategy to address these problems is the synthesis and evaluation of non-geminal bisphosphonates, bisacylphosphonates. It is concluded that a new generation of calcium-binding compounds with antiresorptive and anticalcification properties have been obtained. In comparison to clinically used bisphosphonates, the new compounds possess very low toxicity and improved bioavailability.

Key Words: Bisphosphonates, calcium-related disorders, osteoporosis, calcium, calcification, hypercalcemia

INTRODUCTION

Bisphosphonates are a class of drugs developed about 25 years ago that can be considered stable analogs of pyrophosphate (P-O-P), a physiological regulator of calcification and bone resorption [1]. They are characterized by a non-hydrolyzable P-C-P bond. All bisphosphonates (BP's) are disodium salts of the tetraacids with a molecular weight of ~250 daltons, see Figure:

Geminal bisphosphonate Pyrophosphate



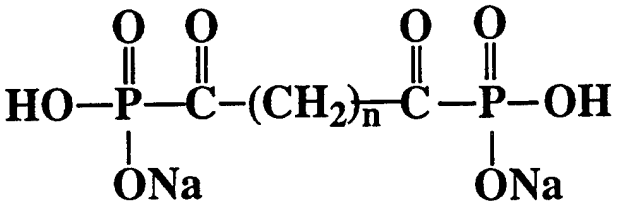
X = OH, Y = CH_3, Etidronate
X = Cl, Y = Cl, Clodronate
X = OH, Y = $(CH_2)_2$ - NH_2, Pamidronate
X = OH, Y = $(CH_2)_3$ - NH_2, Alendronate

A number of such geminal BP's have been approved for clinical use in Paget's disease and hypercalcemia of malignancy, and recently for clinical use in osteoporosis [2, 3, 4, 5]. BP's, like other bone seeking agents, are irreversibly trapped with calcium in sites of new bone formation, a property that underlies their use as bone scanning agents. However, their precise cellular and biochemical mechanisms of action are not fully understood. The inhibitory effect of BP on bone resorption has principally been attributed to a direct action on osteoclasts [6] or to an indirect action through the mediation of osteoblasts. [7] The pharmacologic basis for structure-related differences in potency among the BP's is not completely understood, but it is evident that BP's with an amino group in the side chain or in a heterocyclic ring are the most potent *in vivo*. It is expected that different modes of activity i.e., inhibition of resorption and/or mineralization, and toxic effects are dependent on the structure of the functional groups [8]. An initial requirement for BP's activity is the binding of the compound through its oxygens to bone's hydroxyapatite (HAP) enabling localized pharmacologically active concentrations in the bone [9] . It was postulated that the side-chain of a geminal bisphosphonate is of critical importance for the cellular activity.

RESULTS and DISCUSSION

It had been believed that non-geminal BP's P-$(C)_n$-P with $n \geq 2$ were inactive [1]. However, we found recently [10, 11, 12, 13] that non-geminal BP's with hydroxyimino and especially with keto groups at α positions relative to the

phosphonic groups are active as anticalcification and antiresorption agents (see structures below).



n = 4, AdBP; n = 5, PiBP
n = 6, SuBP; n = 7, AzBP
n = 8, SeBP; n = 10, DoBP

Several *in vitro* and *in vivo*, experimental models were utilized in order to characterize the activity of bisacylphosphonates: 1) inhibition of hydroxyapatite (HAP) formation, 2) inhibition of HAP dissolution, 3) inhibition of the pathological calcification of bioprosthetic tissue implanted subdermally in rats, 4) inhibition of bone resorption in rats, 5) toxicity studies, and 6) bioavailability and disposition. In the models of HAP formation (pH-stat, stable and metastable solutions of calcium-phosphate) pamidronate is more active than AdBP, the most potent bisacylphosphonate, as well as other bisacylphosphonates with longer alkyl chains [13]. In the model of inhibition of HAP dissolution AdBP has comparable activity to that of pamidronate, while the other bisacylphosphonates are inferior. This ranking of activity correlates with the moderate antiresorptive activity of bisacylphosphonates, exhibited in the young intact rat model [8, 13]. The bisacylphosphonates were found highly active in inhibiting the calcification of bioprosthetic tissue implanted subdermally in rats [10, 11, 13]. Tissue calcification was completely inhibited by AdBP, PiBP, SuBP and pamidronate.

Structure-activity-relationship studies revealed that the keto groups in α positions to the phosphonic functions render activity. The BP's with shorter alkyl chains are highly active in the various models studied. General requirements for activity in both geminal- and non-geminal BP's are 2 phosphonic functions (1 or 4 are inferior), and activity was exhibited only when at least three ionizable groups are present in the molecule (the diesters were inactive). Finally, the calcium salt/complexes of bisacylphosphonates are more soluble than the corresponding geminal BP's. This unique characteristics probably responsible for the improved oral bioavailability of bisacylphosphonates, 10 to 20 times higher than that of geminal BP's [14, 15].

CONCLUSION

It appears that there is still a need for compounds with a greater margin between bone resorption inhibitory activity and that of mineralization, without an accompanying increase in toxicity, and at the same time, improved oral bioavailability without gastrointestinal side effects.

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EFFECTIVENESS OF AN EARLY OSTEOPROTECTIVE ADMINISTRATION OF BISPHOSPHONATES AGAINST TUMOR INDUCED OSTEOPATHY AND BONE METASTASES. EXPERIMENTAL FINDINGS

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Abstract. Using the rat model of tumor osteolysis after i. a. injection of tumor cells of the WCS 256 B systemic or local stimulation of bone metabolism (1,25 D_3, fracture trauma) enhances number and progression of tumor osteolysis. This increase can be reduced, when bisphosphonates (BPs) APD and Cl_2MBP are given before, with or after tumor cell injection. A direct inhibitory effect of the BPs on tumor cell proliferation can be excluded. In vitro tumor cell proliferation of the WCS 256 B can be enhanced, when bone conditioned media of fetal rat calvaria after stimulation with PTH are used. This increase can be abolished, when PTH is given together with Cl_2MBP but not with calcitonin. Our studies indicate that the prophylactic administration of BPs not only reduces the progression of tumor osteolysis but also impairs bone dependent tumor cell proliferation. These results are a strong argument for an early preventive administration of BPs in patients with a high risk for the development of bone metastases.

Key Words: bone metastases, bisphosphonates, osteoprotection

INTRODUCTION

As the majority of cancer patients die of the sequelae of metastases, it is clinically important to diagnose the metastases early and to treat or prevent the metastatic tissue and organ destruction. With respect to bone we have to answer the question whether an early pharmacological osteoprotection by osteoclast inhibiting drugs can retard or avoid tumor induced bone destruction and reduce the incidence of bone metastases.

EXPERIMENTAL STUDIES

When tumor cells of the Walker carcinosarcoma are injected into the aorta of rats, osteolytic tumor cell foci of the metaphyses of long bones develop, leading to complete osseous destruction and epiphysiolysis within 10 days. Histolocical examination shows that an abundant number of osteoclasts has been activated by tumor cells, which destroy the bone tissue in the vicinity to tumor cell foci. Systemic enhancement of bone metabolism for instance by 1,25 vitamin D_3 will enlarge the number and extent of osteolytic foci within the skeleton; local activation of bone metabolism by fracture trauma will increase the incidence of blood borne tumor cell foci at the site of trauma (Krempien et al. [4]).

The tumor induced bone destruction will markedly decrease when bisphosphonates are given to the animals showing a close dose dependency. Calcitonin however has been shown to be ineffective in this model of tumor osteolysis. Bisphosphonates when given prophylactically prior to the administration of tumor cells not only reduce the extent of bone destruction but also diminish the number of osteolytic foci within the skeleton (Krempien et al. [5]). However, the osteoprotective potential of the bisphosphonates decreases, when the therapy free intervall between administration of the compounds and tumor cell inoculation increases (Krempien et al. [3]). Our results clearly demonstrate that bisphosphonates have strong osteoprotective potentials and can prevent the development of bone metastases. These properties can be demonstrated both after therapeutical and prophylactical administration. These results are remarkable because bisphosphonates have been shown to pocess no direct effect on tumor growth. Therefore indirect effects must be involved.

We therefore proposed the hypothesis that bisphosphonates evolve their preventive effect on bone metastases by influencing the amount of growth factors, which have been shown to be locally released from the bone matrix by the activity of osteoclasts (Magro et al. [6], Orr et al. [7]). In order to the answer the hypothesis, we used the in vitro model of the 21 day old fetal rat calvaria and produced different kinds of bone conditioned media by stimulation of bone metabolism with PTH or inhibition by the bisphosphonate Cl_2MBP or calcitonin. Bone matrix resorption as measured by the

number of osteoclasts was markedly enhanced by PTH. When PTH was given together with Cl_2MBP this increase of osteoclastic activity was completely abolished, but calcitonin given together with PTH had no effect. Tumor cells of the Walker carcinosarcoma 256 B, which were grown in bone conditioned media of PTH stimulated calvaria, show a significant increase of proliferation in comparison to tumor cells, which had been cultivated in control media of unstimulated calvaria. Again calcitonin was not able to suppress the PTH dependent stimulation of tumor cell growth (Bu and Krempien, [1]).

CONCLUSIONS

According to these in vitro results tumor cell proliferation depend on bone metabolism and can be increased by stimulation or be decreased by inactivation of osteoclasts. Thus we draw the conclusion that the amount of matrix derived growth factors, which are available within the bone conditioned media determine tumor cell growth effectiveley. Bisphosponates but not calcitonin are capable of indirectly reducing tumor cell growth by influencing the breakdown of the bone matrix.

The therapeutic significance of the bisphosphonates is based on their rapidly beginning, selective and prolonged strong inhibition of osteoclasts (Fleisch [2]), which bestowes them a unique superiority over other osteoclast inhibititing drugs. There is now good experimental evidence that bisphosphonates after preventive and protective administration will reduce the development and progression of tumor osteolysis due to their obvious osteoprotective potential. The value of preventive clinical use of these compounds in tumor patients has to be seriously considered. The late diagnosis of osseous metastases means that valuable time is lost for antiosteolytic therapy with bisphosphonates.

In conclusion our experimental data represent a strong argument for an early osteoprotective administration of bisphosphonates to those patients at a high risk for developing bone metastases.

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NEW ANTI-INFLAMMATORY/ANTI-ARTHRITIC HETEROCYCLIC BISPHOSPHONATES

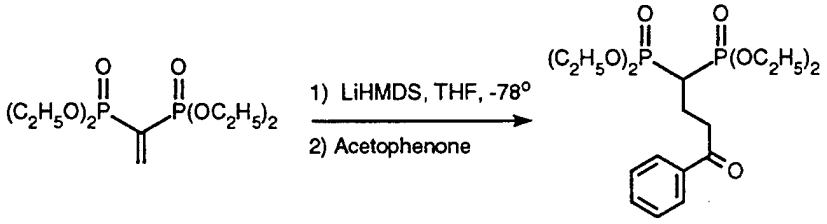
Richard A. Nugent*, Colin J. Dunn, Nigel D. Staite, Michael J. Murphy, Stephen T. Schlachter, Danielle G. Aspar, Sharon K. Shields, and Louise A. Galinet
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Abstract. In the course of research toward a safe and effective treatment for rheumatoid arthritis, we identified new pyrazolo[1,5-a]pyrimidine and 4-pyrimidinone bisphosphonate esters, which are potent inhibitors of a murine model of chronic, cutaneous inflammation (delayed type hypersensitivity granuloma) and a murine antigen induced arthritis model. **9a** has EC_{30} values of 0.01 and 0.005 mg/kg respectively and represents a new class of antiinflammatory/antiarthritic bisphosphonate ester.

Key Words: Bisphosphonate esters, antiarthritic, antiinflammatory, delayed type hypersensitivity, antigen induced arthritis

INTRODUCTION

Bisphosphonic acids are potent antihypercalcemics with utility in therapeutic areas which involve abnormal calcium metabolism, such as Paget's disease, multiple myeloma of bone, and osteoporosis.[1] In addition, bisphosphonic acids are thought to be useful in the control rheumatoid and osteoarthritis. We have described the anti-inflammatory and anti-arthritic properties of ketonic bisphosphonate esters, such as **1**,[2] which are synthesized from **2**[3] and acetophenones. Since bisphosphonate esters do not bind bone and have weak or no effect in bone resorption assays, their anti-inflammatory activity appears to be unrelated to direct effects on calcium metabolism. We continued to search for other reactive methylenes which, with **2**, yield novel anti-inflammatory and anti-arthritic compounds.



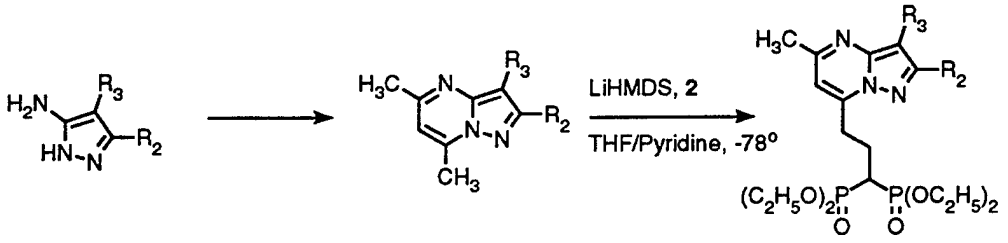
2 **1**

CHEMISTRY

Pyrazolo[1,5-a]pyrimidine Bisphosphonate Esters

The ring system was constructed by reacting a suitably substituted nitrile with triethylorthoacetate (or benzoate), then with hydrazine to give an amino pyrazole **3**. This was condensed with 2,4-pentanedione to yield the pyrazolo[1,5-a]pyrimidine **4**.

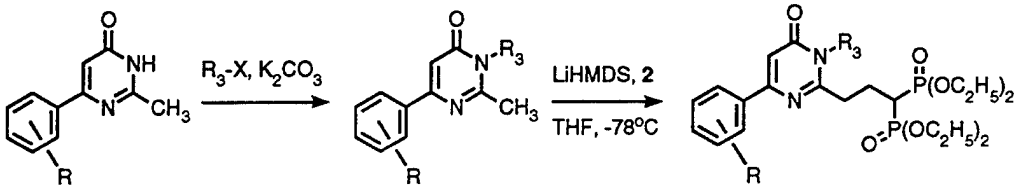
Attempts to deprotonate **4** with LiHMDS in THF at -78°C gave only an incomplete reaction. The problem was found to be the insolubility of **4** in THF at -78°C, but with the addition of pyridine as co-solvent, **4** completely deprotonated and added to give **5**.



3 **4** **5**

4-Pyrimidinone Bisphosphonate Esters

4-Pyrimidinones were synthesized by treating the appropriate β-keto ester with acetamidine to give **6**. Alkylation of the ring nitrogen with an alkyl halide and K_2CO_3 in methanol yielded **7**, though large alkyl groups gave more O-alkylation. **7** was successfully deprotonated with LiHMDS in THF at -78°C, then treated with **2** to give **8**.



6 **7** **8**

RESULTS AND DISCUSSION

Delayed-Type Hypersensitivity Granuloma

The pyrazolopyrimidines were initially screened in a model of chronic inflammation, the delayed type hypersensitivity granuloma (DTH-GRA).[4,5] **5a-h** gave significant inhibition at the standard dose of 10 mg/kg (Table I). The data indicate that methyl is preferred at C-2 over phenyl while bromine and iodine (**5g-h**) are preferred at the C-3 position. In further studies, **5a** was found to have an EC_{30} of 0.1 mg/kg.

TABLE I

Cmpd	R_2	R_3	% Inhibition (10 mg/kg)[6]	mp (°C)	Cmpd	R_2	R_3	% Inhibition (10 mg/kg)	mp (°C)
5a	Me	CN	46	49-50	**5e**	Ph	H	47	51-52
5b	Me	Br	44	oil	**5f**	Ph	Cl	23	66-68
5c	Me	NO_2	41	oil	**5g**	Ph	Br	31	46-48
5d	Ph	CN	26	107	**5h**	Ph	I	53	81-82

4-Pyrimidinones were also investigated in the DTH-GRA (Table II), where we studied two changes to the pyrimidinone ring, modification of the aromatic ring at C-6 and of the alkyl group at N-3. Introducing alkyl groups at either the 3 or 4 position of the phenyl group (**8b-c**) had little effect, but an electron withdrawing group, **8d**, dramatically reduced the activity. Electron donating groups at the 4 position gave mixed results (**8e-g**), but the data show that activity increases with increasing size. Varying the alkyl group at N-3 gave mixed results (**8a**, **8h-j**), but methyl appeared to be preferred. The EC_{30} for **8a** was determined to be 0.01 mg/kg.

TABLE II

Cmpd	R	R_3	% Inhibition (10 mg/kg)[6]	mp (°C)	Cmpd	R	R_3	% Inhibition (10 mg/kg)	mp (°C)
8a	H	Me	60	83-84	**8f**	4-OEt	Me	46	94-96
8b	3-Me	Me	40	90-91	**8g**	4-NMe_2	Me	63	92-94
8c	4-Me	Me	38	90-92	**8h**	H	Et	12	79-81
8d	3-CF_3	Me	6	77-79	**8i**	H	n-Pr	41	oil
8e	4-OCH_3	Me	22	81-83	**8j**	H	Bn	17	72-74

Antigen Induced Arthritis (AIA)

The pathology of AIA involves an initial intense inflammatory synovitis followed by chronic inflammation and severe erosion of articular cartilage and subchondral bone, resembling human rheumatoid arthritis.[7] **5a** and **8a** were tested for their ability to control soft tissue inflammation, pannus formation, and cartilage and bone erosion. **5a** has an EC_{30} of 10 mg/kg, while the EC_{30} of **8a** was 0.005 mg/kg.

CONCLUSION

The DTH-GRA and AIA models have been successfully controlled only by steroids, potent immunosuppressive agents, and bisphosphonates. The bisphosphonate ester **8a**, which has EC_{30} values of 0.01 and 0.005 mg/kg respectively, is the most potent bisphosphonate found so far in these assays and offers the potential to successfully treat inflammatory joint disease in man.

EXPERIMENTAL SECTION

(3-(3-Cyano-5-methyl-2-phenyl-pyrazolo[1,5-a]pyrimidin-7-yl)-propylidene)-bisphosphonic acid tetraethyl ester **5d**. The pyrazolopyrimidine **4d**[8] (621 mg, 2.50 mmol) in pyridine (5.0 ml) at 0°C was treated with LiHMDS (1M in THF, 2.6 ml, 2.6 mmol) and stirred for 30 min. The deep red solution was treated with **2** (750 mg, 2.50 mmol) in THF (0.5 ml). After stirring for 1 hour at 22°C, the reaction was poured onto 10% HCl and extracted 3x CH_2Cl_2. The organics were washed with 1N HCl, $NaHCO_3$, and NaCl, dried with $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by chromatography (CH_2Cl_2, CH_2Cl_2/acetone 9:1, then 1:9) to give **5d**:

600 mg (1.09 mmol, 49%), mp 107°C (methyl t-butyl ether); ^{1}H NMR ($CDCl_3$) δ 8.2 (m, 2 H), 7.5 (m, 2 H), 6.86 (s, 1 H), 4.2 (m, 8 H), 3.54 (t, J = 7.3 Hz, 2 H), 2.68 (s, 3 H), 2.5 (m, 3 H), 1.32 (m, 12 H); IR (mull) 2212, 1624, 1556, 1413, 1393, 1250, 1241, 1072, 1046, 1027, 980, 965, 849, 763, 699 cm^{-1}; MS (EI) *m/z* (rel. intensity) 548 (M+, 12), 301 (12), 289 (11), 288 (99), 261 (43), 260 (9), 233 (11), 218 (7), 177 (7), 152 (29); Anal. Calcd for $C_{25}H_{34}N_4O_6P_2$ x H_2O: C, 53.00; H, 6.40; N, 9.89. Found: C, 53.05; H, 6.49; N, 9.92.

(3-(2-(3-Methyl-4-oxo-6-phenyl-4(3H)-pyrimidinyl))-propylidene)bisphosphonic acid tetraethyl ester, **8a**. To a solution of LiHMDS (1.0 M in THF, 83 ml, 83 mmol) at -78°C was added dropwise a solution of **7a**[9] (15.0 g, 75.0 mmol) in THF (50 ml). After stirring for 30 min at -78°C, **2** (24.75 g, 82.5 mmol) was added and the reaction warmed to 22°C for 1 hour. The reaction was quenched with NH_4Cl, then extracted 3x EtOAc. The organics were washed 2x NaCl, dried with $MgSO_4$, and concentrated *in vacuo*. The crude was recrystallized to give **8a**: 29.1 g (58.1 mmol, 78%), mp 85-86°C (methyl tert-butyl ether); ^{1}H NMR ($CDCl_3$) δ 8.02 (m, 2 H), 7.45 (m, 3 H), 6.81 (s, 1 H), 4.20 (m, 8 H), 3.59 (s, 3 H), 3.22 (t, J = 7.2 Hz, 2 H), 2.83 (tt, J = 23.7, 6.5 Hz, 1 H), 2.58 (m, 2 H), 1.34 (m, 12 H); IR (mull) 1668, 1571, 1551, 1441, 1257, 1240, 1218, 1077, 1034, 1012, 982, 969, 840, 804, 704 cm^{-1}; MS (EI) *m/z* (rel. intensity) 500 (M+, 19), 363 (19), 301 (15), 288 (18), 240 (6), 214 (19), 213 (99), 200 (8), 68 (18), 44 (8); Anal. Calcd for $C_{22}H_{34}N_2O_7P_2$: C, 52.80; H, 6.85; N, 5.60. Found: C, 52.55; H, 6.73; N, 5.53.

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TRANSITION STATE ANALOGS FOR CATALYTIC ANTIBODIES

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ABSTRACT

The first antibodies that behave as enzymes (abzymes) appeared in the literature almost ten years ago and in the intervening years abzymes have been made that catalyze a variety of reactions, including ester hydrolysis, carbonate hydrolysis, amide hydrolysis and aminolysis. It would be useful to have available an enzyme that catalyzes the hydrolysis of organophosphorus anticholinesterases (OPA Hydrolase). Such enzymes are ubiquitous in nature, but are generally very inefficient.One approach to the development of an improved OPA Hydrolase is to produce an abzyme with this activity. This involves the synthesis of a pentacoordinate (trigonal bipyrimid) transition state analog that is stable enough to be attached to a protein carrier and then remain in the body of an animal long enough to elicit antibodies. It is apparent that this is not a simple matter; the only elements that have pentavalent forms are in the vanadium or nitrogen families. While some of those compounds are trigonal bipyramids they are universally unstable in water. Today's challenge is to find ways to make pentacoordinate transition state analogs that can be attached to protein carriers and have a reasonable lifetime in an aqueous environment.

The idea that enzymes differ from antibodies primarily by virtue of the fact that antibodies bind the ground state of their "substrates" while enzymes are designed to bind transition states was first noted by Pauling nearly 50 years ago (1). While that was an interesting observation it was largely ignored for two decades until Jencks suggested that selected reactions could be promoted if antibodies could be found that would stabilize the rate-controlling transition state (2). Again, this was an interesting proposal that could not be practically implemented until a homogeneous population of antibodies could be developed. This key step was taken by Kohler and Milstein (3) with the development of *in vitro* monoclonal antibodies, a population of antibodies with a single, specific molecular structure that could be grown in large numbers.

Thus, by 1975 the tools were available to test the hypothesis that antibodies could be produced that would act as catalysts, and in 1986 Tramontano in Lerner's lab (4) and Pollack in Schultz's lab (5) described the first catalytic antibodies, the former designed to catalyze the hydrolysis of an ester and the latter taking advantage of a natural antibody to catalyze the hydrolysis of a particular carbonate that has a structure similar to the natural ligand. Since that time the field has grown rapidly. There are now reports in the literature of abzymes with novel specificities and reaction mechanisms ranging from hydrolysis of esters and amides to oxidations, isomerization and β-elimination. The

development of a specific abzyme appears to be particularly useful to catalyze those reactions for which there are no natural enzymes.

Several years ago we conceived the idea of protecting soldiers against nerve agent poisoning by pretreating them with scavengers that would reside in the blood stream for an extended period of time. The best candidates were proteins which would be able to neutralize nerve agents between the time of exposure and their arrival at their target molecule. This concept was proven by treating animals with enzymes. Administration of certain enzymes, e.g. butyrylcholinesterase (6), which are known to react very rapidly and irreversibly with nerve agents, followed by exposure to soman, sarin or VX produced protection. It was shown that both rodents and nonhuman primates could tolerate several LD_{50} doses of these nerve agents without measurable side effects when so treated. Furthermore, pretreatment of mice with an OP hydrolyzing enzyme protected them against at least twice the dose of soman that was lethal to all controls (7). Obviously, the catalytic scavenger has many advantages over the stoichiometric scavenger, but there are no OP hydrolyzing enzymes in nature that are efficient enough to afford the required protection at reasonably low doses. One proposal for developing an adequate enzyme is the production of a catalytic antibody, compatible with the human body, that will catalyze the hydrolysis of the organophosphorus nerve agents (8).

While the concept of making catalytic antibodies against nerve agents is attractive, there are several difficulties to be resolved in its accomplishment. The most important of these is the design and synthesis of appropriate haptens that approximate the transition state for organophosphate hydrolysis. While easily made tetrahedral phosphorus compounds are reasonable transition state analogs for carbon chemistry, the transition state for organophosphate hydrolysis is probably pentacoordinate, and presumably, based on what is known about enzyme inhibition kinetics (9), a trigonal bipyrimid [Fig 1.]. This is a problem. Pentacoordinate phosphorus compounds are highly unstable,

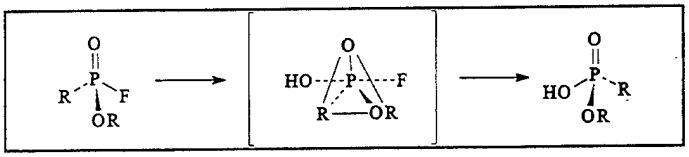


Fig. 1. The generally accepted formation of a trigonal bipyrimidal transition state from the tetrahedral ground state of pentavalent phosphorus compounds upon attack by a nucleophile.

particularly in aqueous solutions. Dr. Moriarty has experienced some success at increasing the stability of such compounds (10) (c.f. Moriarty et al., this volume) but to do so he had to add bulky groups [Fig.2]. As can be seen in the model, that bulk might prevent recognition of the geometry around the phosphorus and thus make it very difficult to obtain antibodies that will catalyze the hydrolysis of organophosphorus esters or acid anhydrides.

Transition State Analogs

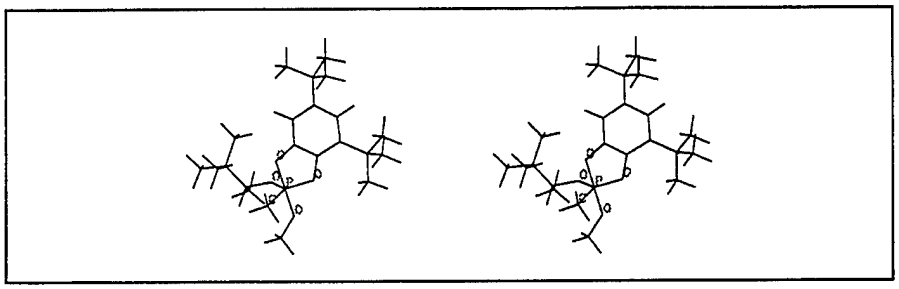
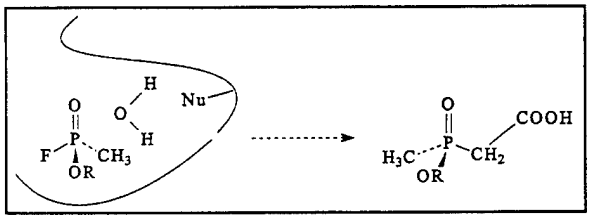


Fig 2. Three dimensional structure of a pentacoordinate transition state analog, stabilized by ring formation and bulky substituents.

One proposal for getting around the instability of pentacoordinate phosphorus transition state analogs was to use a different element that could form the same, trigonal bipyrimidal geometric configuration. Unfortunately, there are very few elements (only those in the Nitrogen or Vanadium series plus a few rare earths) that have pentavalent forms and fewer that have been shown to form trigonal bipyrimids. Furthermore, most of the pentacoordinate organic compounds of these elements are even more unstable than the phosphorus compounds. Dr. Crans and others, notably Ray et al. (11) and Wlodawer et al.(12), have circumvented this difficulty by making coordinate complexes with vanadium that approximate specific transition state structures. Dr. Crans will elaborate on those ideas (Crans, this volume).



3. Schematic design of a bait-and-switch hapten for phosphate ester/anhydride hydrolysis. Note stereospecificity requirements for this hydrolysis scheme. If specific binding sites for R and -OR' groups are induced in the antibody attention must be given to the chirality of the hapten.

Another strategy for eliciting catalytic antibodies, not dependent upon a transition state analog, has been termed "bait and switch". This mechanism involves the design and synthesis of haptens that have the ability to elicit in the antibodies specific combining site residues that might act as chemical groups in catalysis [Fig. 3.]. As can be seen in the figure, the ideal hapten presents both orienting binding sites and an appropriately positioned polar group so that in at least some of the resulting antibodies there will be a nucleophilic center that will be able to catalyze the hydrolysis of the organophosphorus compound. Only one such clone is needed; it can then be expanded into large colonies and its gene isolated. Once the gene of a catalytic molecule is in hand it can be

manipulated to change specificity and other characteristics. It should be pointed out that, in the case of the bait-and-switch hapten, it is necessary to consider the chirality of the desired substrate. In the case of soman, for example, only the $P_{(R)}$ isomers are highly toxic; the others are relatively poor cholinesterase inhibitors (13). If it is desired to destroy the toxic isomers preferentially it would be advantageous to know the absolute configuration of the target substrate and to construct a hapten with the same configuration.

Finally, the "best" hapten would be one that combines transition state stabilization with induction of a catalytic site, thus mimicking the best enzymes. This is a challenge for phosphorus synthesis chemists; it is easy to determine what is needed, but more difficult to synthesize the desired structure. I hope that our discussions in this meeting will produce strategies to attempt the construction of these difficult structures and will ultimately result in a catalytic antibody that will catalyze the rapid destruction of organophosphorus nerve agents. That would be a genuine contribution to world safety.

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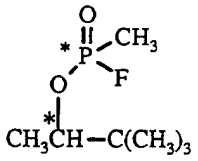
SYNTHESIS OF PENTACOORDINATE PHOSPHORUS HAPTENS FOR CATALYTIC ANTIBODY PRODUCTION. BAIT AND SWITCH CONCEPT

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Abstract: Our objective is to obtain monoclonal antibodies which will catalyse the hydrolysis of phosphorus-based nerve agents. Our syntheses followed three strategies. The first was synthesis of stable pentacoordinate phosphoranes as haptens for the production of monoclonal catalytic antibodies based on the transition state for phosphonate hydrolysis. The second approach is based upon the potential addition of water to the phosphorus atom of a tetracoordinate fluorine containing phosphate to yield an intermediary pentacoordinate system. In the third approach the "bait and switch" concept was used.

INTRODUCTION Our research effort has been directed towards obtaining a monoclonal catalytic antibody against the nerve agent soman (1). The toxic effects of soman (1) result from irreversible inhibition of acetylcholinesterase(AChE) caused by phosphonylation of the active serine unit. [1] Blockage of the AChE activity results in continuous firing of nerves in the affected cholinergic systems leading to fatality by a number of causes the most prominent being respiratory collapse. [2a-c] Strategies for protection against soman (1) use pretreatment with a reversible cholinesterase inhibitor such as carbamate as in the case of physostigimine, in which case the carbamylated enzyme protects a pool of AChE from phosphonylation by soman (1).[3a-e] Another approach involves use of pyridinium oximes nucleophiles to dephosphonylate the AChE ester.[4a-b] A novel approach towards protection against soman (1) is creation of a monoclonal antibody against this molecule, which could act as a scavenger, or as a catalyst for its hydrolysis.[5a-b] Soman (1) possesses two chiral centers, one at carbon and the other at phosphorus. The various stereoisomers show different rates of inhibition of cholinesterases and overall toxicity.[6,7]



C_RP_R, C_RP_S, C_SP_R, C_SP_S,

1

PRESENT RESEARCH

a) Unsymmetrically Substituted Chiral Monocyclic Oxyphosphoranes.

Our design concept for generation of a hapten for production of a catalytic monoclonal antibody against soman (1) is based upon the mechanism of hydrolysis of soman (1), i.e. addition of water to the tetracoordinate tetrahedral phosphorus to yield a pentacoordinate intermediate or transition state analog. Figure 1 shows the pentacoordinate intermediate and the bridging functionality necessary for stabilization of the phosphorane.

In Figure 2 this design concept is translated into a transition state hapten which possesses all the requisite structural features.

Figure 1

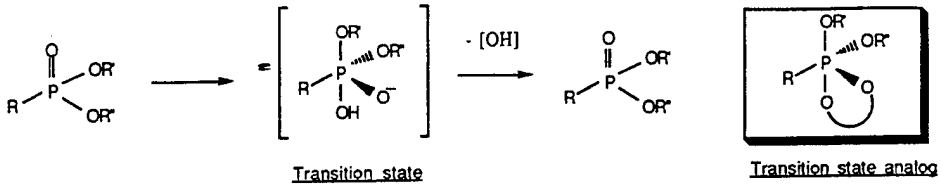
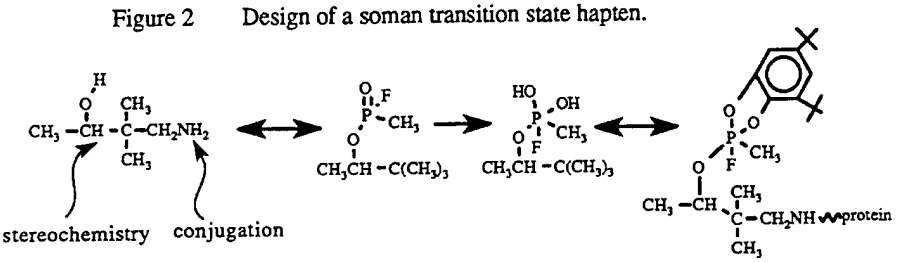
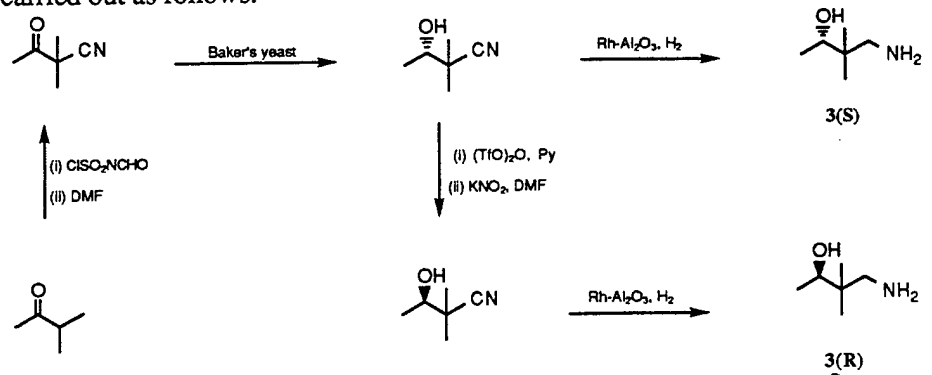


Figure 2 Design of a soman transition state hapten.

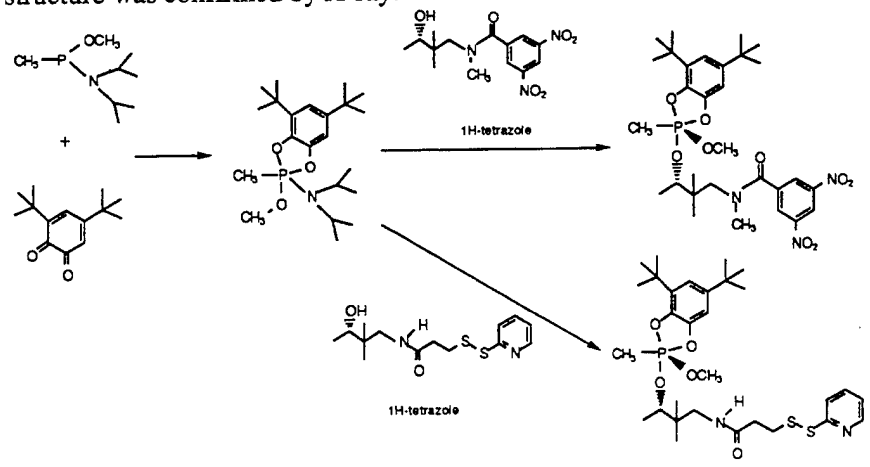


The synthesis of the stereoisomeric 2-aminomethyl-3(*R*) and (*S*)-hydroxybutanes was carried out as follows:



Bakers yeast reduction of the ketone yielded the *S* alcohol[8] and inversion of configuration of the neopentyl type alcohol using appropriate methodology was carried out.[9] The P-F bond of soman as well as the phosphorane in Fig. 2 was substituted by a P-OCH_3. Thus the *R* and *S* alcohols were each phosphonylated using $CH_3P(O)(OCH_3)Cl$ and all four diastereomers separated and characterized by X-ray crystallography. These then were correlated with the separate stereoisomers of soman using NMR spectroscopy.[10]

The synthesis of the pentacoordinate phosphorane hapten is shown below, and the structure was confirmed by X-ray.[11,12]



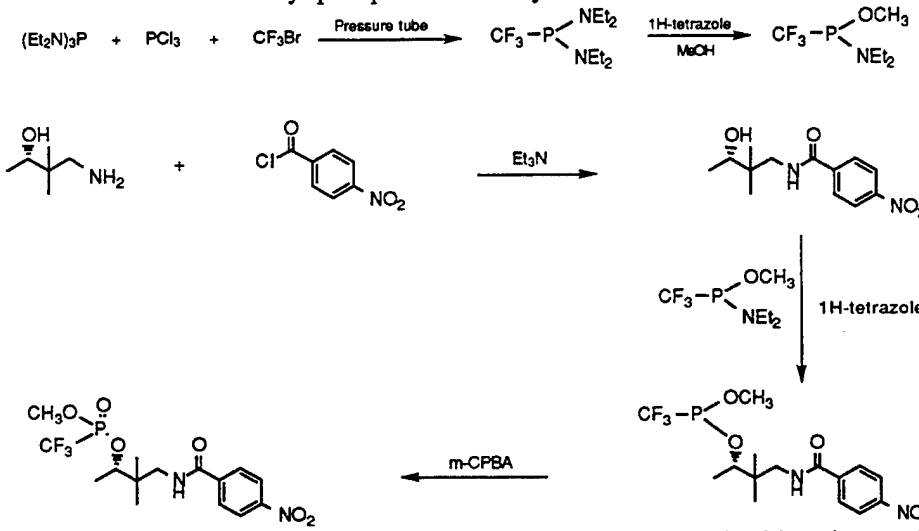
The phosphorane hapten was conjugated to the three carrier proteins BSA, KLH and PTG at three hapten:carrier ratios.

(b)Fluorine-Containing Haptens

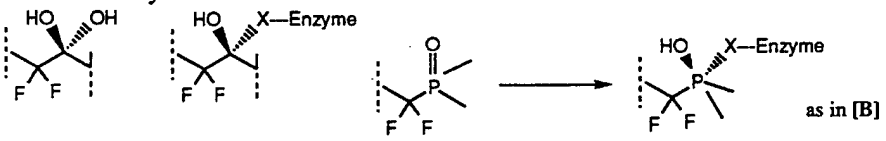
Trifluoromethyl Phosphoranes.

Unsymmetrically substituted monocyclic oxyphosphoranes discussed above were stable in neutral and in basic aqueous solution but were unstable under aqueous acidic conditions. This instability led to the formation of a phosphonate from the phosphorane presumably via initial protonation of the phosphorus-oxygen bond. Replacement of CH_3-P by CF_3P was reasoned to decrease the stability of the phosphonium intermediate.

The trifluoromethyl phosphorane was synthesized as follows:

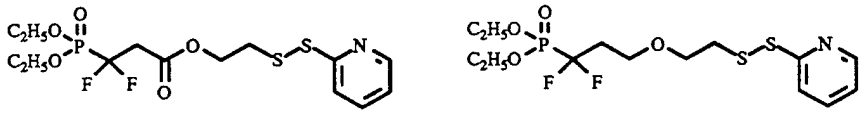


A further interest in the P-CF_3 systems attaches to the idea that a phosphonate possessing the P-CF_3 might be prone to hydration to yield a pentacoordinate phosphorane of the type $(RO)_2$ P-$CF_3(OH)_2$. This approach is based upon analogy with hydration of difluoromethylene ketones.



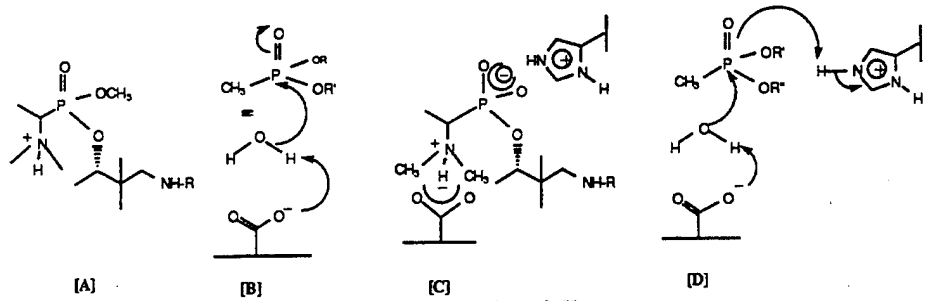
[A] [B]

The following fluorinated haptens were synthesized:



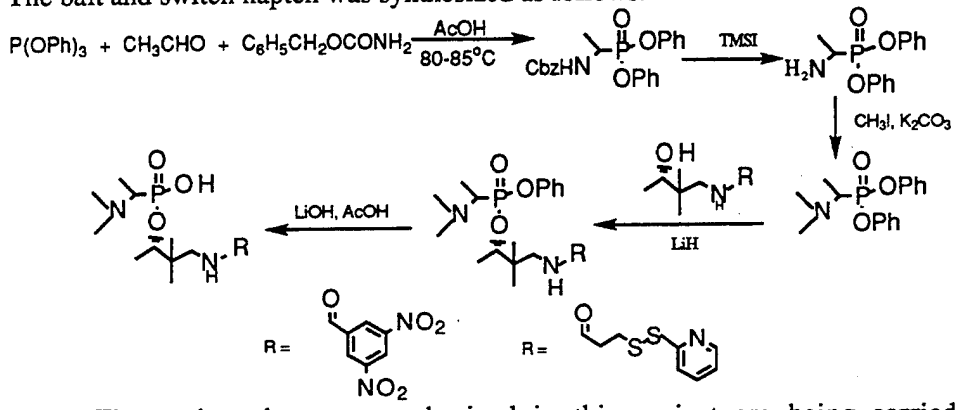
(c) Bait and Switch

Enzymatic catalysis involves binding of a substrate, in order to reduce entropy and also arrange reaction centers in the substrate with complementary reactive groups at the active site of the enzyme. Not only is the distance between the reaction center of the substrate and the complementary group on the enzyme critical, but also stereochemistry and orientation of interacting orbitals. In the case of hydrolysis of a phosphonate intermediates B and D may intervene. Hapten A may induce the complementary acid-base centers as in C.



[A] [B] [C] [D]

The bait and switch hapten was synthesized as follows:



The various haptens synthesized in this project are being carried through immunological studies.

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Synthesis of Stable Spirooxyphosphoranes - Potential Promoters of Catalytic Antibodies

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Abstract Bis-[*ortho*-carboxyaryl]- and bis[*ortho*-amidoaryl]methylphosphine oxides, in acidic medium, spontaneously cyclodehydrate to give trigonal bipyramidal (TBP) spirodioxy- and azoxyphosphoranes, respectively. Regioselectivity with a few nucleophiles and electrophiles, unexpectedly, accompany some of their reactions. Their structural similarity to pentacoordinate intermediates, obtained on the hydrolysis of organophosphorus (OP) poisons, and their stability at the physiological pH, renders them, as transition state analogs (TSA), useful promoters of catalytic antibodies.

Key Words Dioxyphosphoranes, azoxyphosphoranes, transition state analogs, trigonal bipyramids, regioselective reactions, catalytic antibodies.

INTRODUCTION

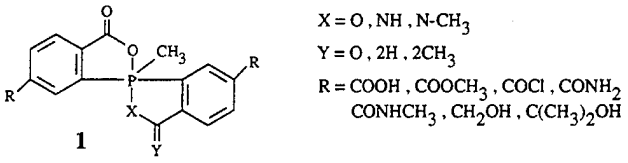
The concept of inducing monoclonal antibodies (Ab) that catalyze hydrolysis reactions, has its roots in pioneering reports published by Schultz[1-2] . Designing TSA's intuitively requires the inclusion, in the hapten, of electronic and structural aspects residing in the actual substrate[3] . Recently, it was demonstrated that mice, immunized with a protein conjugate of a TBP TSA, produced Ab that enhanced the hydrolysis of phosphonates, including soman[4]. Pentacoordinate P-hydroxyphosphoranes, postulated to be intermediates or transition states in non-enzymic or enzymic hydrolysis reactions of tetracoordinate phosphorus[5] , are usually unstable[6] . Modelling such a TBP structure, for mimicking transition states of OP poisons (sarin, soman), requires the challenging synthesis of pentavalent hydroxyphosphoranes that would be stable in aqueous environment. Efficient Ab, produced by that route, are expected to compete with AChE on its deactivation by OP toxicants and significantly enhance their rate of hydrolysis.

RESULTS AND DISCUSSION

Synthesis

In attempting to prepare dioxyphosphoranes and incorporate functional groups comprised

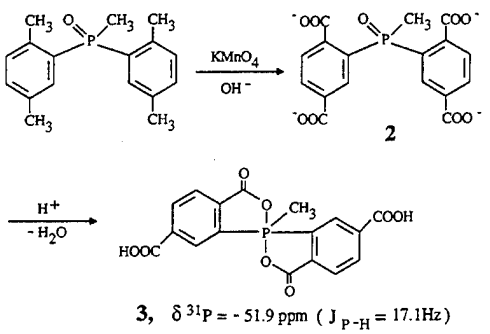
in OP poisons, we synthesized compounds **1** (scheme 1). Stable oxyphosphoranes **1** were obtained on spontaneous cyclodehydration of *ortho*-carboxyarylmethylphosphine oxides **2**, in acid, as outlined in scheme 2 for phosphorane **3**.



Scheme 1. Spirooxy- and azoxyphosphoranes

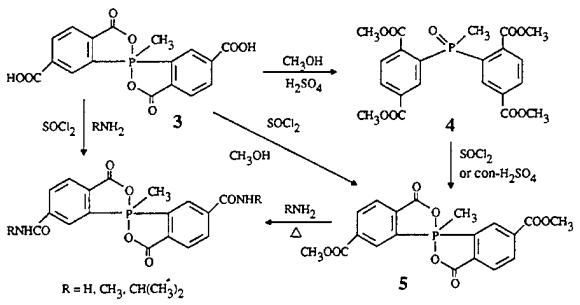
Structure and reactivity

The geometry around the phosphorus atom was directly elucidated using ^{31}P NMR spectroscopy. Thus, the chemical shifts of tetrahedral phosphine oxide analogs of **2** ($\delta\ ^{31}P \sim +25$ppm) significantly shifted upfield ($\Delta\delta = \sim 75$ppm) on conversion to **3**. Likewise, the coupling constant for the P- CH_3 in phosphine oxides **2** (J=13Hz), is considerably higher in phosphoranes (J=17Hz), indicating an equatorial preference for the orientation of the P-methyl in the TBP structure **3**. Being the most electronegative atoms, the two oxygens take preference in occupying the diaxial position[7]. On dissolving in aqueous base (pH 9), phosphorane **3** reverts to phosphine oxide **2**. Surprisingly, on attempted esterification, in refluxing CH_3OH, diacid-phosphorane **3** quantitatively yields tetraester **4** rather than diester **5** (scheme 3), providing a unique way for synthesis of **4**.



Scheme 2. Preparation of a P-methyldioxyphosphorane

Thus, an alternative route for the synthesis of diester-phosphorane **5** is refluxing diacid **3** in $SOCl_2$, followed by methanolysis (scheme 3). Unexpectedly, refluxing tetraester **4** in $SOCl_2$, or dissolving in concentrated H_2SO_4, regioselectively leads to phosphorane **5** while the other two arylesters at *meta*-position to phosphorus, remain intact.



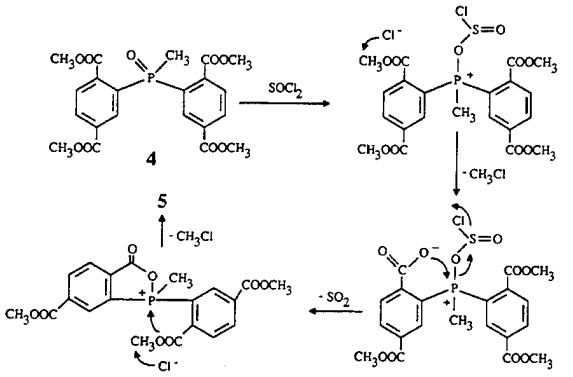
Scheme 3. Esterification and amidation reactions for phosphorane 3

A suggested mechanism is depicted in scheme 4, indicating that regioselectivity is achieved on initial electrophilic thionyl chloride attack at the phosphoryl oxygen, followed by loss of CH_3Cl from within the reaction cage. A similar mechanism was postulated for the $COCl_2$ chlorination of an ^{18}O-alkyl labelled phosphinate ester, whereupon labelling was retained in the ultimate product as ^{18}O=P[8].

Enhanced reactivity towards phosphorus ester

Most intriguing is the reaction of diester-phosphorane **5** with CH_3MgBr. Even with considerable large excess of the reagent (8 or 14 fold), the only product isolated was

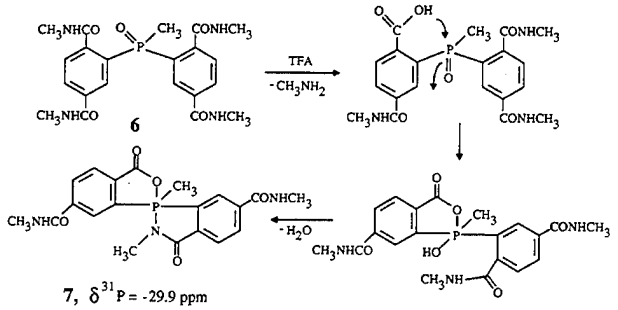
phosphorane **1** {X=O, Y=2CH_3, R=$C(CH_3)_2OH$} with one ester group remaining intact. With 4-fold excess of the reagent, reaction preferably takes place at the phosphorus ester with an ultimate product resulting from reaction at a single ester group. Regioselectivity was also demonstrated with $LiAlH_4$ reduction of phosphorane **5**. Thus, only phosphorane **1** (X=O, Y=2H, R=$COOCH_3$) was isolated with two fold excess of the reagent.



Scheme 4. Regioselective chlorination of 4 leading to diester-phosphorane 5

Azoxyphosphoranes

Tetraamidate **6**, in trifluoroacetic acid (TFA), exclusively leads to azoxyphosphorane **7**, suggesting a reaction route outlined in scheme 5.



Scheme 5. Synthesis of azoxyphosphorane 7 from tetraamidate 6

The initial formation of a carboxyaryl, due to reaction with TFA, affords the first phospholane ring. Subsequent elimination of H_2O from the intermediate, leads to diamido-phosphorane **7**, expressing, again, a regioselecte reaction. The molecular asymmetry in azoxyphosphorane **7** (as opposed to dioxyphosphoranes) is reflected in its ^1H and ^{13}C NMR spectra (Fig.). The aryl protons show up as 6 non-equivalent protons(^1H), along with 4 non-equivalent carbonyls(^{13}C), of which, two are split (J=2.7Hz), due to their proximity to the phosphorus atom.

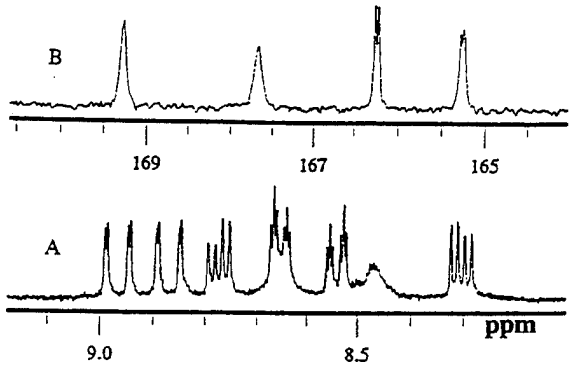


Fig. Partial ^1H aromatics (A) and ^{13}C carbonyls (B) NMR spectra of phosphorane **7**.

Stability in aqueous solutions

The hydrolytic stability of the phosphoranes, at various pH values, was measured by monitoring their ^{31}P NMR spectra in aqueous solutions, comprising 10% DMSO as a cosolvent. All of the dioxyphosphoranes were stable and only converted to the corresponding phosphine oxides at pH > 8.5. Therefore, the spirodioxyphosphoranes are expected to be stable at the physiological pH. In that respect, the azoxyphosphoranes convert to the corresponding phosphine oxides at pH 7.4 and are, thus, unusable as haptens.

Summary

Spirodioxy- and azoxyphosphoranes were obtained on spontaneous conversion of tetrahedral phosphine oxides to TBP in acidic environment. Regioselective electrophilic and nucleophilic reactions were demonstrated on attempted synthesis of some of these phosphoranes. Enhanced reactivity at the ArCOOP moiety, rather than the other aryl ester moiety, was observed with certain nucleophiles. Excluding azoxyphosphoranes, the dioxyphosphoranes were found to be stable at the physiological pH. Although far from an assumed acyclic TBP intermediate structure and much bulkier, these cyclic phosphoranes are characterized by: a) a CH_3-P moiety and an O-alkyl fragment, both typical to most OP chemical warfare agents, b) stability at physiological conditions (excluding azoxyphosphoranes), and c) a functional group for further conjugation to a protein carrier. Therefore, these TBP compounds, as haptens, are potential candidates for the promotion of catalytic antibodies.

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ORGANIC VANADIUM COMPOUNDS - TRANSITION STATE ANALOGY WITH ORGANIC PHOSPHORUS COMPOUNDS[1]

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Abstract Vanadium compounds, particularly in oxidation state V, are potent inhibitors of phosphoryl group transfer enzymes. In this paper the existance of a correlation between the coordination geometry of a series of vanadium dipicolinate complexes and their potency as inhibitors for chicken intestinal alkaline phosphatase is examined. We find that within a limited series of vanadium compounds the five-coordinate derivatives are the most potent inhibitors.

VANADIUM AND PHOSPHORUS ANALOGY

Introduction Vanadium compounds have been used with great success as tools for studies of phosphoryl group transferases amply illustrated by numerous reports of the inhibition of phosphatases, ATPases, and ribonucleases (for reviews see Refs. 2-4). The early suggestion that a vanadate-uridine complex was a potent, transition state mimic of ribonuclease[5] has been confirmed by an X-ray crystal structure[6] although recent aqueous studies modifyed the initially proposed stoichiometry and structure of the vanadate-uridine-type complexes.[7] In contrast, vanadium derivatives have been reported to act as substrates and a cofactor for enzymes catalyzing reactions other than phosphoryl group transfer.[8-10] Perhaps the most interesting example is the ability of NADV, an analog of NADP, to act as a cofactor for dehydrogenases.[10]

Not all attempts to use vanadium compounds as tools in biological studies have been equally successful. Unfortunately, many of these failures can be attributed to the lack of consideration of the aqueous chemistry of vanadium. Given the rapid interconversion among vanadium compounds, specific measures are typically necessary to ensure the existence of a particular vanadium compound in a biological system.[11] In this paper we will briefly describe the vanadium-phosphorus analogy, potential applications of vanadate esters and other vanadium compounds as transition state probes for phosphoryl group transfer reactions. Finally, new results will be presented in which the potencies of a series of vanadium complexes as inhibitors for chicken intestinal alkaline phosphatase (CIAP) correlate with geometry of these compounds.

Vanadium-Phosphorus Similarities and Dissimilarities. In its highest oxidation state, vanadium exists as vanadate in aqueous solution. As a monomer, vanadate is recognized as a structural and electronic (ground state) analog of phosphate.[4,11] This analogy is also generally believed to exist between the organic phosphates and organic vanadates as suggested by their respective pK_a values and the fact that organic vanadates can substitute for organic phosphates as substrates for many enzymes.[8-10]

As a transition metal, the vanadium atom readily adopts four-, five-, six- and seven-coordinate geometries in oxovanadates and vanadium alkoxides. In contrast to five-coordinate phosphate derivatives, five-coordinate vanadium derivatives are often local or global minima, thus making the latter excellent transition state analogs of the former.

A major difference between vanadium and phosphorus is the wide range of redox reactions vanadium can participate in. Aqueous vanadium(IV), in the form of hydrated VO^{2+}, is stable only at acidic pH. At neutral and alkaline pH it is readily oxidized to vanadium(V) even by trace levels of oxygen or other oxidants. Vanadium(V) on the other hand is readily reduced to vanadium(IV) in the presence of thiols and other reducing agents. Generally it is difficult to conduct biological studies without having both vanadium(IV) and V compounds present.[4,11]

Problems in Applications of Vanadium Compounds as Phosphorus Probes in Biological Systems The complexity of vanadium chemistry under physiological conditions is not widely recognized or considered among life scientists. Often, initial attempts to use vanadium compounds to probe enzyme reactions fail, and the approach is abandoned prematurely although one of the following technical reasons is responsible.

1. Many commonly used buffers, substrates, cofactors and other media additives form stable complexes with both vanadium(IV) and V. Formation of such complexes will prevent vanadate and/or vanadium(IV) from interacting with the biological system. Guidelines for biological studies with vanadium have recently been described.[11]
2. Even well-known vanadium derivatives may not remain intact for the desired/required time periods needed to induce the biological response.
3. Although a structural analog of a particular phosphate derivative may form, its formation constant is often small. Unless the enzyme has sufficiently high affinity for the phosphate analog no response may be observed. More typically, a complex equilibrium mixture of several vanadium derivatives forms, some of which could induce responses other than the expected one.
4. The lack of mechanistic information concerning the biological system under study. The vanadium derivative may be used in an inappropriate capacity.

The matter is further complicated by the fact the structures of relevant vanadate esters (and, for that matter, other compounds) in aqueous solution are often not known.

DOES THE POTENCY OF VANADIUM COMPOUNDS AS INHIBITORS CORRELATE WITH THEIR COORDINATION GEOMETRY?

Vanadium Compounds; Selection We chose the series of structurally characterized vanadium complexes shown in Fig. 1 which contain five- (V^{V}dipic)[12], six- (V^{IV}dipic)[13] and seven-coordinate (mpVdipic)[14] vanadium atoms complexed to dipicolinic acid (dipic). In addition, the inhibitory potency of phosphate, arsenate, vanadate and peroxovanadate (bpV) were determined for comparison.

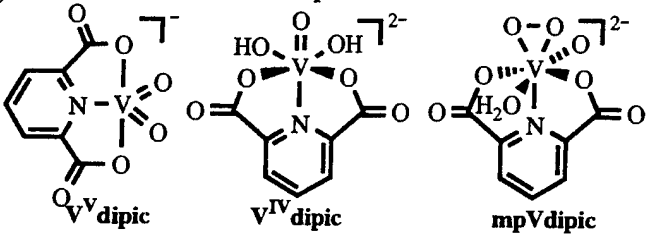


Fig. 1 - The presumed structures of V^{V}dipic,[12] V^{IV}dipic[13] and mpVdipic[14] under alkaline phosphatase assay conditions (pH 8.0).

Stability of Inhibitors During CIAP Assay The stability of phosphate, arsenate, vanadate and peroxovanadate was more than adequate for the duration of the enzyme assay with CIAP. However, the three dipic complexes required careful stability studies. A brief summary will be presented here but the detailed spectroscopic studies of each compound will be reported elsewhere (Crans et al., in preparation).

Dissolving 20.0 mM V^{V}dipic in water generates a stock solution, stable at 4 °C for weeks at pH 5.4 as indicated by ^{51}V NMR spectroscopy. Upon addition of V^{V}dipic to an assay solution, essentially all V^{V}dipic immediately hydrolyzed to form vanadate and free dipic as indicated by the low formation constant under the assay conditions (2.0 ± 0.2 M^{-1}). Two experimental approaches were successful in increasing the V^{V}dipic levels sufficiently at low inhibitor concentrations in the assay solution. First, the pH of the assay

solution was decreased to 7.0 where the formation constant increased to 132 ± 12 M^{-1}. Second, additional free dipic was added significantly increasing the contribution of V^{V}dipic in the assay solution.

V^{IV}dipic (20.0 mM) dissolves readily in aqueous solution at a pH of 3.5, and these solutions are stable at 4 °C for several days as evidenced by both EPR and UV-VIS spectroscopy. Upon addition of V^{IV}dipic to the CIAP assay solution, the complex immediately deprotonates and begins a slower oxidization reaction. The rate of oxidation (disappearance) is monitored by UV spectroscopy at 845 nm and compared to a reference solution. Since the decomposition rate is on the timescale of the enzyme experiment, it is necessary that the enzyme kinetic studies be carried out in a time-specific manner.

The mpVdipic (20.0 mM) dissolves readily in aqueous solution at pH 6.2 and is stable at 4 °C for days as monitored by both ^{51}V NMR and UV-VIS spectroscopy. Upon addition of mpVdipic to the CIAP assay solution, the complex decomposes within a few minutes based on the disappearance of the ^{51}V NMR signal for mpVdipic at -596 ppm and the absorbance peak at 430 nm. The decomposition of mpVdipic to a mixture of mpVdipic, vanadate oligomers, mpV, bpV and $(bpV)_2$ was quantified in a time-dependent manner for the kinetic analysis.

Analysis of Inhibition Data All the inhibitors examined in this study were competitive. For the dipic complexes, more than one inhibitor will be present when measuring the inhibition.[10,11] Assay solutions added V^{V}dipic contains V^{V}dipic, dipic and V_1. The concentrations of these three potential inhibitors in the solution are related through the formation constant, $K_f = [V^{V}dipic]/[V_1][dipic]$, so that the rate expression is simplified (eq. 1). The inhibition experiment is then carried at constant $[V^{V}dipic][/[dipic]$ ratio; the resulting Lineweaver-Burk plot is shown in Fig. 2.

$$\text{slope} = \frac{K_m}{V_{max}}\left(1 + \frac{[V^{V}dipic]}{K_{iVVdipic}} + \frac{[V^{V}dipic]}{K_{iV_1}\,K_f\,[dipic]} + \frac{[dipic]}{K_{idipic}}\right) \qquad (1)$$

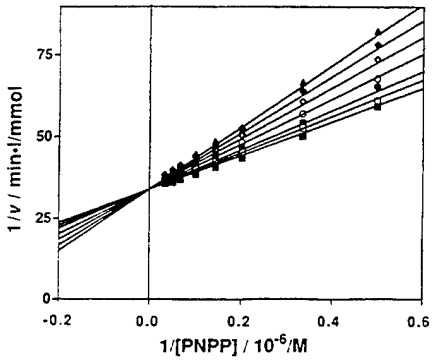


Fig. 2 Lineweaver-Burk plot of inhibition of chicken intestinal alkaline phosphatase by V^{V}dipic (in the presence of V_1 and dipic). The lines shown are calculated with a spreadsheet using the parameters listed in Table I. The experimental points were obtained by adding various amounts of V^{V}dipic and dipic to the assay solution. $[V^{V}dipic]/[dipic]$ added are as follows: 0/0 mM (■), 0.050/0.013 mM (❑); 0.10/0.026 mM (◆); 0.20/0.052 mM (○); 0.30/0.078 mM (◇); 0.40/0.10 mM (◆) and 0.50/0.13 mM (▲).

K_i Values of Vanadium Compounds Acting on CIAP The inhibition constants (K_i) obtained are shown in Table I. The K_i value for phosphate is significantly higher than the K_i value for vanadate as reported previously for yeast and human acid phosphatases[15] but in contrast to studies with *E. coli* alkaline phosphatase.[16,17] This pattern is consistent with the interpretation that vanadate acts as a transition state analog for CIAP.

The K_i value for V^{V}dipic is smaller than the K_i values for V^{IV}dipic, mpVdipic and the other compounds listed in Table I. Also shown is a column in which the K_i values were calculated based on the concentration of complex *added* to the assay solution (in contrast to the concentration of *complex actually present*). K_i values obtained in this manner reveal little information on a possible structure-activity correlation. Inhibition studies with free dipic rule out the possibility that the observed inhibition is caused by dipic alone. In summary, the results in Table I support the hypothesis that the five-coordinate compounds are more potent inhibitors than six- or seven-coordinate compounds for CIAP.

Conclusion and Future Prospects The inhibitor potencies were examined for a series

of five-, six- and seven-coordinate vanadium dipic compounds for chicken intestinal alkaline phosphatase. *A correlation between coordination number around the vanadium atom and inhibitory potency was observed, although it is important to note that all the examined vanadium compounds were strong inhibitors.* The phosphorus-vanadium analogy can be explored successfully when the possible pitfalls in working with labile vanadium compounds are recognized. There is no doubt that when vanadium compounds with the desired structure and stability[18] are prepared, they will have real potential for inhibition of enzymes and generation of catalytic antibodies.

Table I. The K_i values determined for CIAP.[a]

Compound	Coordination number	Charge at pH 8.00	Vanadium oxidation state	K_i value (μM)	Uncorrected[b] K_i value (μM)
P_i	4	-2	-	470±30	
As	4	-3	-	18±1	
V_1	4(5[c])	-1/-2[d]	V	2.8±0.4	
V_1[e]	4(5[c])	-1/-2[d]	V	5.7±1.0[e]	
V^{V}dipic	5	-1	V	1.9±0.6[e]	4.4±0.8[b]
V^{IV} dipic[f]	6	-2[f]	IV	~6[g]	4.9±1.0[b]
mpVdipic	7	-2	V	13±1	4±1[b]
bpV	7	-2	V	23±4	
dipic	-	-2	-	3200±800	

[a] The K_m for CIAP using 5.0 to 50 μM PNPP in 50 mM Hepes, 1.00 M KCl, 5.0 mM $MgCl_2$ at 25 °C and pH 8.00 (±0.05) for CIAP is 9.7 (±1.0) μM. These conditions were used unless otherwise indicated.
[b] These K_i values were calculated assuming 100% of the complex remained after 4 min of incubation in the form they were added to the assay solution.
[c] The coordination number of V_1 may be 4 or 5 (is it in aqueous solution or complexed to an enzyme?).
[d] The two major V_1 species in the assay solution have charges of -1 and -2 (pK_a ranges from 8.0-8.4).
[e] These K_i values were obtained at pH 7.00 (±0.05), under which conditions the K_m for 1.5 to 20 μM PNPP is 1.5 (±0.5) μM for CIAP.
[f] V^{IV}dipic has two pK_a values at 6.7 (±0.2) and 7.0 (±0.2).
[g] Concentrations of inhibitors in this experiment was less than optimal (low accuracy on K_i value).

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INTERACTIONS IN TETRAVALENT AND PENTAVALENT PHOSPHONATE ESTERS OF SER AT THE ACTIVE SITE OF SERINE ENZYMES

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Abstract The stabilizing interactions in pentavalent and tetravalent phosphonate esters of the active-site Ser in selected serine hydrolase enzymes can be used to explain how these man-made molecules recruit enzyme catalytic power up to 70% of that of the natural substrate. The removal of the leaving group of a substrate or inhibitor is very efficient by acetylcholinesterase (AChE) because it is aided by hydrophobic forces and the repulsive interaction with the negatively charged Glu199 at the active site of AChE. The interactions between protein and small molecular fragments were evaluated with molecular mechanics and dynamics. The conclusions should be informative to the design of haptens for antibodies and efforts to drug design and detoxification after enzyme inhibition.

Key Words serine hydrolase inhibition, acetylcholinesterase inhibition, chymotrypsin inhibition, trypsin inhibition, molecular mechanics, molecular dynamics.

INTRODUCTION

Phosphonylation of serine hydrolase enzymes probably takes place via an in-line attack of the Ser nucleophile at the central P with the leaving group at 180 ° from the entering group and involves the formation of a pentacoordinate transient along the reaction path [1-2]. The life-time of the transient depends on the electronic and steric nature of all the substituents not only the leaving group [2-3]. Reactions of the enzymes with organophosphorus compounds that have good leaving groups most likely occur with a nearly concerted departure of the leaving group to Ser attack and the acceleration by the enzymes relative to the uncatalyzed aqueous hydrolysis is astonishing (10^6-10^{11}) [4]. Most recently, we studied the propensity of the catalytic machinery of serine hydrolases to promote leaving-group departure in phosphonates. We generated high-quality geometric and charge parameters by an *ab initio* 6-31$^+$G* basis set (GAMESS) [5] for dimethoxy methylphosphonofluoridate, a trigonal bipyramid. Using the parameters we generated pentavalent adducts of the active-site Ser modified with 2-(3,3- dimethyl-butyl) methylphosphonofluoridate (soman). Soman is one of the most efficient inhibitors of the enzymes [6] and it has a small leaving group, F^-, an advantage in computations. These fragments were then incorporated into the active site of AChE, trypsin and chymotrypsin to evaluate the specific nonbonding interactions that contribute to

molecular recognition of phosphonate esters and the elements that may preferentially promote leaving-group departure. We provide here an analysis of the results that should be informative to the design of haptens for antibodies and efforts to drug design and detoxification after enzyme inhibition.

METHODS

The molecular mechanics-optimized (YETI V5.3) [7] structures reported earlier for the fully solvated AChE, trypsin and chymotrypsin were used in these calculations [2]. Both nitrogens Nϵ and Nδ were protonated on the catalytic His to represent the protonation state of phosphorylated adducts according to earlier measurements on trypsin and chymotrysin [8]. Each diastereomer of the serine ester of soman was then incorporated into the structure of the enzyme to be studied and the entire structure was again energy-minimized in YETI. Molecular dynamics simulations were carried out with program CHARMM (Vc22g5) [9] on energy-minimized native AChE and trypsin and covalently modified AChE all solvated with one water shell. All atoms were represented explicitly. The TIP3P model, as implemented in CHARMM was employed for the simulation of solvate water molecules. The parameters for the amino acid residues were from the standard parameter file of the CHARMM program. No H-bonding term was used in the empirical potential energy function. The stochastic boundary calculation was carried out with a < 18 Å radius reaction zone centered on Ser200 Oγ, a 2 Å shell buffer zone, and the region beyond the 20 Å radius was kept constant. Langevin dynamics were used in the buffer zone. Numerical integration by the leap frog integrator with a 1 fs step size was used for the molecular dynamics calculations. A switching function was used on the force for the long range non-bonding energy terms with the cutoff value of 12 Å.

RESULTS AND DISCUSSION

The geometric parameters for critical interactions are in Table 1. Figure 1 shows the equilibrium structures of the active site of AChE, trypsin and chymotrypsin with the pentavalent intermediate formed immediately after attack of the catalytic Ser on soman.

TABLE I

Distances (Å) between the F atom and stabilizing residues in the pentavalent adducts of serine hydrolases with diastereomers of soman; residue numbering AChE/trypsin

Interaction[a]	AChE		Trypsin		Chymotrypsin	
	P_SC_S	P_RC_S	P_SC_S	P_RC_S	P_SC_S	P_RC_S
Gly119/193N-H---FP	2.73	3.09	3.74	3.74	3.02	3.60
Glu199O1---FP	6.14	5.94				
Glu199O2---FP	6.58	6.42				
WAT536O---FP	4.49	4.45	2.60	2.68	3.30	4.24

The P_SC_S diastereomers is formed in an in-line attack by Ser on the faster-reacting soman diastereomers.

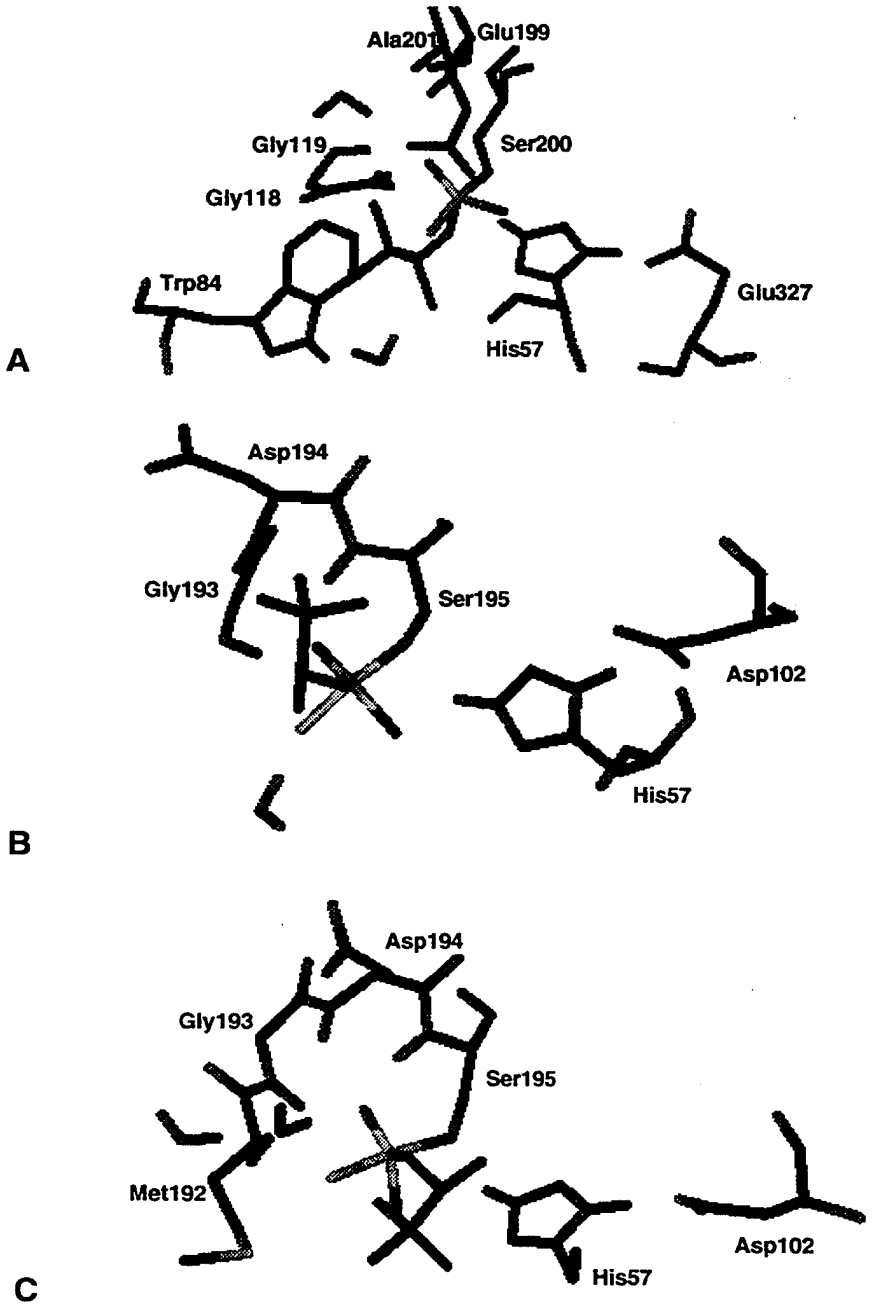


Figure 1. Active-site interactions in the pentavalent P_SC_S dieastereomers of soman-inhibited A. AChE, B trypsin and C chymotrypsin. Protein-protein interactions were within 5 kcal/mol for each adduct of an enzyme and protein-water interactions were within 100 kcal/mol corresponding to no more than a difference of 2-8 water molecules.

A salient feature of the results is the much more crowded active site of AChE than those of the serine proteases. Although the total sum of stabilizing energies are greater for the AChE structures, favorable electrostatic and H-bonding interactions are often counter-balanced by severe van der Waals repulsions reflected in a net repulsive interaction within the phosphonate fragment. Repulsion energies are also observable in the Glu-His diad. Molecular dynamics simulation of the structure on the 200 ps time scale ameliorated the repulsion within the protein but compressed the pentavalent structure. The interactions in the oxyanion hole were diminished during the simulation and those with the F^- were enhanced. The observation is consistent with propositions for the origins of enzyme catalytic power in general and serine hydrolase catalysis in particular. Earlier mechanistic investigations indicate that the distortions, at least partly, could precede bond formation with the active-site Ser [1a,d,f]. Inactivation of AChE by soman was characterized by a partly rate-determining conformational adjustment that probably serves to optimize the fit between active site and inhibitor. Apparently, the adjustment needs to be gradual and is induced as the inhibitor tumbles down the active-site gorge and approaches the bottom.

A key focus of the calculations was the general question of leaving group departure from the pentavalent transient. The F atom was placed in the apical position as expected by the Westheimer rules [10]. Elimination of F^- from these structures is very efficient, which requires the presence of stabilizing forces. Since the protein was adequately solvated, the promotion of F^- departure comes partly from solvation and partly from the strong positive electrostatic field in the oxyanion hole. In addition, an electrostatic push from Glu199 of AChE may play a role in stabilizing the departing F^-. This would also be consistent with the great efficiency of AChE inactivation.

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TRANSITION STATE ANALYSIS WITHIN A PANEL OF CATALYTIC ANTIBODIES GENERATED AGAINST A PHOSPHONATE TRANSITION STATE ANALOG

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Abstract The biochemical properties within a panel of six hydrolytic catalytic antibodies elicited against a phosphonate transition state analog were investigated. Although the individual values for *k*cat, *K*m, and *K*TSA (the affinity for the transition state analog) of the six antibodies differed substantially, the transition state analysis (*k*cat /*k*uncat versus *K*S/*K*TSA) displayed a linear relationship (slope = 0.99) with the four antibodies 6D9, 8D11, 4D5, and 9C10, which have homologous primary amino acid sequences, providing evidence that all of the differential binding energy of the transition state vs the ground state is available for the rate enhancement. This also suggested that these four antibodies catalyze the hydrolysis by variations of the same basic mechanism of transition state stabilization. The analysis of the substrate specificity suggested that the catalytic antibodies with highly homologous primary amino acid sequences possess homogeneous binding modes to the substrate or hapten.

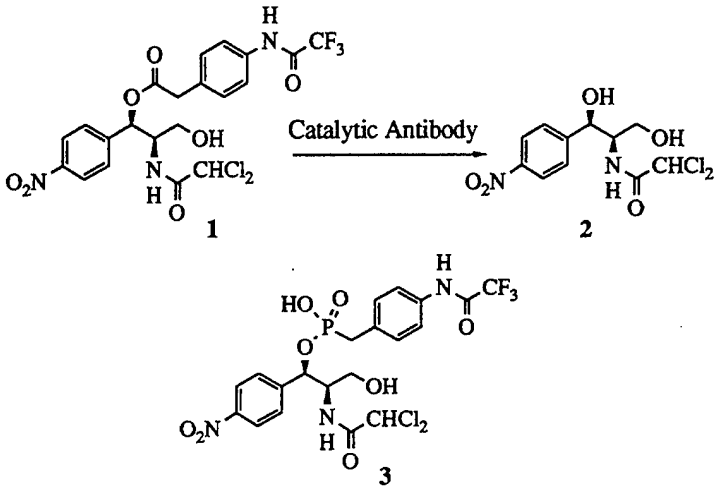
Key Words: Catalytic antibody, Transition state analog, Antibody diversity, Ester hydrolysis, Antigen-combining site.

INTRODUCTION

The diversity of the immune response, which can provide a panel of catalytic antibodies with varying degrees of catalytic activity and substrate specificity by immunization with a single hapten, raises the question concerning the extent to which a rationally designed hapten dictates the paratopes for catalytic function in the antigen-combining site. The study of the correlation between the antigen-combining-site structures and the chemical properties within a panel of catalytic antibodies elicited against a single hapten can potentially provide a more global understanding of the molecular mechanisms by which catalytic antibodies are generated in immune responses.

Previously, we have reported prodrug activation via catalytic antibodies that catalyze the hydrolysis of the nonbioactive chloramphenicol monoester derivative **1** to generate chloramphenicol **2**.[1] Immunization with a KLH conjugate of the transition state analog **3**, designed on the basis of the transition state stabilization concept, yielded 12 immunoglobulin G (Ig G) proteins binding to the hapten **3**, six of which were found

to catalyze the hydrolysis with varying degrees of activity. Despite the antibody diversity, the catalytic antibodies, 6D9, 8D11, 4B5, 9C10, and 3G6, share significant structural identity to one another and have 89-95% and 74-84% sequence homology in the complete VL and VH regions, respectively.[2] An exception is antibody 7C8, which was found to be catalytic, but its structure was different from the other five catalytic antibodies. In this work, we report the detailed biochemical properties of the six catalytic antibodies, to enhance our understanding of the active site structure and function relationship assignments.



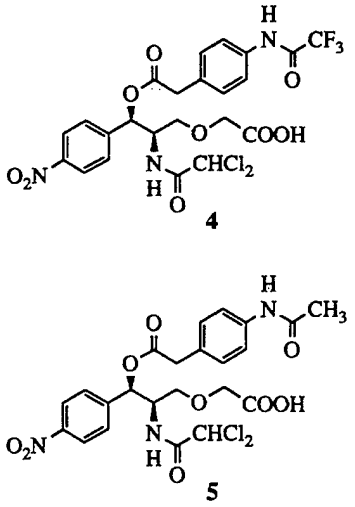
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CATALYTIC AND BINDING ASSAYS

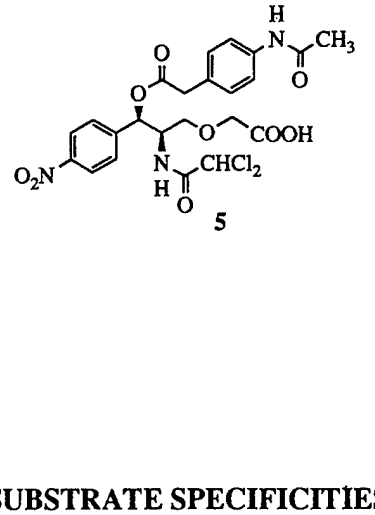
To survey the catalytic activity within the six catalytic antibodies, the kinetic parameters of the antibody-catalyzed hydrolysis with substrate **4** were determined at 25 °C in 10% DMSO/50 mM Tris (pH 8.0). The first-order rate constants per antigen-combining site (*k*cat) and Michaelis constants (*K*m) in the six catalytic antibodies were in the range of 0.008-0.145 min^{-1} and 2.5-60 μM, respectively.

According to transition state theory, under ideal conditions, one can predict the rate enhancement of an antibody-catalyzed reaction from the ratio of the affinity for the substrate relative to the affinity for the transition state. Since we have generated monoclonal antibodies against the putative transition state analog, with the expectation that the antibodies may be catalytic by virtue of the theoretical relationship between the affinity for the transition state and the catalytic efficiency, the ratio of the affinity (*K*S) for the substrate **4** relative to the affinity (*K*TSA) for the transition state analog **3** within the six catalytic antibodies was determined by competitive inhibition enzyme immunoassay (CIEIA) and was analyzed on the basis of transition state theory. Figure 1 shows plots of *k*cat/*k*uncat versus *K*S/*K*TSA for the six catalytic antibodies. Although

the catalytic antibodies possess varying values of *K*m, *k*cat, *K*s, and *K*TSA, the transition state analysis displays a linear relationship among antibodies 6D9, 8D11, 4B5, and 9C10, with high homologous amino acid sequences. The slope of the straight line is 0.99. This suggests that the entire differential binding energy of the four catalytic antibodies to the transition state vs the ground state might be available for rate enhancement. On the other hand, the plots for antibodies 7C8 and 3G6 deviate from the linear relationship, suggesting that factors other than transition state stabilization, such as a functioning acid or base or nucleophilic catalyst, are involved in the catalysis.



4



5

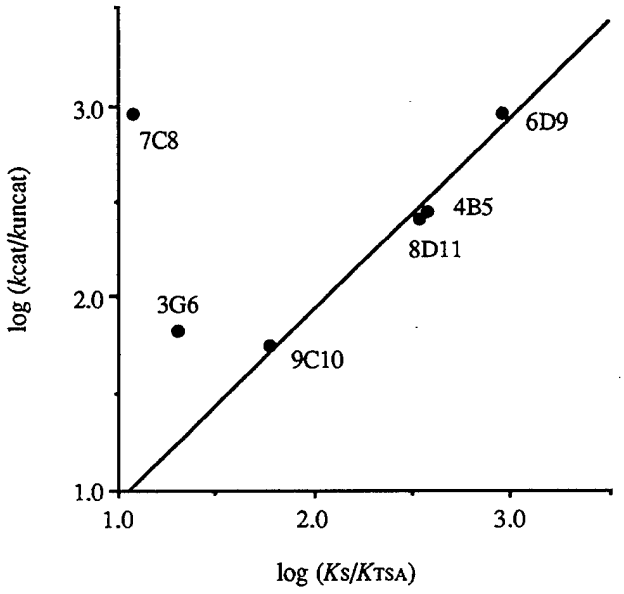


Figure 1. Plot of log (*K*s/*K*TSA) versus log (*k*cat/*k*uncat) for catalytic antibodies generated against phosphonate transition state analog **3**. A linear relationship was obtained for antibodies 6D9, 4B5, 8D11, and 9C10, suggesting that the antigen-combining sites act as catalysts by stabilizing the transition state; slope = 0.99, R^2 = 0.98.

SUBSTRATE SPECIFICITIES

The substrate specificity of the antibodies was examined using substrate **4** and its derivative **5**, in which the trifluoroacetyl group of **4** was converted to an acetyl group. If the combining-site structures and the binding modes to the hapten and the substrates of these catalytic antibodies are related each other, the antibodies should display a homologous substrate specificity.

The relative velocities for substrates **4** and **5** in the antibody-catalyzed hydrolysis with the six catalytic antibodies were compared under the conditions of 5 μM of antibody and 200 μM of substrate in 10 % DMSO/50 mM Tris (pH 8.0). Antibodies 6D9, 8D11, 4B5, 9C10, and 3G6, with highly homologous amino acid sequences,

displayed reduced catalytic activities for **5**, with rates of 3.5-14 times lower than those for **4**. On the other hand, antibody 7C8, with an amino acid sequence different from those of the other five antibodies, was found to catalyze the hydrolysis of substrate **4** and **5** with the same rate enhancement.

CHEMICAL MODIFICATIONS

Chemical modification of the antibodies showed that the hydrolytic activity for substrate **4** was reduced by tyrosine-, and especially histidine-specific reagents. When the six catalytic antibodies were treated with diethyl pyrocarbonate (DEPC) to modify any histidine residues, antibodies 6D9, 8D11, 4B5, and 9C10 completely lost the hydrolytic activity. Antibody 3G6 had a 40% reduction in activity under the same conditions. On the other hand, antibody 7C8 resisted chemical modification with DEPC under the same conditions and retained the same activity as that before the modification. Nitration of tyrosine residues by tetranitromethane reduced the activity of the antibodies by 60-75%, with the exception of antibody 3G6. In the case of antibody 3G6, treatment with tetranitromethane completely abolished the hydrolytic activity.

His (L27d) in the CDR 1 of the light chain is conserved in the catalytic antibodies 6D9, 8D11, 4B5, 9C10, while antibody 3G6 has a tyrosine residue at the corresponding position. We suspected, therefore, that the His at position L27d is a catalytic amino acid residue participating in transition state stabilization in the antibody-catalyzed reactions.

CONCLUSION

It is noteworthy that the majority of these catalytic antibodies, generated against a single transition state analog, display high homology in the biochemical and structural properties and catalyze the reaction with the same mechanism expected from designing the transition state analog. These findings emphasize the critical importance of hapten affinity to transition state stabilization and of chemically designing haptens that closely resemble the true transition state for the generation of catalytic antibodies.[3]

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STEREOCHEMISTRY OF DBU-ASSISTED REACTION OF NUCLEOSIDE 3'-O-(2-THIONO-1.3.2-OXATHIAPHOSPHOLANES) WITH 5'-HYDROXYNUCLEOSIDES

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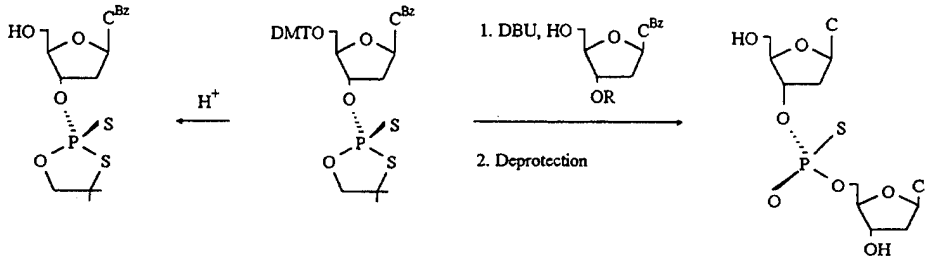
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It has been demonstrated that reaction of diastereomerically pure 5'-*O*-DMT-nucleoside-3'-*O*-(2-thiono-1.3.2-oxathiaphospholanes) with 5'-*O*-unprotected nucleosides occurs, assisted by DBU, with high stereospecificity providing diastereomerically pure dinucleoside(3',5')phosphorothioates.[1] Model studies involving 2-*N*(α-naphthylethyl)amino-2-thiono-1.3.2-oxathiaphospholane evidently indicated that DBU-assisted methanolysis provides *O*-methyl-*N*(α-naphthylethyl)-phosphoroamidothioate with net *retention* of configuration.[2] This result, promptly documented by X-ray crystallography of substrates and products of aforementioned conversion, allowed to anticipate that 1.3.2-oxathiaphospholane ring-opening process occurs *via* "adjacent" type mechanism involving an attack of MeOH on phosphorus collinear with endocyclic P-O bond; pentacoordinate phosphorane intermediate before collapse has to undergo the single pseudorotation process, placing endocyclic P-S bond in apical position. Such analysis allowed for implication that reaction of 5'-*O*-DMT-nucleoside-3'-*O*-(2-thiono-1.3.2-oxathiaphospholane) with 5'-unprotected nucleoside or nucleotide occurs according the same rules and prediction, that diastereomerically pure oxathiaphospholane substrate for [Rp]-dinucleoside (3',5')-phosphorothioate has to be of [Rp]-configuration.[2]

In this report we present experimental evidence that oxathiaphospholane substrate has the same absolute configuration of P-atom as that of resulting dinucleoside (3',5')phosphorothioate. 5'-*O*-DMT-N^4-benzoylcytidine-3'-*O*-(2-thiono-4,4,-dimethyl-1.3.2-oxathiaphospholane) (**1**) has been prepared in tetrazole-catalyzed reaction of 5'-*O*-DMT-N^4-benzoylcytidine with 2-*N,N*-diisopropylamino-4,4-dimethyl-1.3.2-oxathiaphospholane[3], followed by oxidation with elemental sulphur. Column chromatography on silica gel 60H with ethyl acetate/butyl acetate (2:1, v/v) as eluting system gave pure FAST-eluted diastereomer of **1** (FAST-**1**);

^{31}P NMR: 107.76 (CD_3CN); MS FAB$^+$: 840.3 $(M+K)^+$, MS FAB$^-$: 839.4 $(M-K)^-$. This isomer of **1** was reacted with N^4-benzoylcytidine anchored *via* its 3'-*O*-group on a solid support LCA-CPG[4] performed in the presence of a 200-fold molar excess of DBU to give, after cleavage from the support and base deprotection[5] [Rp]-dicytidine (3',5')-phosphorothioate (**2**). Identification of this product was based upon its comparison with genuine sample of [Rp]-**2**.[6]

SCHEME 1



[Rp]-**3** [Rp]-**1** [Rp]-**2**

DMT = 4,4'-dimethoxytrityl; C = Cytosin-1-yl; C^{Bz} = N^4-Benzoylcytosin-1-yl; R = linker to solid support

Independently, FAST-1 was treated with p-toluenesulphonic acid/methylene chloride for removal of the dimethoxytrityl protective group and after purification on chromatographic column (silica gel 60 with chloroform/methanol = 90:10 as eluting system), gave N^4-benzoylcytidine 3'-*O*-(2-thiono-4,4-dimethyl-1.3.2-oxathiaphospholane) (**3**). The product was dissolved in toluene/methylene chloride/diethyl ether (10:2:0.5, v/v) and left for slow crystallization. The crystals collected (m.p. 119-121°C; ^{31}P NMR (CD_3CN): 107.57 ppm; MS FAB$^+$: 498.2, MS FAB$^-$: 496.1) were subjected for X-ray analysis which showed that the absolute configuration at phosphorus is [Rp] (Fig.1). Therefore, the absolute configuration of the parent FAST-1 must be also [Rp]. This result is consistent with the mechanism we proposed earlier,[2] indicating that substrates **1** and resulting products **2** are of the same absolute configuration of phosphorus atom. Results of *ab initio* calculations performed by Taira and Uchimaru[7] are in favor of this mechanism (data not presented).

This mechanism implies that DBU assists the reaction as the strong base.[8] However, evidence was reported recently that chlorobis(diisopropylamino)phosphane and DBU in acetonitrile solution form a cationic phosphane[9] and evidently DBU acts

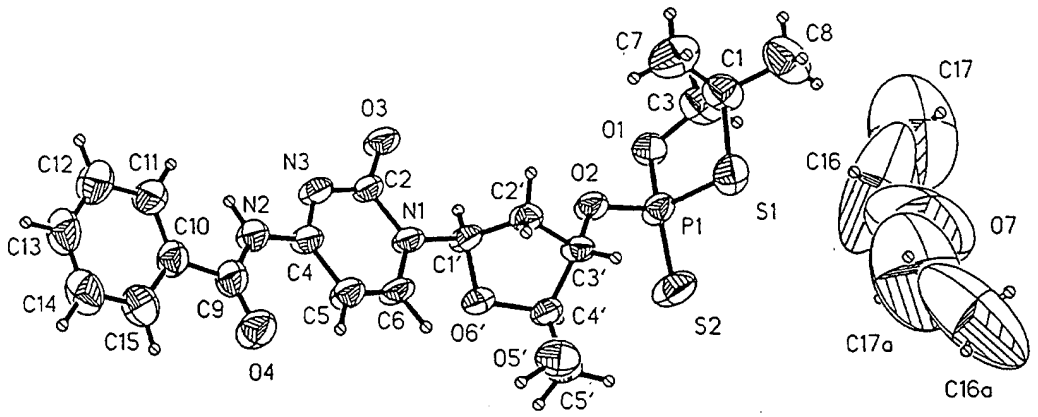
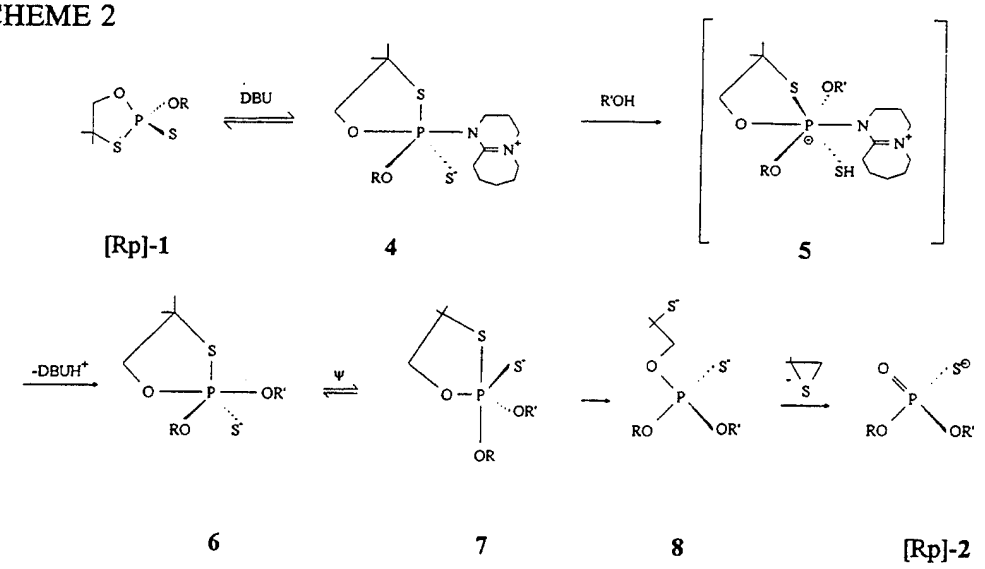


Fig.1. Molecular structure of "Fast-related"-**3**.

in this system as a nucleophile. This conclusion is consistent with our earlier observation that DBU, generally accepted as "non-nucleophilic strong base",[8] may participate in the process of nucleophilic substitution at tetracoordinate phosphorus atom.[10] For example, the DBU-promoted epimerization of nucleoside-3'-*O*-(*O*-4-nitrophenyl methanephosphonates) has been explained by an attack of DBU on phosphorus and the release of 4-nitrophenoxy anion. Such a function of the DBU would explain the observed phenomenon that nonbicyclic amidine bases such as 1,8-bis(dimethylamino)naphthalene, *N,N,N',N'*-tetramethylethylenediamine, tetramethylguanidine, 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine are far less effective than DBU in promoting reaction between **1** and 5'-*O*-unprotected nucleosides.[3] We therefore formulate the further hypothesis that, in the process of 1.3.2-oxathiaphospholane ring opening condensation, the function of DBU is not that of deprotonation of the alcohol; it must act as a nucleophile, which in the first stage attacks at phosphorus in the 1.3.2-oxathiaphospholane ring system from the side opposite to endocyclic P-O bond (Scheme 2). The resulting pentacoordinate trigonal bipyramide **4** is stabilized *via* attractive interactions between negatively charged sulphur and positively charged bridgehead nitrogen atom. This intermediate undergoes slow reaction with alcohol *via* addition-elimination mode and hexacoordinate tetragonal bypiramide transition state **5** with negative charge located at phosphorus atom. Elimination of the protonated DBU generates intermediate **6** which undergoes pseudorotation, as indicated in Scheme 2. Collapse of **7** *via* cleavage of the P-S bond followed by elimination of episulfide gives the phosphorothioate diester of [Rp]-configuration.

One question remains unanswered. Why does replacement of the protonated DBU by the alkoxide ligand occur with retention of configuration? This remains obscure since the rules of ligand exchange at hexacoordinate phosphorus are not fully understood.[11]

SCHEME 2



R = 3'-nucleoside; R' = 5'-nucleoside

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EXPLORING REACTIONS OF NUCLEOSIDE H-PHOSPHONATES WITH BIFUNCTIONAL REAGENTS

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Abstract
Studies on reactions of nucleoside H-phosphonates with various amino alcohols showed that: (i) condensations of H-phosphonate monoesters with amino alcohols proceed with a complete chemoselectivity producing H-phosphonate diesters exclusively; (ii) H-phosphonate diesters undergo transesterification with amino alcohols and afford various products depending on the reaction conditions; (iii) the course of the oxidative coupling of nucleoside H-phosphonate diesters with amino alcohols can be controlled by protonation of the amino function, and thus the reaction can be steered to afford aminoalkyl phosphotriesters or hydroxyalkyl phosphoramidates.

INTRODUCTION

Rapid development of molecular medicinal diagnostic in recent years caused high demand for molecular probes enabling detection of specific gene sequences[1]. Due to some inherent problems connected with the handling of radioactive tracers, synthetic oligonucleotides equipped with various reporter groups detectable by fluorescent or enzymatic method are gaining interest[2]. In order to introduce to oligonucleotides a functional group amenable to the subsequent attachment of various reporter molecules, we have recently embarked on investigations of nucleotides modifications with bifunctional reagents (Fig. 1). In this paper we give a short account of our studies on reactions of amino alcohols, in which two nucleophilic centers are spaced by different numbers of methylene groups, with H-phosphonate mono- and H-phosphonate diesters.

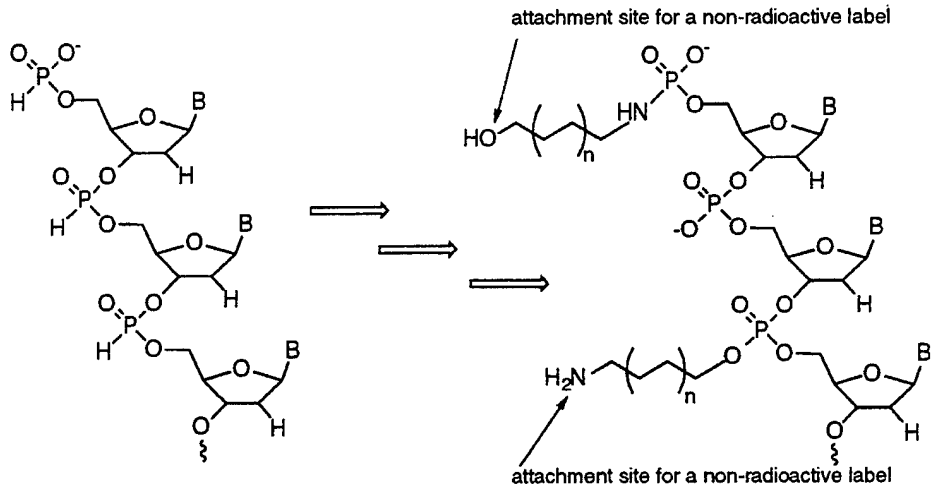


Fig. 1. Functionalization of oligonucleotides for the attachment of non-radioactive labels

RESULTS AND DISCUSSION

Condensations of nucleoside H-phosphonate monoesters with amino alcohols was investigated[3] using various condensing agents [pivaloyl chloride (PV-Cl), 2-chloro-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphinane (NEP)]. It was found, that irrespective of a coupling agent used, the reactions proceed with complete chemoselectivity affording the corresponding H-phosphonate diesters exclusively (Fig. 2). The chemoselectivity, which reflects a preferable attack of the O- *vs* N-nucleophile on the phosphorus centre of activated species derived from H-phosphonate monoesters may, in part, be enhanced due to a partial protonation of the amino group of amino alcohols under the reaction conditions. For synthesis of compounds of type **3** with a free amino function, NEP is recommended since the use of PV-Cl affords N-acylated compounds **2**. Similar results to those as in the reaction with NEP were also obtained with DCC (3 equiv.) and pyridinium chloride (3 equiv.) as a coupling system[4]. The reaction showed the same chemoselectivity, was clean and went to completion within 3 h.

Oxidation of H-phosphonate diesters **3** with iodine was studies under various experimental conditions[3]. In anhydrous media, the corresponding cyclic phosphoramidates or/and sym-pyrophosphates were formed, depending on the length of the methylene spacer in an alkyl residue. In the presence of water, oxidation of **3** (n=1-4) afforded exclusively acylic phosphodiesters with a free amino group in the alkyl chain. The exception was 2-aminoethyl nucleoside H-phosphonate **3** (n=0) which produced nucleoside 2-hydroxyethyl phosphoramidate, most likely *via* the 1,3,2-oxazaphospholidin-2-one intermediate.

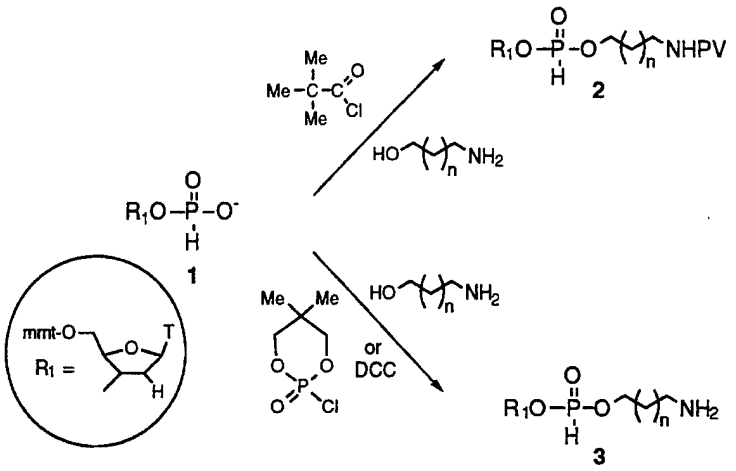
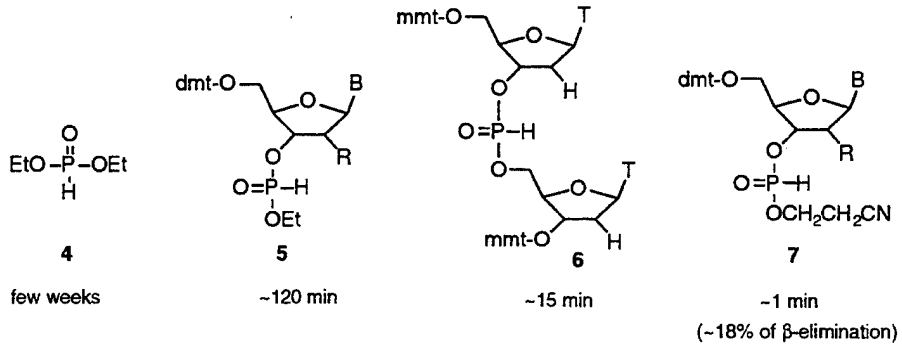


Fig. 2. Reactions of nucleoside H-phosphonate monoesters with amino alcohols

Reactivity of the -OH *vs* -NH_2 groups of amino alcohols toward the phosphorus centre in H-phosphonate diesters also was investigated[5,6]. The primary products of the reactions were found to be the mixed and the symmetrical H-phosphonate diesters. No evidence for the attack of the phosphorus centre by the amino group, which should result in the formation of H-phosphonamidates, was obtained. Since under these conditions mixture of products usually are formed, the reactions seem of less synthetic value for functionalization of oligonucleotides.

It is worth mentioning that among H-phosphonate diesters there are often significant differences in rates of transesterification with amino alcohols[6] (Fig. 3).



Reaction conditions: 10 equiv. of ethanoloamine in pyridine, RT. Time refers to a complete disappearance of the starting H-phosphonate diesters.

Fig. 3. Rates of transesterification of various H-phosphonate diesters with ethanoloamine

These one should bear in mind when oligonucleotides containing H-phosphonate bonds are subjected to various reactions on a solid support.

Our studies on the iodine promoted oxidative coupling of H-phosphonate diesters[7] with amino alcohols showed that in this reaction chemoselectivity (P-O *vs* P-N bond formation) can be controlled by protonation of the amino function (Fig. 4). This phenomenon can be exploited for functionalization of oligonucleotides by converting

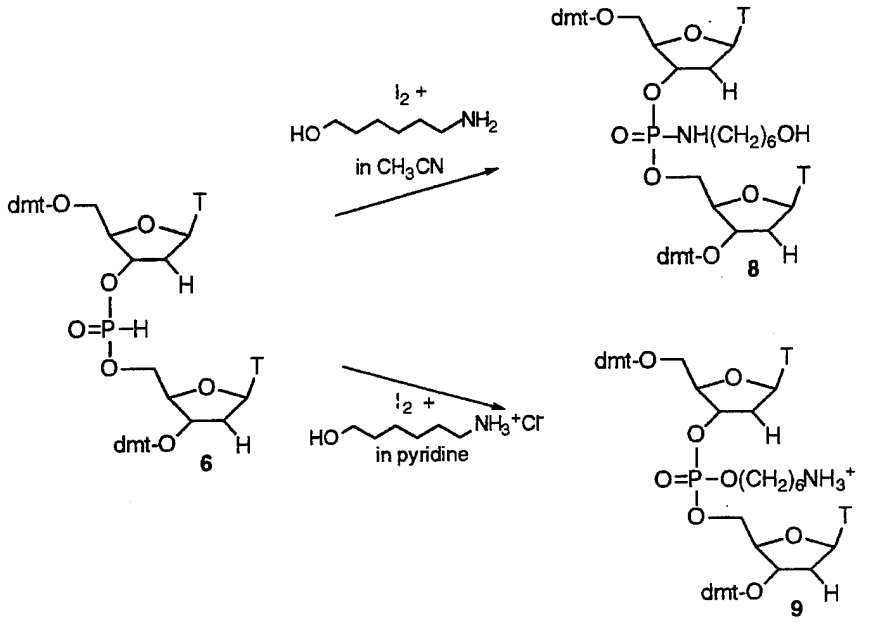


Fig. 4. Oxidative coupling of H-phosphonate diesters with amino alcohols

an H-phosphonate diester function into hydroxyalkyl phosphoramidate (**8**) or aminoalkyl phosphotriester (**9**). The transformation seems to be fully compatible with a machine-assisted solid phase synthesis of oligonucleotides and can be implemented as an optional step into the standard protocol.

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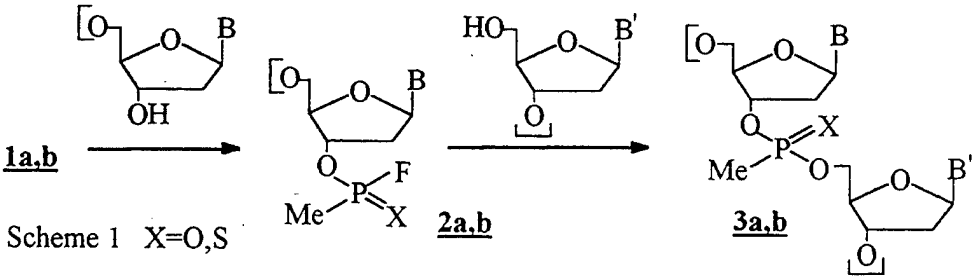
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NOVEL CHEMISTRY AND STEREOCHEMISTRY OF P-F MODIFIED OLIGONUCLEOTIDES

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This communication deals with further progress in chemistry and stereochemistry of deoxynucleosidylphosphorofluoridates and fluoridites [1].

Methylphosphonate oligonucleotides are important antisense inhibitors of gene expression and possess the criteria to become useful as therapeutic agents [2]. Synthesis of methylphosphonates oligonucleotides via P(III) intermediates has proved costly, and inefficient to conduct on a large scale. In our search for an improved synthesis of these compounds we concluded that a route via P(IV) coordinate phosphorus compounds was feasible. It is known that replacement of the first fluorine ligand in compounds $RP(O)F_2$ and $RP(S)F_2$ is faster than that of the second. This should be even more pronouced in the reactions with 3'-OH nucleosides. Our recent work showed that these expectations are correct. Methylphosphonodifluoridate $MeP(O)F_2$ **1a** and its sulfur analogue $MeP(S)F_2$ **1b** can be readily prepared in one-flask procedures from the commercially available dichlorides $MeP(S)Cl_2$ or $MeP(S)Cl_2$ in over 90% yield. [1]



Scheme 1 X=O,S

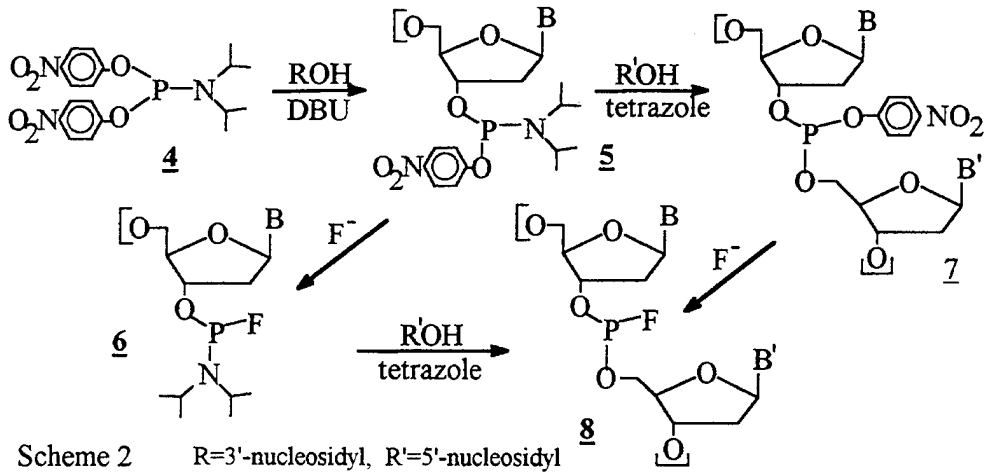
When the 5'-O-protected deoxynucleosides were allowed to react with difluorides **1a,b** in the presence of triethylamine in the proportion 1:1, the 3'-

deoxynucleosidylphosphonofluoridates **2a** or the 3'-deoxynucleosidylfluoridomethylphosphonothionates **2b** are formed in over 95% yield [3].

Both fluorides **2a,b** are formed as 1:1 mixture of diastereoisomers. High reactivity of **2a** prevented their separation into pure diastereoisomers. In contrast thioanalogues **2b** are more stable and were separated into „slow" and „fast" diastereomers by silica-gel column chromatography. Coupling of the fluoridate **2a** or **2b** in the presence of DBU or NaH with another nucleosides led to di(deoxynucleosidyl)phosphonates **3a** or their thioanalogues **3b** respectively. As expected difluoride **1b** and fluoride **2b** containing the P(S) group undergo condensation reactions with nucleosides more slowly than **1a** and **2a** [3]. Work is in progress to use pure diastereomers **2b** in stereoselective preparation of compounds **3b** and other derivatives.

Relatively little is known about the chemistry and stereochemistry of compounds containing a P(III)-F functional center. Cyclic diastereomeric phosphorofluoridite has been prepared by Mikołajczyk et al.[4], and the first resolution of free fluorophosphane MePhPF has been achieved only recently [5]. In the past the chemistry of modified nucleotides containing P(III)-F bond was a void field. Recently this type of compounds became of great importance in our studies[6].

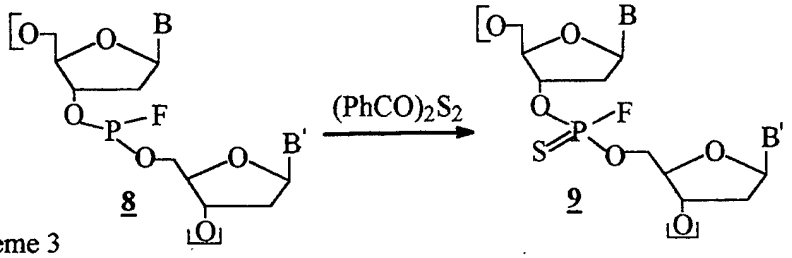
In connection with this chemistry new phosphitylating reagents containing the 4-nitrophenoxy leaving group have been devised. Our strategy can be exemplified by phosphitylation reactions employing amidophosphite **4** [7].



Scheme 2 R=3'-nucleosidyl, R'=5'-nucleosidyl

The reaction of **4** with a nucleoside in the presence of DBU allows quantitative formation of the amidite **5** which reacts in a highly selective way with $Bu_4N^+F^-$ to give the nucleosidyl phosphoroamidofluoridite **6**. There are two pathways leading to dimers **8** as shown in Scheme 2. Surprisingly, the monofluoride **6** can be transformed into the dimer **8** without affecting the P-F bond. The nucleosidyl phosphoroamidofluoridites **6** are formed with some degree of stereoselectivity and can be separated into pure diastereoisomers. However, their coupling reaction with nucleosides in the presence of tetrazole under normal conditions affords diastereoisomers **8** as 1:1 mixtures in almost quantitative yield. The high configurational and chemical stability of phosphorofluorides **8** can be explained by the presence of the electronegative fluorine ligand and steric hindrance exerted by the nucleosidyl groups [7].

To underline the desirable features of phosphorofluoridites **8,** their use in stereospecific synthesis of phosphorofluoridothionates and their hydrolytic stability can be cited. The reaction of the phosphorofluoridite **8** with bis(benzoyl)disulfide leads to a single diastereomer **9** (Scheme 3).

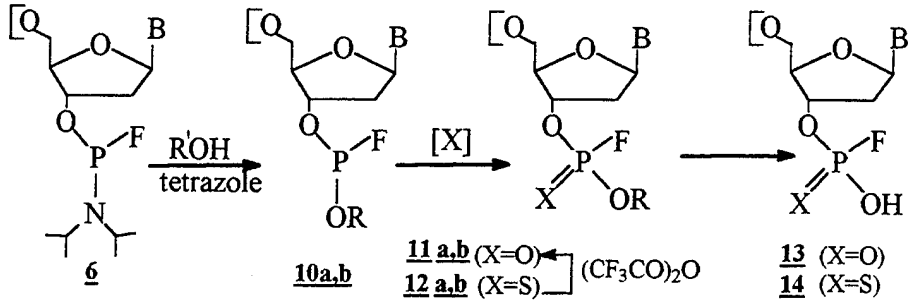


Scheme 3

Compounds **9** containing a thiophosphoryl group are distinctly more resistant towards hydrolysis and other nucleophilic displacements than their oxo analogues. Hydrolytic susceptibility of phosphorofluoridates and phosphorofluoridothionates is strongly influenced by the presence of fluoride ions. The same phenomenon was also observed in our studies [7]. Unexpected high stability of phosphorofluoridites **8** towards hydrolysis is somewhat surprising.

Another example of our strategy is a novel approach towards synthesis of ionic 3'- or 5'-nucleosidylphosphorofluoridates RO-P(O)(OH)F **13** and 3'- or 5'-nucleosidyl phosphorofluoridothionates RO-P(S)(OH)F **14** via P(III)-intermediates **6**. Thioacids **14** were unknown within nucleotide chemistry.

Thiophosphoroamidofluoridites **6** react smoothly at room temperature in the presence of tetrazole with an equivalent amount of tert-butanol or 2-cyanoethanol to give the corresponding fluoridites **10**.



Scheme 4 **a:**R=Bu^t **b:** R=CH_2CH_2CN B: Th,Ad(Bz)

Oxidation of phosphorofluoridities **10a,b** by tert-butylhydroperoxide or addition of elemental sulfur gave the fluoridates **11a,b** or fluoridothionates **12a,b**. Both compounds **11a,b** and **12a,b** were converted by elimination of 2-methyl-1-propen or vinyl cyanide into the desired final products **13** and **14**. Phosphorofluoridothionates **12a,b** were converted by trifluoroacetyl anhydride into the corresponding oxo derivatives **11a,b.** Compounds **14** have a chiral phosphorus center and their separation into pure diastereoisomers is currently being studied.

We believe, that further developments in the field of P(III)-F modified nucleotides may lead up to even more significant discoveries of general importance in bioorganic chemistry.

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OLIGONUCLEOTIDES SHACKLED WITH TETRAPHENYLPORPHYRIN

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Abstract Phosphorus(V)porphyrin derivative photocleaved a double stranded circular DNA, ϕx 174FRI, in the absence of oxygen. The potential of photoexcited phosphorus(V)porphyrin derivative has sufficient oxidation potential to oxidize nucleic acid bases. Photocleavage of DNA by a direct electron transfer mechanism was confirmed. Several definite-sequenced oligonucleotides shackled with tetraphenylporphyrin were synthesized. They hybridized with their complementary oligonucleotides, respectively. A sharply sequence targeted photocleavage of DNA through the direct electron transfer was suggested.

Key Words Oligonulceotide/ Tetraphenylporphyrin/ Artificial restrictive enzyme/ Oligonucleotide shackled with porphyrin

1. INTRODUCTION

Photofunctional oligonucleotide derivatives chemically modified by photoactive molecules are employed for non-radioactive probes, artificial photoenzymes, and tools for photochemical examining of gene expression. We have reported phosphorus(V)tetraphenylporphyrin (P(V)TPP) derivatives[1~7] are useful and artificial photonuclease in which photo-induced electron transfer was investigated.[8~12] In this paper, DNA photocleaving ability of P(V)TPP, syntheses of novel oligonuleotide derivatives shackled with tetraphenylporphyrin (TPP) at the phosphorus atom of an internucleotide phosphodiester without change of backbone of the nucleotide and their interactive properties with their complementary oligonucleotide are investigated, and the possibility of an artificial restrictive photonuclease is suggested.

2. P(V)TPP, OLIGONUCLEOTIDE SHACKLED WITH TPP AND THEIR DERIVATIVES

The followings are examples of P(V)porphyrins and oligonucleotide shackled with porphyrins. The oligonucleotides shackled with TPP were synthesized by DNA synthesizer using a key molecule which is shown in Fig.1.

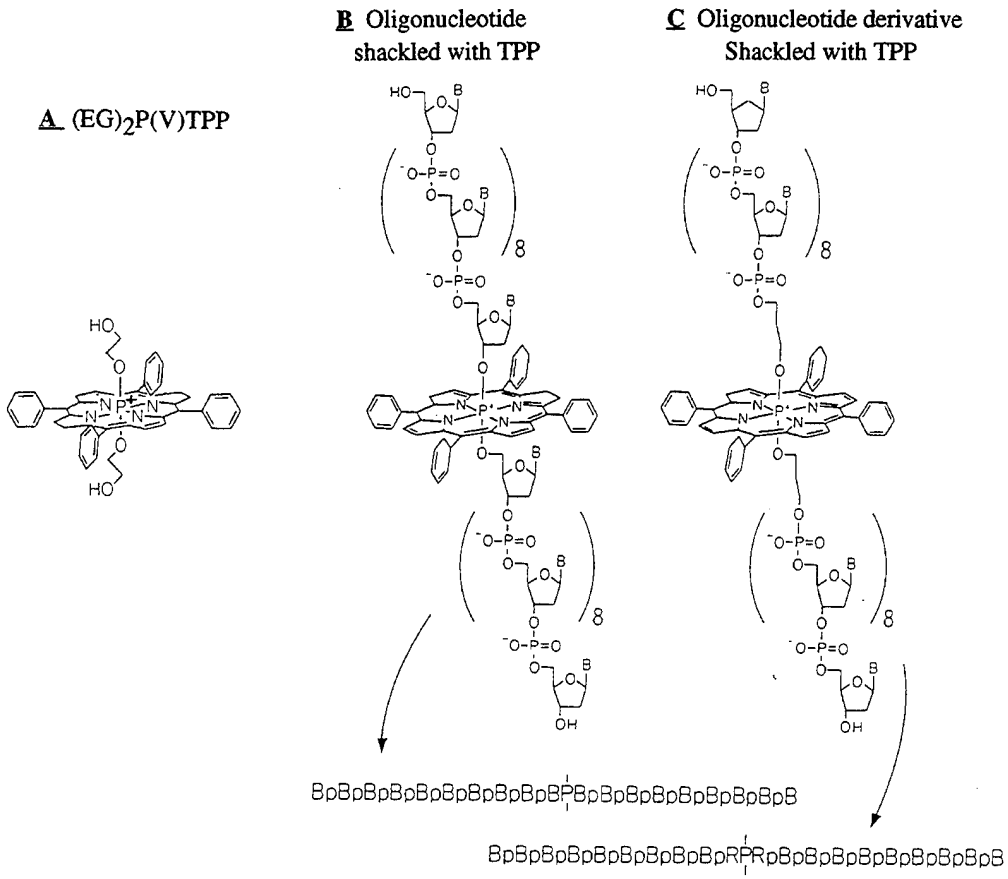


Fig.1 $(EG)_2P(V)TPP$, oligonucleotides shackled with TPP and their derivatives (examples)

3.PHOTOCLEAVAGES OF DOUBLE-STRANDED ΦX 174 DNA WITH P(V)TPP DERIVATIVE

The photograph in Fig.2 shows typical examples of the photoceavage of DNA by visible light irradiation of ϕx 174RFI DNA in the presence of the $(EG)_2P(V)TPP$ in aerated solution resulted in the appearance of open circular DNA (form II) and a small amount of linear DNA (form III). The photocleavage was enhanced by the increase of the concentration of the $(EG)_2P(V)TPP$ and irrradiation time. No strand scission was observed in the absence of $(EG)_2P(V)TPP$ and in the dark . To detect the reactive oxygen species in the photoreaction, the effects of scavengers were examined. As shown in lanes 3-5, NaN_3 effectively inhibited the DNA cleavage. However, SOD and D-mannitol did not inhibit the DNA cleavage. These findings suggest that the main reactive species in the photocleavage in air is singlet oxygen ($^1O_2$), but not superoxide anion radical or hydroxy radical. Energy transfer from the triplet excited state of the $(EG)_2P(V)TPP$ to O_2 is considered to have resulted in the formation of $^1O_2$, which causes oxidative cleavage of the DNA. In fact, the time-resolved absorption spectroscopy indicated that the lifetime of the triplet excited state of the $(EG)_2P(V)TPP$ was shortened with O_2. Interestingly, the

single-strand scission of DNA was also observed even in the absence of $^1O_2$ (lane 6). This result suggests the photocleavage of DNA by the direct electron transfer between the $(EG)_2P(V)TPP$ and DNA. In general, decompositionof DNA by direct electron transfer is initiated from the oxidation of nuclei acid bases, mainly guanine in the absence of $^1O_2$. The reduction potentials of the $(EG)_2P(V)TPP$ in the singlet and the triplet excited states are estimated +1.83V and +1.44 (vs NHE), respectively. These values are considered to be high enough to oxidize all nucleic acid bases. Fig.3 shows mechanism of the photocleavage.

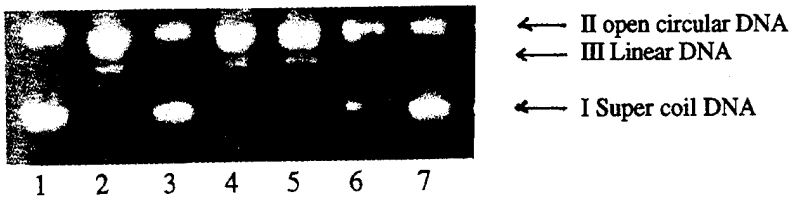


Fig.2. Agarose gel electrophoresis showing relaxation of ϕx 174RFI DNA (40mM) due to photocleavage by $(EG)_2P(V)TPP$ (20mM) in 20 mM Tris HCl buffer, pH 6.8 containing 10mM NaCl. Lane1, DNA only: Lane2, DNA+P(V)TPP in air: Lane3, Lane2+NaN3 (100mM). Lane4, Lane2+SOD (10ng/ml): Lane5, Lane2+D-mannitol (100mM): Lane6, DNA+P(V)TPP in argon saturated aqueous solution. All irradiation were performed for 1 hr. Control experiments, lane7 was performed without irradiation.

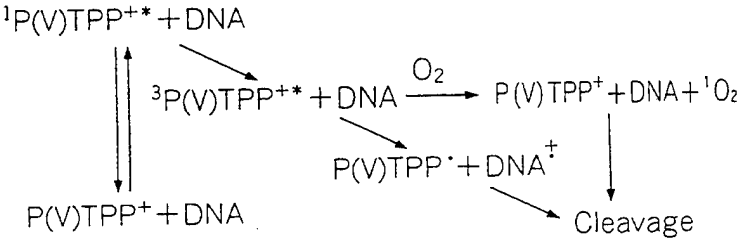


Fig.3. Mechanism of photocleavage of ϕx 174RFI DNA by $(EG)_2P(V)TPP$.

4. HYBRIDIZATION OF THE OLIGONUCLEOTIDE DERIVATIVES SHACKLED WITH TETRAPHENYLPORPHYRIN AND THEIR COMPLEMENTARY OLIGONUCLEOTIDE

The specific interactions, hybridizations, of the oligonucleotide derivatives with their complementary oligonucleotides were investigated by temperature-dependent UV spectra. Table 1 shows examples of melting points of hybrid. In table, Nos. 1 ~ 6 were for homooligonucleotides and Nos. 7 ~ 9 were for sequence-defined derivatives. Compared derative series (Nos. 2,3, and 4) with a native one (No.1), both porphyrin and abasic spacer decreases hybridization a little, however sharp meltings were observed. The sequence-defined derivatives seems to be more preferable for antisense pairing.

Fluorescence quenching were reduced in the molten temperature range, which suggests possibility of a direct electron transfer from a base to excited porphyrin in hybrid.
CD spectra of these hybrid were almost similar to those of complementary native oligonucleotide.

Table 1. Melting temperature of Hybrids

No.		mp/°C
1	TpTpTpTpTpTpTpTpTpTpTpTpTpTpTpTpTpTpT ApApApApApApApApApApApApApApApApApApA	48
2	TpTpTpTpTpTpTpTpTpTPTpTpTpTpTpTpTpTpT ApApApApApApApApApApApApApApApApApApApA	33
3	TpTpTpTpTpTpTpTpTpRPRpTpTpTpTpTpTpTpTpT ApApApApApApApApApApApApApApApApApApApA	32~33
4	TpTpTpTpTpTpTpTpTpRpRpTpTpTpTpTpTpTpTpT ApApApApApApApApApApApApApApApApApApApA	32~33
5	TpTpTpTpTpTpTpTpTpRPRpTpTpTpTpTpTpTpTpT ···pApApApApApApApApApApApApApApApApApApApApAp···	33~34
6	TpTpTpTpTpTpTpTpTpRPRpTpTpTpTpTpTpTpTpT ApApApApApApApApApA	22
7	TpTpApTpApApApTpTpTpTpTpTpApApApTpApTpT ApApTpApTpTpTpApApApApApTpTpTpApTpApA	41
8	TpTpApTpApApApTpTpTPTpTpTpApApApTpApTpT ApApTpApTpTpTpApApApApApTpTpTpApTpApA	29
9	TpTpApTpApApApTpTpRPRpTpTpApApApTpApTpT ApApTpApTpTpTpApApApApApTpTpTpApTpApA	20~21

These results imply that hybrids of oligonucleotide shackled with TPP and its complementary oligonucleotide are almost similar tight shape as native ones, and a photoceavage of the targeted DNA sequence by photo-induced direct electron transfer is suggested.

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MAGNESIUM-MEDIATED CLEAVAGE OF PHOSPHORUS-OXYGEN BOND: A RIBOZYME REACTION

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Abstract The hammerhead ribozyme belongs to the class of molecules known as antisense RNAs. However, because of short extra sequences that form the so-called catalytic loop, it can act as an enzyme. Since the catalytic domain captures Mg^{2+} ions and Mg^{2+} ions can cleave phosphodiester bonds, hammerhead ribozymes are recognized as metalloenzymes. In general, the cleavage of phosphodiester bonds involves acid/base catalysis, with proton transfer occurring in the transition state. When the possibility of such a proton-transfer process was examined by measuring solvent isotope effects, it became apparent that no proton transfer occurs in the transition state during reactions catalyzed by a hammerhead ribozyme. It is likely, therefore, that hammerhead ribozymes exploit the general double-metal-ion mechanism of catalysis, with Mg^{2+} ions coordinating directly with the attacking and leaving oxygen moieties. Moreover, NMR data suggest that Mg^{2+} ions are not only important as the true catalysts in the function of ribozyme-type metalloenzymes but they also induce the structural change in the R32 hammerhead ribozyme that is necessary for establishment of the active form of the ribozyme-substrate complex.

Key Words: RNA; NMR; ribozyme; mechanism, cleavage, magnesium.

INTRODUCTION

Naturally occurring hammerhead ribozymes were found within RNA viruses and they act "in *cis*" during viral replication by the rolling circle mechanism [1]. Hammerhead ribozymes have been engineered in such a way that they can act "in *trans*" against other RNA molecules [2,3]. The *trans*-acting hammerhead ribozyme developed by Haseloff and Gerlach [3] consists of an antisense section (stems I and III) and a catalytic domain with a flanking stem II and loop section (Fig. 1a). Because of the small size of hammerhead ribozymes, they are very suitable for mechanistic studies, being good representatives of catalytic RNA. Over the past few years, it has become apparent that ribozymes are metalloenzymes [4-11]. The first direct evidence that a Mg^{2+} ion acts as

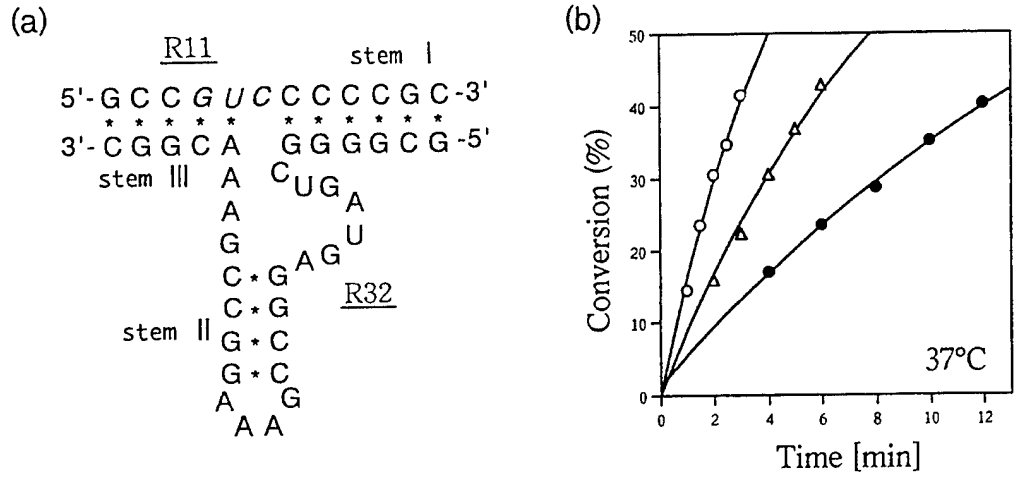


FIGURE 1 (a) *Trans*-acting hammerhead ribozyme (R32) and its substrate (R11). (b) Time courses of product formation. Reactions were followed in a solution that contained 2.5 μM ribozyme (R32), 0.5 μM substrate (R11), and 25 mM $MgCl_2$, in 50 mM MES buffer (pH 6.0) at 37 °C (single-turnover conditions). All the reagents were prepared and kinetics were examined in (i) H_2O (open circles), (ii) 50% D_2O (open triangles), or (iii) pure D_2O (closed circles).

a Lewis acid via coordination to the leaving 3'-oxygen, with stabilization of the developing negative charge on the leaving 3'-oxygen, was obtained from studies of the *Tetrahymena* ribozyme; such a mechanism was apparent from a switch in metal ion specificity with a 3'-thio-substrate [5]. Base catalysis mediated by Mg^{2+}-hydroxide was proposed on the basis of pH-rate profiles of various metal ion-catalyzed reactions of the hammerhead ribozyme [4]. Although the number of Mg^{2+} ions involved in catalysis by hammerhead ribozymes remains to be determined unequivocally, a general two-metal-ion mechanism would be well suited to a phosphotransfer reaction catalyzed by ribozymes or by protein enzymes, such as polymerases and alkaline phosphatase [8].

In the case of RNase A, a protein that is not a metalloenzyme, the reaction is initiated by a histidine residue at position 12 (His12), which acts as a base catalyst by abstracting a proton from 2'-OH (Fig. 2a). Then the resulting, more nucleophilic 2'-oxygen attacks phosphorus to generate a pentacoordinate intermediate/transition state. Finally, His119 acts as an acid catalyst by supplying a proton to the leaving 5'-oxygen, with the resultant cleavage of the exocyclic P-O(5') bond. The acid/base system

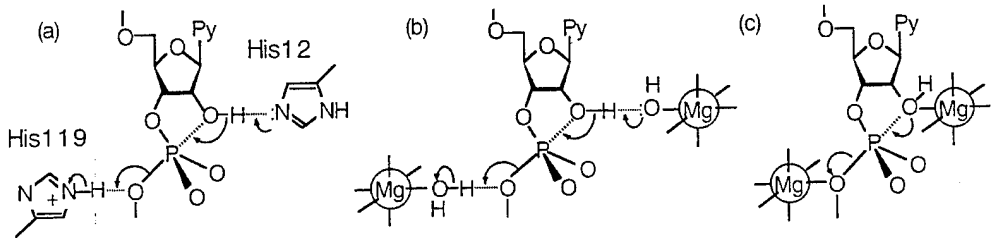


FIGURE 2 (a) Reaction mechanism for the cleavage of a phosphodiester bond by RNase A. Two histidine residues act as an acid (His119) and a base (His12) catalyst, respectively. (b) Magnesium-bound water molecules at the cleavage site of a hammerhead ribozyme catalyze the reaction by functioning as an acid and a base catalyst. (c) Catalytic magnesium ions at the cleavage site of a hammerhead ribozyme catalyze the reaction by directly coordinating to attacking and leaving oxygens. At least one magnesium ion is also directly coordinated with the *pro*-R phosphoryl oxygen.

provded by the two histidine residues in RNase A can, in principle, be replaced by Mg^{2+}-bound water moieties (Fig. 2b) [12]. Alternatively, according to our molecular orbital calculations [7,10,13-19], direct coordination of Mg^{2+} ions with the attacking or the leaving oxygen can promote formation or cleavage of the P-O bond (Fig. 2c). The latter two mechanisms [Fig. 2 (b) and (c)] should be distinguishable because the former (Fig. 2b) involves a proton- transfer process during the transition state whereas the latter (Fig. 2c) does not [11]. In order to examine whether a proton-transfer process occurs at the transition state in reactions catalyzed by hammerhead ribozymes, we measured solvent isotope effects for the 32-mer ribozyme (R32; Fig. 1a). We chose R32 because, in this case, the chemical cleavage step has been proven unambiguously to be the sole rate-limiting step in this system [11,20-23]. Moreover, in order to examine the conformational properties of the R32 ribozyme and the role of Mg^{2+} ions, we analyzed the structure by high-resolution NMR spectroscopy.

RESULTS AND DISCUSSION

In order to examine whether proton-transfer occurs during the transition state of reactions catalyzed by hammerhead ribozyme, we measured solvent isotope effects for R32 under single-turnover conditions. Figure 1b shows the time courses of product formation. All the reagents were prepared and kinetics were examined (i) in H_2O, (ii) in 50% D_2O, and (iii) in pure D_2O. The cleavage rate constant in H_2O was 3.9 times larger than the corresponding value in D_2O at 37 °C. The rate constant in 50% D_2O was intermediate between these two values. Similar effects of deuterium were observed at 25 °C [11]. Since the concentration of Mg^{2+}-OD in D_2O is several-fold lower than that of Mg^{2+}-OH in H_2O at a fixed pH, the reduction in the level of the active species, Mg^{2+}-OD, in D_2O (ΔpK_a) is the sole cause of the lower rate of the reaction in D_2O [11]. The lower activities of ribozymes (metalloenzymes) in D_2O should, therefore, be the result of reduced concentrations of the catalytically active species, Mg^{2+}-OH. Thus, the absence of any kinetic isotope effects, after the correction of ΔpK_a, in the step that leads to cleavage of phosphodiester bonds by ribozymes can be interpreted only in terms of a mechanism in which proton transfer does not take place during the transition state (Fig. 2c).

Direct proof of the mechanism, shown in Figure 2c, should be obtainable using compound **E** (Fig. 3). When we analyzed the stability of **E**, we found that the half-life of **E** was less than one hour at neutral pH and room temperature. **E** appears to be more labile than compound **A**, used by Cech's group [5]. In the case of **E**, the attack of the 2' oxygen produces **F**, wherein the 5' sulfur is placed at the apical position and is ready for departure. By contrast, in **A**, the attack of the 2' oxygen produces **B** wherein the 5' sulfur is at an equatorial position and, thus, unless pseudorotation takes place to produce **C**, the P-S bond is protected [14]. The higher reactivity of **E** makes it more difficult to use **E** in mechanistic studies.

NMR data (not shown) can be summarized as follows: 1) the R32-substrate complex cannot form without Mg^{2+} ions because the recognition arms of R32 form intramolecular base pairs (the recognition arms are closed); and 2) the addition of Mg^{2+} ions causes the recognition arms to be opened (a prerequisite for the ribozyme-substrate interaction since Mg^{2+} ions induce binding of the substrate RNA to the R32 ribozyme). Therefore, Mg^{2+} ions function not only as true catalysts but also to induce structural changes that are favorable for recognition of the substrate RNA.

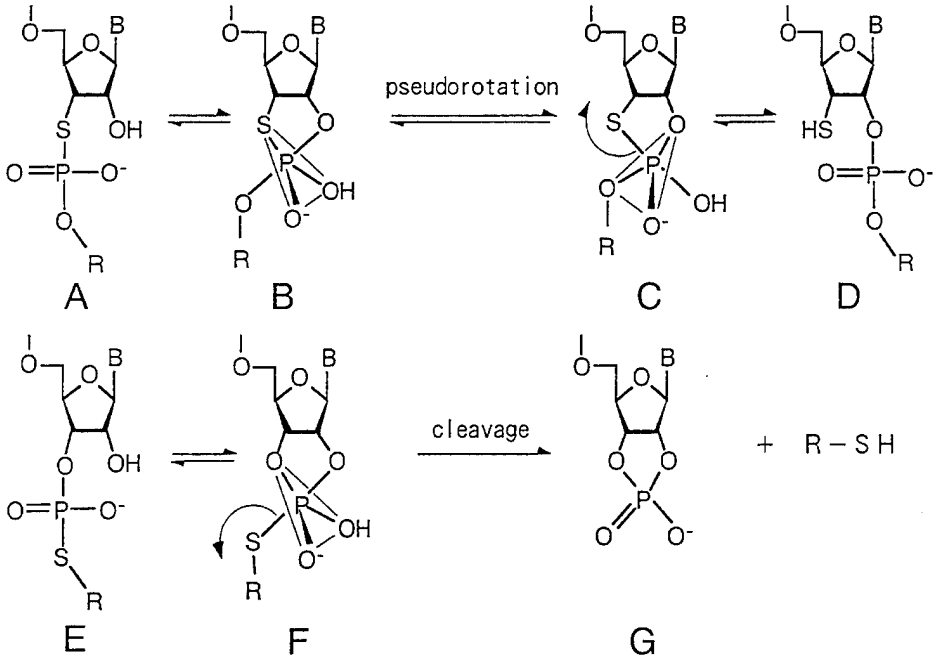


FIGURE 3 Cleavage of phosphorus-sulfur bond for 3'-thio (compound **A**) and 5'-thio (compound **E**) substituted RNA. **E** is more labile than **A** because in **E** the sulfur atom can be placed at the apical position without a requiremnet for pseudorotation.

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DESIGN OF RIBONUCLEASE MIMICS FOR SEQUENCE SPECIFIC CLEAVAGE OF RNA

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Abstract. Hydrolysis of RNA by imidazole conjugates capable of binding to RNA have been investigated. Spermine-imidazole conjugate in the presence of imidazole buffer cleaves RNA at the single-stranded pyrimidine-purine sequences. Oligonucleotides with a diimidazole construction at the terminal phosphate cleave tRNA target in vicinity of the complementary sequences.

Key words antisense oligonucleotides; ribonuclease mimics; tRNA; RNA cleavage.

INTRODUCTION

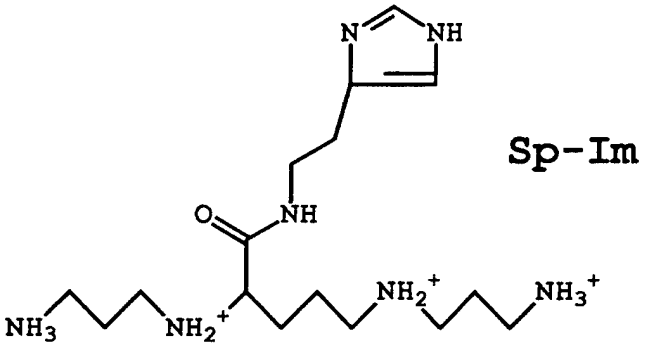
Small specific RNA cleaving agents are required for a number of important applications including development of probes for investigation of RNA structure [1] and design of efficient reactive groups for antisense oligonucleotide derivatives [2]. A few types of RNA cleaving groups including some complexes of metals, peptides and amines were conjugated to intercalating molecules and to oligonucleotides in order to prepare sequence specific artificial RNases [3-8]. Recently we have shown a possibility to mimic the active center of RNase A with small molecules containing two imidazole residues conjugated to an intercalating phenazine dye by linkers of variable length and flexibility (8). In this paper we describe hydrolysis of RNA by conjugates of imidazole with spermine and by oligonucleotides linked to a construction with two imidazole residues.

MATERIALS AND METHODS

Oligonucleotides **1** and **2** complementary to yeast phenylalanine tRNA were synthesized according to standard methods. Spermine- imidazole conjugate **Sp-Im** was synthesized as described in [9].

Synthesis of the diimidazole construction **R** will be described elsewhere. The construction was attached to the terminal phosphates of oligonucleotides by phosphorylation of the amino group with active 4-(N,N-dimethylamino)pyridinium derivatives of oligonucleotides. The latters were prepared by activation of the phosphate residue of oligonucleotides with mixture of triphenylphosphine and 2,2'-dipyridyldisulfide in the presence of 4-(N,N-dimethylamino)pyridine. The conjugates

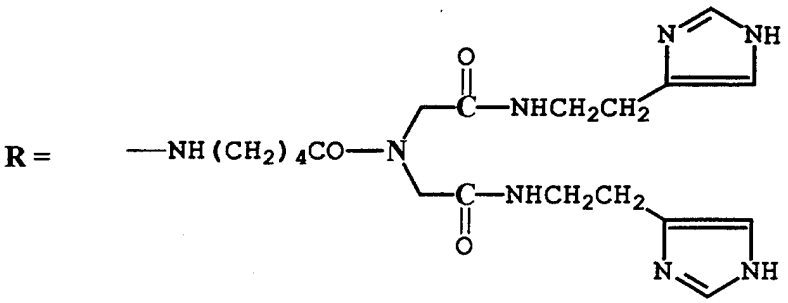
were purified by reverse-phase HPLC and characterized by gel electrophoresis, UV spectroscopy and polyacrylamide gel electrophoresis.



Sp-Im

R-1 R-pGATCGAACACAGGACCT

2-R TGGTGCGAATTCTp-R



Reaction mixtures contained 3'-end labeled $tRNA^{Phe}$ (50 to 100,000 Cerenkov counts) supplemented by 1 μg of carrier tRNA, dissolved in 20 μl of buffer. After the incubation, 20 μl of 0.3 M sodium acetate at pH 5.0 was added to each probe followed by 400 μl of a 2% solution of lithium perchlorate in acetone. The precipitated RNA samples were recovered by centrifugation, washed with acetone, dried and analyzed by electrophoresis.

RESULTS AND DISCUSSION

We expected that **Sp-Im** will bind to RNA electrostatically and deliver imidazole residue to the RNA backbone. The second imidazole needed for the reaction was expected to be provided as a free molecule by the buffer. Indeed it was found that **Sp-Im** cleaves tRNA in the presence of 10-50 mM imidazole buffer. **Sp-Im** alone as well as 50 mM imidazole buffer alone do not cleave tRNA, which proves specific nature of the reaction and eliminates a possibility of hydrolysis by some contaminants. The cleavage of phosphodiester bonds occurs predominantly within the single-stranded regions of the tRNA cloverleaf structure (Fig. 1 A). The major cleavages occur at positions 55 and 20. A reproducible cleavage was observed also at positions 8, 13, 36 and 43. The cleavage occurs after pyrimidines, in particular, in sequences CpA. This is in a general agreement

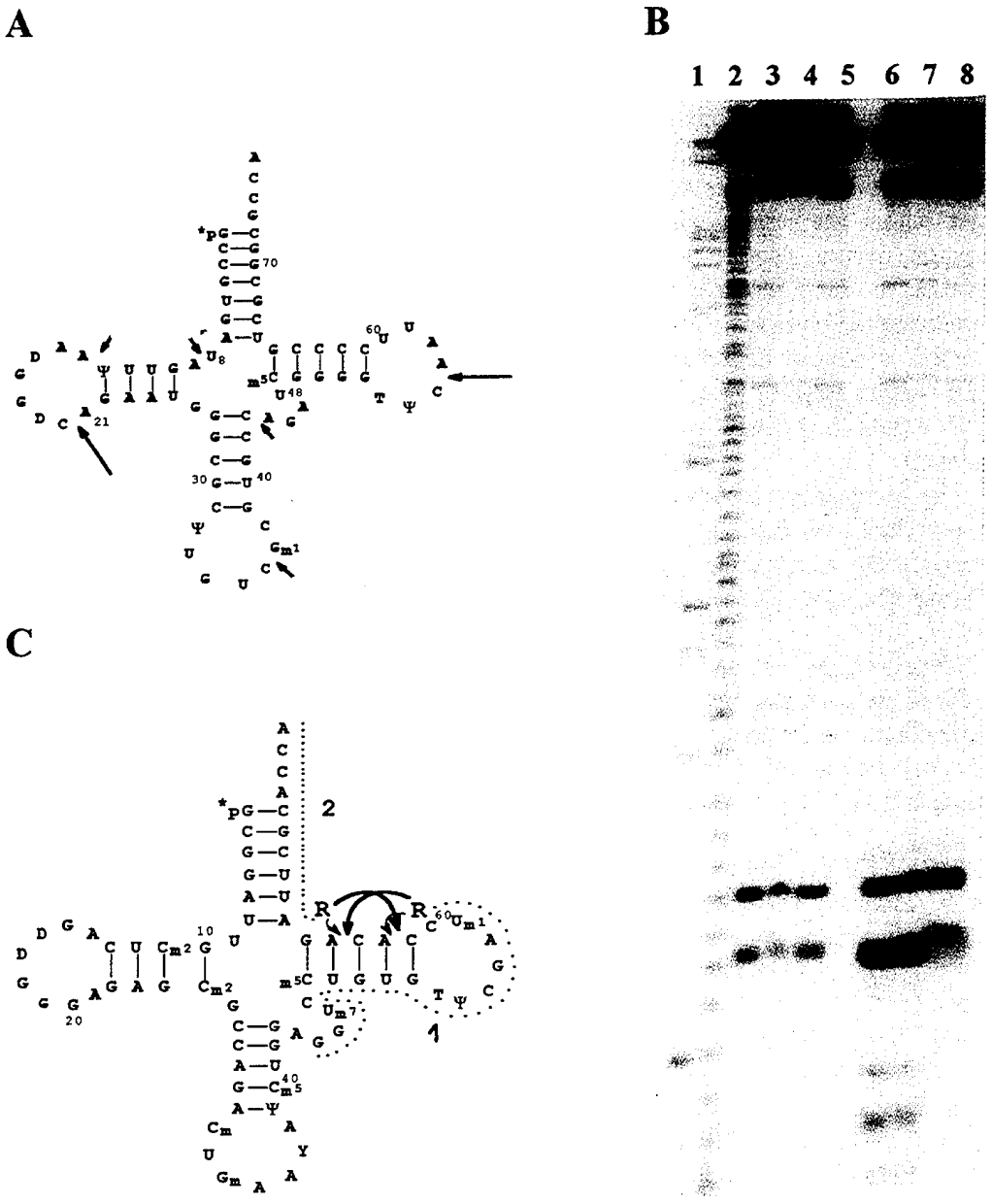


FIGURE 1. **A** $tRNA^{Asp}$. Phosphodiester linkages cleaved by the spermine-imidazole conjugate are indicated by arrows which lengths are proportional to the intensity of the cuts.

B. Cleavage of the 3'-end labeled $tRNA^{Phe}$ by oligonucleotides bearing diimidazole groups. Autoradiogram of a 15% denaturing polyacrylamide gel. The tRNA was incubated in 10 mM HEPES, 0.5 mM EDTA for 10 h at 37^0.

1, RNase T1 digest; 2, Ladder; 3-5 - **2-R**; 6-8 - **R-1**. Concentration of the conjugates was). 0.05 μM. In 4 and 7, the buffer contained 10 mM NaCl. In 8, oligonucleotide 1 was present (0.2 μM).

C. $tRNA^{Phe}$. Oligonucleotide conjugates are shown by zigzag lines along the complementary sequences. Arrows indicate the attacked phosphodiester bonds.

with fragile sites in RNA structure attacked most easily by RNase A and by bis-imidazole constructs tested earlier [8].

For oligonucleotide conjugates, yeast phenylalanine tRNA was used as a target. Results shown in Fig. 1 B,C evidence, that incubation of the tRNA with complementary oligonucleotide conjugates results in scission of phosphodiester bonds 61 and 63 of the target within the region where the imidazole groups were expected to be located. Cleavage occurs also at the phosphodiester bond 8, perhaps it juxtaposed of the sequence to the oligonuleotides binding site in the tertiary structure of the tRNA-oligonucleotide complex. Degradation of tRNA in in the absence of the reagents, in the presence of oligonucleotides without imidazole group or in the presence of the free group was negligible. Excess of the parent nonmodified oligonucleotide inhibited the cleavage which proves that the reaction was mediated by complementary complex formation.

The compounds investigated in this work represent a new family of RNA cleaving groups which can find applications as probes for investigation of RNA structure and function. The diimidazole groups can be used for design of the second generation antisense oligonucleotide derivatives for biological and therapeutic application.

ACKNOWLEDGEMENTS

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ENHANCED PROCLIVITY TO SELF-AGGREGATION OF PHOSPHORUS-BASED AMPHIPHILES WHEN PERFLUOROALKYLATED : THE (PERFLUOROALKYL)ALKYL DIMORPHOLINOPHOSPHATES

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Abstract Dimorpholinophosphates **1**, with a single perfluoroalkyl chain, self-aggregate when dispersed in water to give tubular structures which reversibly transform into giant vesicles when heated. Compounds **1** also allow the preparation of stable reverse water-in-fluorocarbon emulsions destined to pulmonary drug delivery. None of this could be achieved with non-fluorinated analogs.

Key words : Fluorinated phosphorylated amphiphile, fluorinated surfactant, liposome, tubules, water-in-fluorocarbon emulsion, reverse emulsion, drug delivery, fluorocarbon.

INTRODUCTION

A variety of well-defined phosphorus-based amphiphiles fitted with one or two perfluoroalkylated chains have recently been synthesized in our laboratory, and their self-aggregation and emulsion-stabilizing properties were investigated. These amphiphiles include single-chain phosphocholine and double-chain phosphatidylcholine derivatives [1], single- and double-chain glycophospholipids [2] and mono- and dimorpholinophosphates [1a,3]. Earlier work on the colloidal behavior of fluorinated phosphorus-based amphiphiles includes that of Kunitake [4], Ringsdorf et al. [5] and Hui et al. [6].

The impact of the fluorinated chain(s) on the physicochemical and biological properties of amphiphiles has been analyzed in relation to their potential as components of drug carrier and delivery systems [7]. The intense hydrophobic effect developed by these chains results in the formation, not only of vesicles, but also of tubules and other fibers, even from single-chain amphiphiles [8]. When fluorinated vesicles form, they usually withstand heat sterilization [8,9]. Fluorinated liposomes were also obtained from combinations of standard phospholipids with (perfluoroalkyl)alkanes [10]. Perfluoroalkylated phosphocholines were shown to form long flexible fibers without recourse to hydrogen bonding, chiral effect or polymerization [11]. Bilayers made from

fluorinated phospholipids are characterized by the presence of a fluorinated film within the bilayer membrane, which results in enhanced stability and lower permeability to both hydrophilic and lipophilic drugs and other materials [7].

Perfluoroalkylated dimorpholinophosphates $C_nF_{2n+1}(CH_2)_mOP(O)[N(CH_2CH_2)_2O]_2$ **1**, were readily obtained in 65-80 % yields in two steps [3]. They constitute poorly hydrophilic, highly fluorophilic surfactants. Preliminary acute toxicity tests indicate LD_{50} values superior to 1g per kg body weight intravenously in mice for **1** (n = 8, m = 11); no hemolytic activity was found (n = 6 or 8, m = 2), even at a concentration of 5 g/L; and an inverse emulsion (see below) based on 1% of **1** (n = 8, m = 11), when injected intraperitonealy at a dose of 25 mL/kg in mice, was well tolerated. Actually, these truly miraculous dimorpholinophosphates were developed by pure chance and malice, to keep an unruly, though amiable, she-student busy.

TUBULAR SUPRAMOLECULAR AGGREGATES

When the dimorpholinophosphate with a hydrocarbon chain, $C_mH_{2m+1}OP(O)[N(CH_2CH_2)O]_2$, with m = 10, was dispersed in water (up to 20% w/v), no aggregates larger than micelles were observed to form, in line with the usual behavior of single chain amphiphiles. Dispersions of the longer analog (m = 15) underwent rapid phase separation. On the contrary, when fluorinated compounds **1** (n = 8 or 10, m = 2 or 5) were dispersed in water at a 1 to 6% w/v concentration, tubular assemblies were readily obtained. Within hours the tubules of **1** (n = 8, m = 2) typically reached 10 to 50 μm in length and 0.1 to 0.5 μm in diameter. For certain compounds, for example **1** (n = 8, m = 5), the tubules can reach several hundreds of nm (fig. 1a). These tubules appear to consist of rolled up bilayers (fig. 1b). Upon heating, one observes their reversible conversion into giant vesicles. The transformation temperature increases with the length of the fluorinated chain (40°C for n = 8, m = 2; 65°C for n = 10, m = 2). Optical polarization microscopy of the giant vesicles showed maltese crosses revealing a lamellar arrangement of the surfactant. These characteristic defects were no longer present in the tubules, indicating a more ordered, more crystalline structure. The formation of such highly organized structures from short single-chain amphiphiles, without the help of a chiral center, rigid rod(s) or hydrogen bonds usually required [12,13], while no such constructs were obtained from non-fluorinated analogs, illustrates the powerful driving force towards self-aggregation exerted by the strongly hydrophobic and bulkier perfluoroalkyl chains. Tubular self-assemblies were also obtained in non aqueous organic solvents such as dimethylformamide [14].

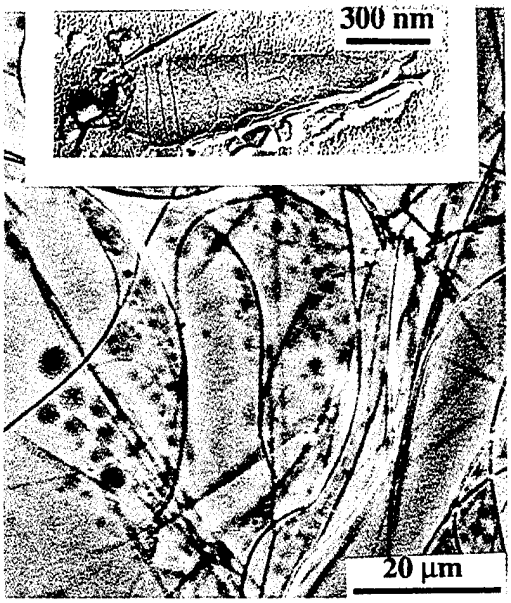


FIGURE 1: Optical and freeze fracture electron micrographs of a 6% aqueous dispersion of **1** (n = 8, m = 5) showing tubular structures .

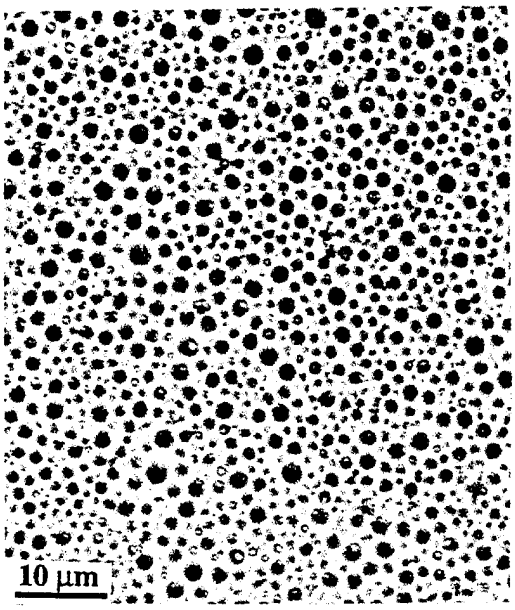


FIGURE 2: Optical micrograph (phase contrast) of a reverse water-in-perfluoroctyl bromide emulsion stabilized by **1** (n = 8, m = 11), obtained by simple hand-shaking.

STABLE WATER-IN-FLUOROCARBON REVERSE EMULSIONS

The dimorpholinophosphates **1** were also found to strongly stabilize reverse water-in-fluorocarbon emulsions [15]. Such emulsions show promise for pulmonary administration of drugs. They can be loaded with a variety of drugs, contrast agents, surfactants, immunoactive agents, genetic and other materials. Reverse emulsions also give access to multiple emulsions, including hydrocarbon-in-water-in-fluorocarbon emulsions and water-in-fluorocarbon-in-water emulsions. When an aqueous inner space is present, it can also be filled with vesicles, capsules, micelles, polymers, etc. Such systems could provide protection and controlled release for biologically active materials, as well as depot and other effects.

A series of water-in-fluorocarbon emulsions were obtained with a water content ranging from *ca* 1 to 30% v/v in a variety of linear and cyclic fluorocarbons. A typical emulsion with 5% v/v of water and 2% w/v of **1** (n = 8, m = 11) in perfluorooctyl bromide had an average particle size of *ca* 500 nm for 1 month at room temperature (fig. 2). This emulsion was stable enough to withstand heat sterilization (121°C, 15 min, 15 N m^{-2}). The reverse water-in-oil situation was verified by phase-contrast optical

microscopy after including a water soluble dye, and by the fact that these emulsions can easily be diluted in a fluorocarbon, but not in water. Smaller average particle sizes and further stabilization were achieved by addition of electrolytes such as NaCl, KI or $CaCl_2$. No stable emulsion could be obtained with dimorpholinophosphates that did not bear a fluorocarbon chain, while the fluorinated compounds **1** readily produced a stable film at the water/fluorocarbon interface.

Pulmonary drugs that were incorporated in such emulsions include acetyl cysteine (a mucolytic agent), pyrazinamide (a tuberculostatic agent), epinephrine (a bronchodilator) and prednisone.

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Phospholipid-Alcohol Interactions: Effects of Chain-length and Headgroup Variations

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Introduction: Solvated phospholipids exhibit a rich polymorphism which depends not only on the lipid chemical structure but also on the characteristics of the bathing solution [1]. This is due to the strong and influential interactions between the lipid headgroups and the solvent or solute molecules. Particularly efficient in this respect are various cationic molecules or molecules with a high propensity to hydrogen bond formation which all bind avidly to the lipid phosphate groups. The di- and polyvalent cations, for example, are electrostatically attracted by the negative electronic cloud around the (typically ionized) PO_4^--group; protons donating or accepting molecules, such as the amino-compounds or the molecules with the readily accessible OH-residues, bind directly to the OH-groups on the phosphates via H-bonds. Water and various alcohols are the most prominent examples for this latter type of interaction.

In all practical phospholipid applications such interactions must be kept in mind and should also be well understood. We have thus attempted to highlight the molecular mechanisms of the solute- or solvent-glycerophosphate interactions but also their effects on the colloidal and phase properties of several common phospholipids. To this end we have studied systematically the outcome of alcohol interactions with the fully hydrated diacylphosphatidylcholines (PC-s) and related compounds [2, 3, 4, 5]. Specifically, the shifts of the lipid chain-melting (order-disorder = gel-to-fluid = $P'_\beta \rightarrow L_\alpha$) phase transition, pretransition ($L'_\beta \rightarrow P'_\beta$) and subtransition ($L'_c \rightarrow L'_\beta$) temperature as well as the changes in lipid vesicle morphology were determined as a function of the bulk alcohol concentration. The scanning differential calorimetry, X-ray diffractometry, the dynamic light scattering as well as fluorescent marker leakage studies afforded a fairly clear and general picture of the processes that are involved in the binding of solutes (and solvents) to the phosphate groups on the lipid molecules.

Materials and Methods: 1,2-Dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC, purity > 99 %) was from Boehringer-Mannheim (D) or Sygena (Liesthal, CH). Ethanol (EtOH, p.a.) was obtained from Merck (Darmstadt, D). Water (18 MΩ cm) was doubly distilled in an all glass apparatus and was reprocessed by a water purification unit (Elgastat HQ). Differential scanning calorimetry was done with the multi-lamellar suspensions (usually 5 mM and aged, if necessary, for several weeks) in a MC2 scanning calorimeter (MicroCal, Inc., Amherst, MA) with the original data acquisition and analysis software (ORIGIN). X-ray diffractogrammes were measured with a Guinier x-ray diffraction camera (Huber Diffraktionstechnik, Rimsting, D) using a copper $L_{\alpha 1}$ line and approx. 150 mM multi-bilayer samples in the glass capillary positioned in a brass holder thermostated to ±0.1°C; by lifting the film holder and simultaneously changing the sample temperature continuous temperature scans were recorded.

To prepare the samples for the optical measurements, suspensions of multilamellar lipid vesicles (75 mM DPPC) in water were sonicated (Heat Systems W 380, USA) at 42°C) or extruded (LiposoFast, Avestin, Ottawa, Can) through a microporous (most often 100 nm (Poretics)) filter until the average vesicle diameter was approximately 50 to 60 nm. Vesicle size in the resulting (sterile) preparation was controlled prior to each experiment; it remained stable for several weeks, at least.

Results and Discussion: It is well known that the solvation of phospholipids in any protic solvent depends on the lipid affinity for the solvent as well as on the range of the inter-solvent interactions [7]. Phospholipid hydration first involves the water binding to the anionic phosphate group oxygens and then phosphodiester bridging by the water molecules [6]. (The avidity of water association with the other polar groups, such as amino-, choline, or glycerol-group, is lower than for the phosphate.)

Phosphate groups, consequently, are pushed apart by solvation which thence forces the phospholipid aggregates to swell in all directions [7]. In the low-temperature, ordered phase, characterized by the tight contacts and strong van der Waals attraction between the lipid chains, the resulting molecular area expansion, ΔA_L, is accompanied by the sliding of the parallel hydrocarbon chains along their long axes; simultaneously the lipid chain tilt, ϕ_{tilt}, increases [8]. The thickness of the interfacial region, d_p, which encompasses the lipid headgroups as well as the bound water molecules, also gets greater with increasing hydration [9]. The swelling-associated effects are limited, however, by the maximum number of the directly bound water molecules achievable and by the relatively short range of the strong inter-water interactions ($\Lambda_{eff} \sim \underline{0.1} \cdots 0.3$ nm) [7]. These maximum values were estimated to be $\Delta A_L \leq 25$ % [8], $d_p \geq 100$ %, and $\phi_{tilt} \leq 30$o [10] which suffices for the induction of the isothermal lipid phase transitions in appropriate temperature and water-concentration ranges [11].

The short chain alcohols also bind to the phosphate groups like the first tightly bound water molecules. Alcohol binding thence involves the hydrogen bond formation between the anionic oxygens on the PO_4^--groups and the alcohol OH-residue. Some of the phospholipid's water of hydration, consequently, is replaced (or displaced) by the bound alcohol, as concluding from the FT-IR spectra of the phosphate and carbonyl-group regions (N. Nagel and G. Cevc, to be published). The interaction of alcohol's aliphatic chains with the outer membrane region is also important, the longer the alcohol the more so. The effects of alcohol partitioning into or binding to the bilayer are precisely the opposite, however, in the gel- and fluid-lipid phases. While the lipid chain packing in the former, ordered phase is improved by the presence of alcohols [3], the alcohol binding to the fluid-phase bilayers promotes the chain disorder [12]. Chain ordering is mirrored in the much sharper Bragg-peaks in the small-angle X-ray diffraction patterns of the multilamellar stack for the lipids with bound alcohol [4]; enhanced chain disorder is reflected in the more rapidly decaying order parameter profiles measured for the per-deuterated phospholipid chains by the ^{2}H-nuclear magnetic resonance (L. Löbbecke and G. Cevc, to be published).

In spite of such apparent discrepancy both effects have the same roots: any short-chain alcohol-lipid association always promotes the lateral as well as the transverse repulsion between the phospholipid molecules but the resulting stress may be dissipated differently in different phases.

In the ordered (L'_β-phase), the alcohol-induced lateral expansion has to enlarge the tilt of the ordered, fully extended, parallel and strongly interacting hydrocarbon chains (by up to 23°) [4]. The area of phosphatidylcholine molecules in the L'_β-phase, moreover, is increased by $\leq$ 40 % to the maximum possible value of $A_L \simeq 0.7$ nm^2 in the presence of alcohols. Alcohol-phospholipid association, furthermore, broadens the lipid-water interface and promotes the membrane solvation (inter-membrane separation). Gel-phase PC bilayers, consequently, accommodate up to 130 % more alcohol-water mixture than pure water [4].

When the solvation-induced hydrocarbon tilt reaches its sterically permissible maximum value of 53°, any further area increase must involve a different type of membrane adaptation. Chain-interdigitation is the most obvious and common solution to this problem as it doubles the area per lipid headgroup and yet maintains the close contacts between the chains.

Extensive alcohol binding therefore provokes the successive interdigitation of the ordered hydrocarbon chains. This occurs in molecular clusters due to the packing incompatibility between the interdigitated and normal bilayer regions. It seems that the interdigitated domains are distributed uniformly over the whole lipid membrane which forces the surface of all lipid vesicles in the presence of alcohols to get fragmented into the co-existing, but not parallel domains. Throughout the phase-coexistence region the highly permeable and perturbed boundaries are therefore formed in any gel-phase diacylphosphatidylcholine layer. Such domain borders are most abundant when the lipid interdigitation exceeds just about 50 % and are easily identifiable by an 'anomalous' decrease in the average vesicle diameter [3] or in the concomitant lipid (bi)layer permeability increase in the coexistence region [12].

This point is reached at some characteristic stoichiometric lipid/alcohol ratio (which decreases from 7 for the short chain alcohols to 2 for the longer chains) and corresponds to the mono-domain lipid membranes with un-tilted chains. Further rising the amount of the bound alcohol—and thus increasing the lateral repulsion—is again compensated by the chain tilting. The maximum chain tilt in the interdigitated seems to be the same as in the normal lipid bilayer, 53°.

In the fluid L_α phase the phospholipid molecules are less constrained in their conformational freedom than in the L_β state. They are therefore not forced to adapt themselves to the ambient stress in cohorts, as in the gel phase. Lipids above their chain-melting phase transition temperature, consequently, increase their area simply by the progressive chain fluidization. This permits any initial structural changes originating from the alcohol binding to be gradual. (The propensity of the fluid, alcohol-doped membranes to fuse [4] provides a circumstantial evidence for the conclusion that domains of different alcohol/phospholipid stoichiometry may exist.)

Ultimately, the fluid phase phospholipids are solubilized by the bound alcohol molecules. This transition occurs in several steps and is complete when the PC/alcohol molar association ratio exceeds the value of 2-3 [12].

The chain-melting phase transition temperature of fully solvated phospholipids, T_m, depends on the chain-length of the added alcohol: short-chain alcohols (up to n-propanol) first decrease and then increase the T_m-value. For the alcohols with longer chains (up to n-heptanol), however, the T_m-value decreases over the whole investigated alcohol concentration range, however [5]. Both pretransition as well as subtransition

temperature of PC-s are first monotonously (but non-linearly) lowered by increasing the bulk alcohol concentration. The former transition disappears at some characteristic, chain-length dependent alcohol concentration. This point, K, in the solute-dependent phase diagram of PC marks the complete hydrocarbon interdigitation [5].

The K-value, and most other alcohol-dependent lipid layer characteristics, decreases with increasing alcohol chain-length and is largely determined by the free energy of transfer of alcohols from the aqueous sub-phase into the phospholipid layer. n-Alcohols as well as alcohols with OH-groups at the second or third position on aliphatic chain obey this trend, provided that their length does not exceed approximately half of the phospholipid chain length. This experimentally established functional dependence can be described quantitatively within the framework of an apparent chain-length concept allowing for the fact that the long-chain alcohols have a much higher probability to partition into the bilayer than the short-chain ones [5]; going from methanol to heptanol thus decreases the K-value from 3 M to 8 mM, for example, in the log-linear manner. Phosphatidylcholine solubilization follows the same trend.

Phospholipids sensitivity to the perturbation by the phosphate-bound alcohol increases with their lipid chain-length [12] and, in particular, with the headgroup polarity [13]. This confirms indirectly our view that the alcohol-induced hydrocarbon interdigitation is, indeed, chiefly a consequence of the solute-induced lateral repulsion (and of the resulting expansion) in the phospholipid headgroup region. When this effect is balanced by the corresponding repulsion in the lipid chain region no chain interdigitation is observed. This explains why the long-chain alcohols, which disorder the phospholipid chains, do not induce interdigitation. On the other hand, this is also the reason why the less polar phospholipids (such as phosphatidylethanolamine-N,N-dimethyl) interdigitate less readily than phosphatidylcholines.

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THE DEVELOPMENT OF IMPROVED CATIONIC LIPIDS FOR GENE TRANSFER INTO CYSTIC FIBROSIS AIRWAY EPITHELIAL CELLS

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Abstract In an effort to improve the efficiency of cationic lipid mediated gene transfer, over 90 novel cationic lipids of diverse structural types were synthesized and evaluated *in vitro*. Four cationic lipids derived from phospholipids were examined. The most promising cationic lipid formulations were tested *in vivo* by intranasal or transtracheal instillation into the lungs of BALB/c mice. The most active formulations gave CAT reporter gene expression levels which are greater than 500 fold over that which could be attained using free DNA alone. Certain cationic lipid formulations have been shown to facilitate substantial expression of the CFTR (cystic fibrosis transmembrane conductance regulator) gene *in vitro* as determined by the SPQ and Ussing Chamber assays.

Key Words: cystic fibrosis, gene transfer, cationic lipids, phospholipids

INTRODUCTION

Cationic lipids are able to introduce genes into a variety of different cell types [1]. They offer a number of advantages over the use of viral vectors, the most important of which is their potential lack of immunogenicity. However, the efficiency of cationic lipid mediated gene transfer is less than that achieved by viral-based approaches. We at Genzyme have a multi-disciplinary program focused on the development of effective non-viral gene transfer technology for use in the treatment of cystic fibrosis.

RESULTS AND DISCUSSION

In an effort to improve the efficiency of cationic lipid mediated gene transfer, over 90 novel cationic lipids of diverse structural types were synthesized and evaluated using a high-throughput 96 well-based assay. In many cases, cationic lipid formulations that contained dioleoylphosphatidylethanolamine as a co-lipid were found to have the highest transfection efficiencies. A process for the synthesis of dioleoylphosphatidyl-ethanolamine was developed based on Genzyme phospholipid synthesis technology [2] and GLP grade material was prepared via this route (Figure 1). We have evaluated four cationic lipids based on phospholipids (Figure 2). DOGE and DMGE (Avanti Polar Lipids) were found to have transfection efficiencies which were approximately 1.5 to 2 fold greater than DMRIE or DC-chol *in vitro*. DMRIE [3] and DC-chol [3, 4] have been used in gene transfection clinical trials. Cationic Lipids #21 and #54 were only marginally active *in vitro* and not active *in vivo*, under the respective test conditions.

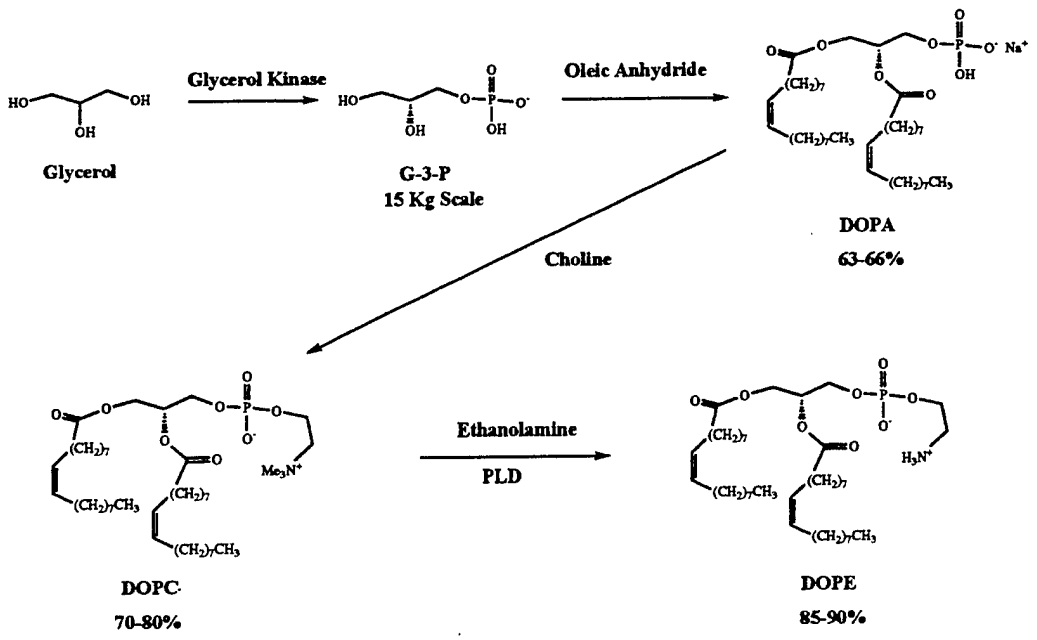


FIGURE 1 Synthesis of dioleoylphosphatidylethanolamine.

Several new cationic lipids with improved transfection efficiencies (greater than 3-fold DMRIE or DC-chol) were identified (Figure 3). Using the optimal conditions, transfection of greater than 80% of airway cells *in vitro* could be achieved. Transfection of CF airway epithelial cells using a CFTR-encoding plasmid restored cAMP-stimulated chloride channel activity as assessed using the SPQ assay [5] and corrected the cAMP-mediated chloride current using the Ussing chamber assay [6]. The most promising cationic lipid formulations were tested *in vivo* by intranasal or transtracheal instillation into the lungs of BALB/c mice. Using a formulation of cationic lipid #67 and the pCMVHI-CAT vector (a reporter gene vector), expression of up to 400 ng of chloramphenicol acyltransferase (CAT) enzyme per mouse lung was achieved. These levels are greater than 500 fold over that which could be attained using free DNA alone. Although expression decreased markedly after a few days, CAT activity could be detected up to 21 days post-instillation.

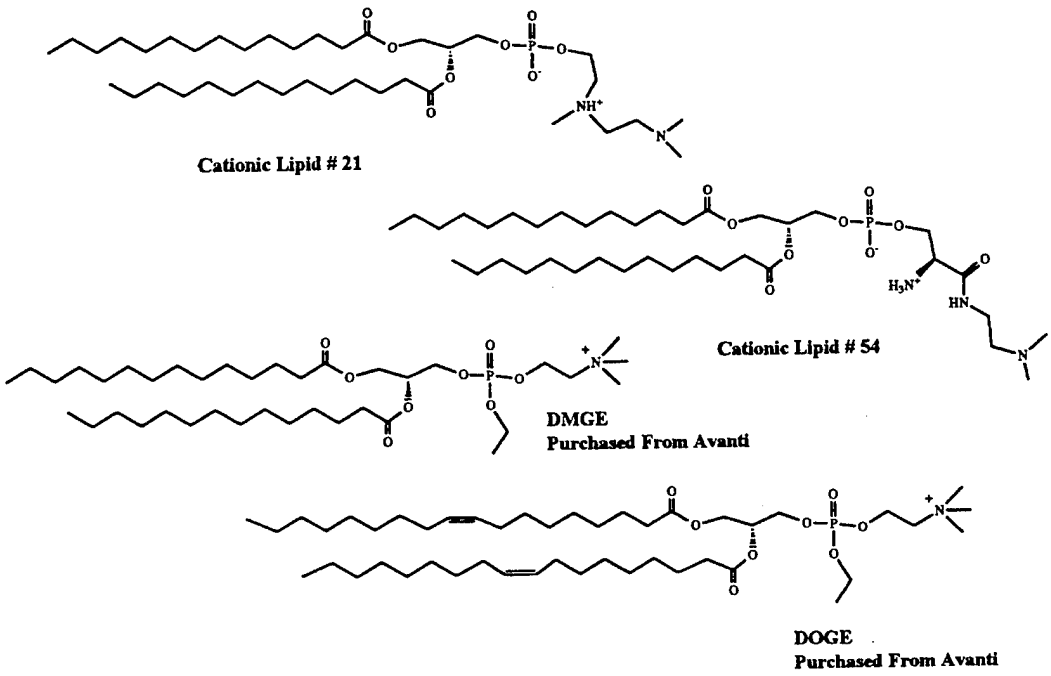


FIGURE 2 Phospholipid Based cationic lipids.

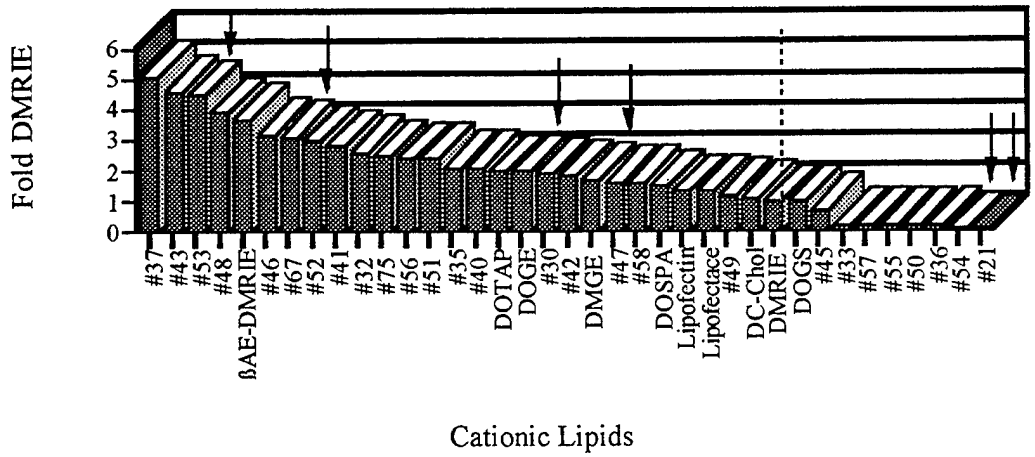


FIGURE 3 Rank order of cationic lipids on CFT1 cells.

CONCLUSIONS

Significant progress has been achieved in increasing the efficiency of cationic lipid mediated gene transfer. These results suggest that with further optimization, cationic lipid mediated gene transfer may be clinically efficacious for the treatment of cystic fibrosis.

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STERICALLY STABILIZED DOXORUBICIN LOADED LIPOSOMES (DOX-SL™): FROM BASICS TO THE CLINICS

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Abstract

This short paper describes the problems, and their solutions, of formulating liposomal dosage forms for clinical use, as exemplified in tumor therapy by liposomal doxorubicin. We will demonstrate that the development of an efficacious drug delivery system requires fitting the delivery system to the micro-anatomy of the tumor. Many tumors have gaps in their capillaries which permit particles smaller than 120 nm to slowly extravasate into the tumor. Therefore small liposomes having a prolonged circulation time may be suitable drug carriers for tumor therapy. Recently a liposomal doxorubicin formulation (DOX-SL™) was recommended for approval by the US FDA, with indications of treating Kaposi's sarcoma. These liposomes seem to be efficacious in other types of tumors as well.The unique features of this formulation include: control of the biodistribution and pharmacokinetics of the intact liposomes through liposome lipid composition, especially the role of steric stabilization of the liposomes which enable prolonging their circulation time (human $t_{1/2}$ > 50 h); stable loading of a sufficient level of drug through an ammonium sulfate gradient; and small particle size (100 nm) These special features enable the development of liposomal doxorubicin which in humans delivers the active drug to the tumor more efficiently than the use of the free drug. These novel liposomal formulations may provide the means for realizing Paul Erlich's dream of active targeting by a "magic bullet".

Key Words: tumor targeting, sterically stabilized liposomes, doxorubicin, ammonium sulfate gradients, drug loading, extravasation.

INTRODUCTION

The main advantage of a drug carrier is its ability to modify the pharmacokinetics and biodistribution of the drug, so that the drug level at the target is sufficient for therapeutic benefits, and low in the non relevant tissues. This can be described by three parameters, two of them, the drug-to-carrier partition coefficient ($K_{p,c}$) and the rate of drug release from the carrier (k_{off}), are related to drug–carrier interactions; the third one is the rate of carrier clearance (k_c). We demonstrate that carrier performance for drugs associated with the carrier amphiphile(s) is determined to a large extent by $K_{p,c}$, while for drugs encapsulated in the aqueous phase of the carrier it is important that k_{off} will be similar to k_c. These conclusions are based on two examples,of liposomal doxorubicin which consisted of either doxorubicin associated with the membrane of negatively-charged, fluid oligolamellar liposomes (L-DOX), or doxorubicin loaded by an ammonium sulfate gradient into small, unilamellar, rigid liposomes having steric stabilizing lipid grafted in their lipid bilayer, (S-DOX).

RESULTS AND DISCUSSION

I. Doxorubicin in Liposomes: System Characterization

For liposome associated drug the mode of drug association with the liposomes is controlled by the combination of $K_{p,c}$ and k_{off} which have major effect on the stability of in vivo encapsulation. Combining optimization of liposome composition and size determine k_c and the ability to reach extrahepatic tumors and inflammation sites (1,2). We take advantage that the same drug (doxorubicin) was used with 2 different liposomal formulations as described by Amselem et al. (3) and Gabizon et al. (4). For both formulations studies were performed which include in vitro characterization, toxicity, pharmacokinetic and efficacy studies in mice (rev. in 3,5) and in human (3,4,6,7).

The major relevant differences between the 2 formulations is that L-DOX are oligolamellar, negatively-charged, fluid liposomes having the drug (DOX) associated with the liposome bilayers (5,8). After i.v. injection it concentrates in the RES of the mice (8). The S-DOX are smaller-size unilamellar rigid liposomes which contain a steric stabilizing lipid ^{2000}PEG-DSPE grafted in the bilayer (being attached to the amino group of distearoyl phosphatidylethanolamine (DSPE)) which reduces uptake by the RES and therefore prolongs their circulation time (1,2,4,7). The S-DOX doxorubicin is encapsulated in the intraliposomal aqueous phase as a DOX-sulfate precipitate (9,10,11,12). The main differences between these 2 formulations in their performance in humans is related to the large differences in their $K_{p,c}$, k_{off}, and k_c .

II. Comparison Between the Pharmacokinetic Performance of L-DOX and S-DOX in Humans

The detailed pharmacokinetic performance of L-DOX and S-DOX in humans is described elsewhere (6,7). It demonstrates drastic (2–3 orders of magnitude) differences in the plasma level of DOX upon administration of equal doses of 50 mg/m^2 body surface area of the 2 formulations. The DOX delivered as L-DOX is cleared much faster, with a typical biphasic kinetics, large volume of distribution, and distribution $t_{1/2} << 10$ min. (7). The level of plasma DOX measured 5 min after L-DOX infusion is 10-fold lower than the level of drug in plasma 24 h after S-DOX injection. The pharmacokinetics of DOX delivered as L-DOX resembles more the behavior of free drug than liposome-associated drug. Careful examination of L-DOX pharmacokinetics, especially the clearance of liposome-associated drug and the liposomes reveals that after the i.v. injection more than 60% of the drug was released in human plasma in less than 1 s (3,6). This fast release rate can be explained by 3000 fold dilution induced release in vitro. During the i.v. infusion of L-DOX to humans the dilution varied in the range of 1000–200 in the beginning and the end of the infusion respectively, followed by 2000-fold dilution 3 h post infusion. Based on the DOX liposomes/buffer dilution-dependent $K_{p,c}$ of 4500 to 60000 (for low and high dilution respectively, 3) such a high level of release is expected to occur during the infusion. The fast release rate indicates that k_{off} is very short, as was also found for the in vitro release. The $t_{1/2}$ of the L-DOX liposomes (the carrier) is about 30 min, but of the drug is much shorter, namely that k_{off} is shorter than k_c, and k_{off} determines the clearance of the drug delivered as L-DOX. The DOX delivered as S-DOX has a small volume of distribution (7), which is slightly larger than the plasma volume. Its clearance is close to monophasic and is much slower: 168 h post infusion the plasma still contain 6–8% of the injected dose (which is slightly higher than the level achieved 5 min after the injection of an equal dose of L-DOX). For S-DOX, in spite of the low $K_{p,c}$, there is almost no drug release, and the fact that k_{off} is slower than k_c indicates that k_{off} is in the same order of magnitude as k_c. Then the carrier determines the pharmacokinetics of the drug in the human circulation. We found that the release kinetics of DOX induced by 3000-fold dilution of either L-DOX or S-DOX is very different. While the release of

DOX from L-DOX was almost instantaneous, from S-DOX it was at least million times slower. What determines the low k_{off} obtained for DOX-SL? From studies of us and others it is clear that it is a combination of the use of ammonium sulfate for the drug loading together with the high "rigidity" of the liposome bilayer (composed of HPC:cholesterol:PEG–DSPE) A more careful examination of the role of the ammonium gradient reveals that DOX-sulfate is precipitated in the liposomal aqueous phase as bundles of parallel fibers, Solubility product (K_S) of DOX-sulfate is low to the extent that in S-DOX 98% of the loaded drug is in the intraliposomal precipitate. These physical features explain the much high stability of DOX encapsulation of S-DOX (12), which explain the very long circulation time of S-DOX (DOX-SL).

III. Implications on Liposome Performance

Long cirulation time of liposomes loaded with drug is the first requirement for efficacy. The other requirments to be met include the abiltiy to extravasate to the tumor tissues, and obtaining sufficient level of bioavaiable drug in the tumor cells. This was indeed acheived for DOX-SL as demonstrated by our clinical studies which show that DOX-SL deliver 3-10 times more DOX to the tumor site than free drug (7). This is explained by the extravasation of of the DOX-SL vesicles which are ~100 nm in diameter, a size which enable selective "slipping" through the gaps in the tumor vascular system (7). Using the follow up of the intracellular metabolism of DOX we demonstrate that DOX delivered via DOX-SL is bioavailable to the tumor cells (7). All the above explain the superior terapeutic efficacy of DOX-SL over free DOX which led to the recent recommendation for approval for clinical use with indication to Kaposi's sarcoma. This unique properties of DOX-SL also enable to revisit the Paul Ehrlich concept of the "Magic Bullet" as exemplify by the passive targeting discussed here or by immunotargeting (13).

ACKNOWLEDGEMENTS

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Abbreviations: DOX, doxorubicin; PC, phosphatidylcholine; L-DOX, doxorubicin associated with egg PC:egg PG:cholesterol oligolamellar vesicles; S-DOX (DOX-SL™), doxorubicin remote loaded into sterically stabilized small unilamellar vesicles; ; RES, reticuloendothelial system; SSL, sterically stabilized liposomes.

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NEW POTENTIALITIES OF TRIVALENT PHOSPHORUS REAGENTS IN PHOSPHOLIPID SYNTHESES

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The design of phospholipids can be based on various synthetic strategies. We have chosen the strategy, which includes two main stages. The first stage is the phosphorylation with simple reagents, and the second stage is the modification of primary products to form natural lipids and their analogues.

We now direct our attention to the problems of phosphorylation, which is traditionally investigated in many scientific centers. It is very important to note that, for a long time, all scientific centers in the world have used only the reagents of pentavalent phosphorus for the synthesis of phospholipids. The similar strategy was applied to obtain nucleic acids and other phosphorus-containing natural compounds. One can explain this situation by the fact, that the reagents of pentavalent phosphorus were rather available and well-understood and that their applicability for the purposes of fine organic synthesis was evident. Whereas, these reagents had many considerable defects. So, they provided only small rates of phosphorylation and tended to alkylate the electrophiles, present in reaction system, and to participate in other side processes; in addition, the reagents of pentavalent phosphorus have the narrow range of synthetic potentialities.

In connection with the foregoing, in the chemistry of phospholipids there is a tendency to turn to the reagents of trivalent phosphorus, which differ from the reagents of pentavalent phosphorus by their high phosphorylating ability, preparative efficiency and design variability.

We have shown, that the amide method is the most convenient way to phosphorylate glycerols and other oligools:

$$R{-}OH + R'_2N{-}P\!\!\swarrow \longrightarrow RO{-}P\!\!\swarrow + HNR'_2$$

The phosphamides were found to be efficient and soft reagents. Their application furnished the maximum selectivity and efficiency of phosphorylation. The use of phosphamides, in addition to target esters, gives also amides, which can be easily evacuated from the reaction mixture and do not destruct the initial substances and reaction products. It is necessary to point out, that the substituents at the nitrogen atom can strongly affect the activity of phosphamides.

Today the phosphamides find use in the syntheses of various lipid systems. So, it is proposed to apply phosphorous monoamides for the phosphorylation of glycerol acetals and corresponding esters.

Amides of cyclic phosphites and amidophosphites are especially convenient in handling and promising for further transformations. To by the present time, a series of reactions with amides of phospholanes, phosphorinanes, phosphepanes, oxaazaphospholanes and oxaazaphosphorinanes have been investigated.

Phosphorous diamides are yet in more wide use, they are proposed as a base to produce mono- and diphosphoglycerides, par example, in the design of compounds, which includes fragment of spatially hindered phenols.

These and other similar compounds can be built in the biological membranes and protect them from homolytic oxidation.

Phosphorous triamides are also proposed to be used as phosphorylating agents. In this case, mono- or diglyceroamidophosphites can be obtained, depending on the reagents' ratio. We have successfully used phosphorous amides in the syntheses of nonglyceride phospholipids: derivatives of ascorbic acid, 1,1,1-trimethylolalkanes, pentaerythritol, glycols.

Amido- and diamidophosphites of oligools have attracted considerable attention not only by their availability and convenience in work. They are optimum half-products in syntheses of a variety of phospholipids, because they easily phosphorylate nucleophiles, which insert choline, aminoalkyl, carbohydrate, acylglycerol, amino acid, and other important synthons into phospholipid systems.

We also proposed to apply hydrophosphoryl derivatives like diesters and diamides of phosphorous acid for the phosphorylation of glycerols.It may be useful to use hydrophosphoryl compounds for the oxidative phosphorylation of glycerols after Todd-Atherton too.

Alongside with glycerols, we used glycols and amino alcohols in oxidative phosphorylation. In the latter case, the conditions for a selective N-phosphorylation were found. In this way, little-studied amidoalcohol phospholipids can be obtained

Another line of the work was concerned with the transformations of glycerol phosphites and amidophosphites into phospholipids.

It was shown, that one can easily oxidize glycerophosphites and introduce them in the reaction with sulfur. The resulting neutral phosphates, after removal of alkyl protections at the phosphorus atom, readily change to phosphatidic and thiophosphatidic acids.

The second direction in use of glycerol amidophosphates consists in their reactions with proton-containing nucleophiles. We have shown, that a directed monophosphorylation takes place in the reaction of these diamidophosphites with equimolar amounts of amino alcohols, carbohydrates, amino acids, spatially hindered phenols, and other compounds, which are carriers of bioregulator action. The phosphorylation with glycerol monoamidophosphites proceeds in a similar way

In this case, diacylate derivatives and acetals can be used as the glycerol components. In the latter case, the acylation occurs at the last stages of synthetic pattern. The group X, linked to the phosphorus, can be easily changed, for example, to benzyloxy one. Then O-X lipid is intended for the synthesis of natural compounds. These cyclophosphites take part in various modifications of Arbuzov reaction with opening of the ring system. An alkyl radical with a terminal functional group is here formed at the phosphorus atom. The synthesis of phospholipids, which contain an arylene moiety in the side phosphate chane, can be of interest for some problems. We suggest to study these lipids on the basis of glycerol benzophosphepanes.

Focus our attention to glycerol dioxaphosphepanes. Their molecules already contain nearly all structural elements of numerous complex phospholipids. It is even possible to consider these compounds as the synthetic equivalents for the central synthons of glycerol phosphatides

In fact, just a terminal substituent in the ester radical and an anion center at the phosphorus atom are lacking here. Meanwhile, they can be created in one step by the chemical contact of phospholane with a prototype of the β-substituent, for example, with trimethylamine. This and some similar possibilities were successfully realized.

We also lanched the study on the interaction of glycerol phosphites and amidophosphites with the salts of heavy metals. In this case, phosphito-metallocomplexes of lipids are formed, which are apparently of interest for the creation of membrans with physical and chemical peculiarities.

The work is begun on the creation of phosphitolipid complexes. It is shown, that phosphites and amidophosphites easily form stable complexes with the salts of monovalent copper, as well as with monovalent rhodium and divalent platinum.

The structure and behavior of these complexes can be investigated by means of ^{31}P NMR spectroscopy, including the study of the spin-spin coupling of phosphorus atom on the nuclei of rhodium and platinum. It is interesting, that the chemical shifts and, especially, coupling constants appreciably depend on the structure of glycerol unity of molecule, that is, on the fact, whether this unity is acetal or ester.

Unfortunately, these complexes are often not so stable. To have more stable systems, we obtain chelate complexes on the basis of glycerol aldehydes.

Such complexes are considerably more stable than the above compounds. At present, the study of their chemical and physical properties is in progress.

Thus, glycerol derivatives of trivalent phosphorus represent a new large-scale and promising class of lipid compounds.

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FROM OLIGONUCLEOTIDES TO PHOSPHOLIPIDS: CROSS-FERTILIZATION THROUGH COMPLEMENTARY CHEMISTRY

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With expanded research efforts targeted towards developing gene therapies, oligonucleotide chemistry is enjoying a parallel renaissance. Oligonucleotides and their congeners are utilized as complementary sequence-specific strands in DNA and/or RNA hybridization techniques and, therefore, can also be utilized in vivo to modify the course of various oncological, viral, parasitic, and genetic diseases. This paper illustrates how advances in oligonucleotide chemistry have been applied to the seemingly unrelated area of phospholipid chemistry. A specific example to be addressed is the synthesis of C-14-radiolabeled natural N-palmitoyl D-erythro-sphingomyelin using methods adopted from oligonucleotide chemistry. This and related compounds are valuable analytical tools for the investigation of Niemann-Pick disease, a sphingolipidosis characterized by an inherited sphingomyelinase deficiency. The cross-fertilization of these two chemistries and utilization of the resultant novel approaches in design and synthesis are demonstrated.

Sphingomyelin (N-acyl sphingosyl phosphorylcholine, SPM, is an important constituent of biological membranes and blood plasma lipoproteins. The stereochemical configuration of sphingosyl fragment of naturally occuring SPMs is D-***erythro*** and usually 18 carbon atoms long. The chemical structure of sphingosine is defined as (2S, 3R, 4E)-2-amino-4-octadecen-1,3-diol. The precise composition of natural SPMs, which is a multi-compound mixture, depends on their biological source and usually varies in their N-acyl long chain residues.

Abnormalities in metabolism of SPMs is the cause of Niemann-Pick disease and has been associated with atherosclerosis and cancer. Recently, it was suggested that SPM plays an important role in cell regulation and intracellular signal transduction. Niemann-Pick disease (NPD) is a lysosomal storage disorder which result is caused by a profound deficiency of the enzyme sphongomyelinase that catalyzes the hydrolytic cleavage of sphingomyelin to ceramide and phosphocholine, which has a reported high incidence rate in the Ashkenazic Jewish population. Type A NPD is a fatal disorder of infancy characterized by failure to thrive, hepatosplenomegaly and a rapidly progressive neurodegenerative course that leads to death by 2 to 3 years of age. In contrast, type B NPD is a phenotypically variable disorder that is usually diagnosed in childhood by the presence of hepatosplenomegaly. Most type B patients have little or no neurologic involvement and survive into adulthood. Compared to the general population, Ashkenazic Jewish individuals have a higher incidence of type A NPD 1:120; the estimated carrier frequency for type A NPD in this population is about 1:60.

Although the biological significance of SPM has been increasingly recognized, it is well documented that the sphingomyelins isolated from natural sources are heterogeneous in regard to the N-acyl chain and the length of the sphingosyl backbone fragment. Although most of the

* This lecture is dedicated to the memory of the late Prof. David Shapiro, the pioneer of sphingolipid chemistry.

earlier biochemical studies have been performed with natural mixture of sphingomyelins, semi-synthetic **(1)** or fully synthetic racemic, (±) - erythro-sphingomyelin **(2)**, precise biophysical studies usually require highly pure homogeneous sphingomyelin. The evident shortcomings is in reproduceability of the biophysical parameters of natural and semi-synthetic sphingomyelins, since natural materials are a multicomponent mixture dependent on source and the semi-synthetic material is usually a not-well-defined mixture of enantiomers as a result of epimerisation during the hydrolytic deacylation. The fully synthetic racemic material not only has a 50% ballast of unnatural material, but also often negatively influences the biochemical measurements.

Therefore, it is obvious that there is a demand for an efficient synthetic procedure leading to enantiomerically pure, high quality, homogenous D-*erythro*-sphingomyelin, which could also be adapted to isotopic labeling of the sphingomyelins.

In order to precisely evaluation the specific activity of enzymes necessary for the treatment of patients with NPD, a highly pure radiolabeled substrate must be synthesized.

In 1986 -88, we were approached by several research groups interested in multigram quantities of highly pure homogenic synthetic sphingomyelins having natural D-erythro configuration and containing one of three fatty acid residues: palmitoyl (C16:0), stearoyl (C18:0) or lignoceryl (C24:0). At the same time, the National Institutes of Health was soliciting proposals for synthesis of ^{14}C labeled pure sphingolipids, including radiolabeled N-palmitoyl D-erythro-sphingomyelin.

The first synthetic sphingomyelin, although racemic, was elegantly prepared by D Shapiro and co-workers in the early sixties. This material was also synthesized in radioactive form. In the mid-80s, our lab, along with others (ref), synthesized pure D-*erythro* sphingosine and established a platform for preparation of synthetic enantiomerically pure sphingolipids.

As part of our program directed toward synthesis of ^{14}C labeled enantiomerically pure, homogeneous sphingomyelin, we prepared N-palmitoyl-3-*O*-t-butyldiphenylsilyl ceramide. Three sources of radioactive starting materials were identified : ^{14}C methyl iodide; ^{14}C trimethylamine hydrochloride; and ^{14}C-choline hydrochloride. . Basing ourselves on retrosynthetic analysis and literature data, several synthetic schemes were designed for the preparation of ^{14}C labeled *N*-palmitoyl sphingomyelin. The first procedure was an improved Shapiro method utilizing enantiomerically pure ceramide. This process was unsuitable for radioactive synthesis because of the high cost and low-yield of sphingomyelin, as well as the difficulties related to handling of the ^{14}C labeled trimethyl amine,

Our strong interest and involvement at that time in oligonucleotide synthesis for antisense/triplex applications in gene therapyled to the design of two schemes to prepare sphingomyelin from ceramide using the phosphoramidite technology. While this coupling approach could, in principle, be applied to sphingomyelin synthesis, it was considerably refined and optimized so that a 95% yield was achieved in each reaction step **(3)**.

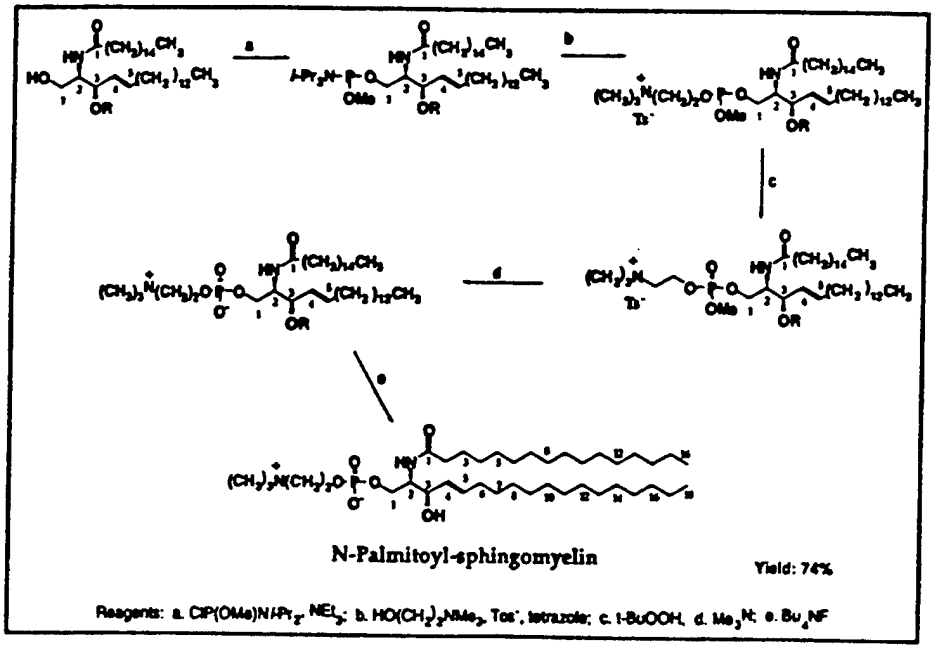
The first scheme utilized ceramide and dimethylaminoethanol as substrates for phosphoramidite synthesis, followed by methylation using methyl iodide to achieve sphongomyeline.This methodology was expected to enable ^{14}C labeling by using radioactive methyl iodide in the methylation step. To our surprise, the usually quantitative phosphoramidite coupling reaction gaave several products and an isolated yeild of about 55%. The methylation procedure required an excess of methyl iodide; and, based on the cost and difficulties in purification, this synthesis was not feasible for preparation of radiolabeled material.

The second scheme utilized choline tosylate (which can be obtained in radioactive form from commercially available choline hydrochloride) as a second component of the phosphoramidite synthesis.

In parallel to our investigations, two papers appeared in the literature using the same concept for synthesis of sphongomyelin (**4**). Reproduction and optimization of Bruzik's synthetic scheme allowed us to prepare ^{14}C labeled sphongomyelin in 79% yeild starting from ceramide.

The synthesis of D-*erythro*-SPM and its analogues is outlined in the Scheme below.

^{14}C Labeled Sphingomyelin



D-*erythro*-3-*O*-(diphenyl-t-butylsilyt)-2-*N*-stearoylsphingosine was separately treated with chloro-*N,N*-di-isopropylamino-methoxy-phosphine in the presence of triethylamine in chloroform. The resulting pohsphoramidite was treated with a mixture of choline tosylate and tetrazone in the acetonitrile-THF. The phosphite obtained in this way was oxidized with t-butyl hydroperoxide in THF to give the corresponding phosphate. The desired phosphodiester was obtained by dimethylation of its respective triester with anydrous trimethylamine in toluene. The final product, D-*erythro* \SPM was formed in the desilylation reaction of 3-*O*-silyl-protected derivative with tetrabutylammonium fluoride and yielded the desired sphingomyelin in 79 percent. This one-pot procedure did not involve isolation of the intermediate products and was therefore adopted as an efficient radiolabeling approach.

Subsequently two facile synthetic approaches to sphingomyelin were developed, one using 2-chloro-2-oxo-1,3,2-dioxaphospholane and trimethylamine **(5)** and the other involving $POCl_3$ and choline tosylate **(6)**.

Acknowledgements

The author is grateful to Dr Roscoe O Brady for the kind provision of illustrations of patients with Gaucher, Niemann Pick, Fabry and Tay-Sachs diseases as well for the valuable discussions of Niemann-Pick Disease.

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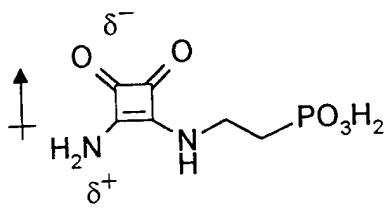
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THE 3-CYCLOBUTENE-1,2-DIONE GROUP: VERSATILE TEMPLATE FOR BIOISOSTERE CONSTRUCTION

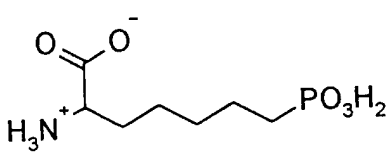
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Abstract The 3,4-diamino-3-cyclobutene-1,2-dione group was utilized as a unique α-amino carboxylic acid bioisostere in a series of *in vivo* active NMDA antagonists, which have potential as neuroprotectants. In order to investigate SAR in this series, a new free radical approach to alkyl substituted 3-cyclobutene-1,2-diones was developed utilizing 3-isopropoxy-4-tributyltin-3-cyclobutene-1,2-dione (Liebeskind's reagent). This methodology also allowed access to amino acids glycine, β-alanine, and GABA substituted with the 3-hydroxy-3-cylcobutene-1,2-dione group, which we had shown to be a carboxylic acid or tetrazole bioisostere in a series of angiotensin-II antagonists. The orally active hydroxycyclobutenedione derivative was prepared by a palladium catalyzed Stille cross-coupling of an iodobiphenyl moiety with Liebeskind's reagent.

All chemical entities known to be competitive NMDA-receptor antagonists contain an α-amino carboxylic acid connected to a phosphonic acid through a variable length spacer. For instance, 2-amino-7-phosphonoheptanoic acid and 2-amino-5-phosphonopentanoic acid (AP7 and AP5) were early examples of this trend. No examples of NMDA antagonists have appeared in which the amino acid group is replaced by a bioisosteric group; in fact, there are few examples of such a bioisostere. It was our belief that in order to have a different efficacy and/or side effect profile versus existing NMDA antagonists, it was imperative to introduce novel functionalities.

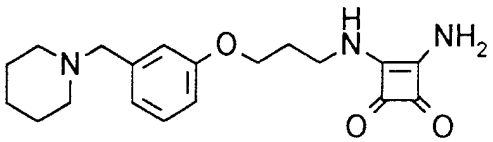


1



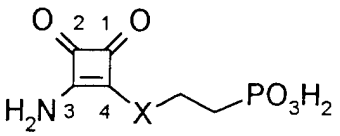
AP7

It was found that the 3,4-diamino-3-cyclobutene-1,2-dione functionality was such a bioisostere, and when connected to a phosphonic acid residue by an ethyl spacer, **1** was as effective as AP7 *in vitro* in a [^{3}H]CPP binding assay and *in vivo* in an NMDA induced lethality assay [1]. The equivalence was predicted based on the isoelectronic nature of an ammonium carboxylate to a dipolar diaminocyclobutenedione. Although these groups are isoelectronic, the diaminocyclobutenedione functionality is not acidic or basic and lacks a nucleophilic nitrogen. Therefore, this functional group would be less likely to have effects at other targets where such interactions are important; for example, a nucleophilic amine is necessary for amino acid decarboxylase enzymes. So this group might have advantages on selectivity grounds.



BMY-25,368

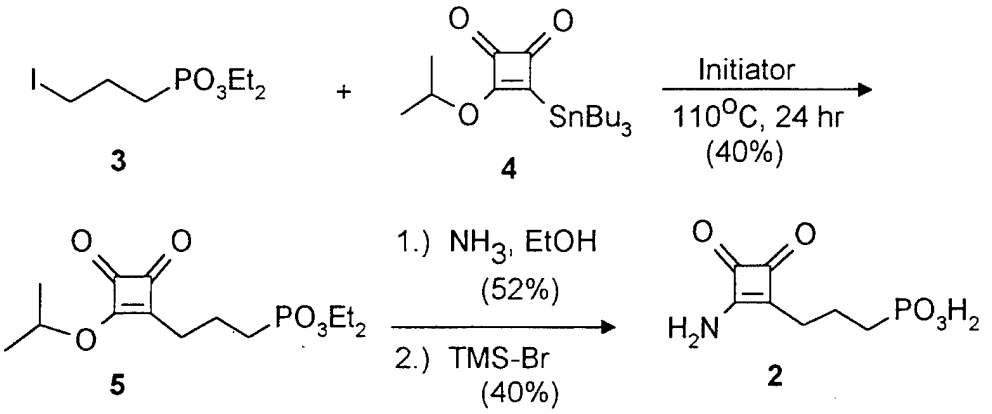
The 3,4-diamino-3-cyclobutene-1,2-dione group has been used in medicinal chemistry as a thiourea bioisostere in the potent histamine-2 receptor antagonist BMY-25,368. This compound advanced as far as phase III clinical studies for duodenal and gastric ulcers [2]. This demonstrates that the functionality has no apparent toxicity problems associated with it. Therefore, one has a novel functional group for NMDA antagonists with potential differences from known amino acid based drugs, and at the same time there is clinical safety experience with the group.



X = NH (**1**), CH_2 (**2**)

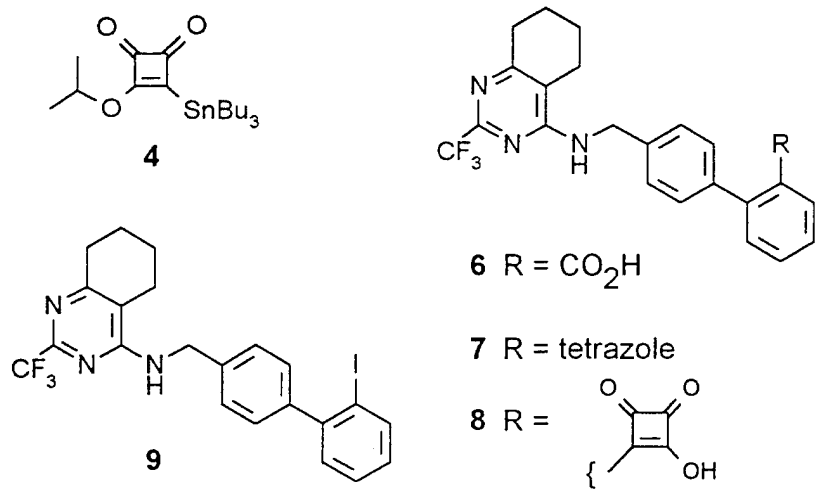
The necessity of the 4-amino substituent of the novel amino acid bioisostere contained in **1** was investigated by preparing **2**, which contains a carbon for nitrogen replacement. In order to avoid organometallic approaches, which were incompatible with the phosphonic acid ester functionality, a novel approach was devised [3]. The alkyl radical, generated from the alkyl iodide **3** (**Scheme I**) with azobiscyclohexylnitrile in toluene, added to Liebeskind's reagent **4** [4] with the elimination of tributyltin radical to afford the desired phosphono-substituted cyclobutenedione **5**. It was converted in two steps to the desired analog **2**, which was devoid of activity at the NMDA receptor, demonstrating the necessity of the 4-amino group for this amino acid bioisostere.

Scheme I



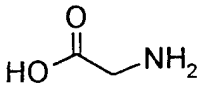
In the course of our investigations into novel angiotensin II antagonists, it became of interest to explore novel carboxylic acid bioisosteres, which might have broad application in drug design (**Scheme II**) [5]. We felt the 3-hydroxy-3-cyclobutene-1,2-dione had potential, because of its marked acidity and structural similarity to a carboxylic acid. The target to investigate this new carboxylic acid bioisostere relative to the carboxylic acid (**6**) and tetrazole derivatives (**7**) was **8**. Due to the work of Liebeskind [4], the palladium-catalyzed Stille cross coupling of aryl halides to Liebeskind's reagent **4** was well precedented. The elaborate aryl iodide **9** was coupled with **4** with catalytic *trans*-benzyl(chloro)bis(triphenyl-phosphine)palladium (II) and CuI in acetonitrile at 70°C to afford the aryl-hydroxycyclobutenedione isopropyl ester in 71% yield. Acid hydrolysis yielded the desired derivative **8** in 83% yield. The IC_{50} values for the three derivatives **6**, **7**, and **8** at the AII-receptor were 275 nM, 3 nM, and 25 nM respectively, demonstrating the utility of the 3-hydroxy-3-cyclobutene-1,2-dione group as a

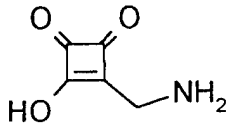
Scheme II



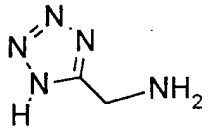
carboxylic acid or tetrazole bioisostere; others have also shown this at a different biological target [6]. Importantly, compound **8** also demonstrated *in vivo* activity as an antihypertensive in rats, even when administered orally, further suggesting the utility of cyclobutenedione based groups in medicinal chemistry.

Because of our interest in inhibiting the NMDA receptor, we thought 3-hydroxy-3-cyclobutene-1,2-dione group could be further investigated as a carboxylic acid bioisostere in the glycine derivative **10**; it was expected that it might inhibit the strychnine-insensitive glycine modulatory site on the NMDA receptor by mimicking glycine [7]. The target was synthesized utilizing the free radical method described above with a phthalimido protecting group. However, derivative **10** was found to be inactive at the glycine receptor, as **11** was shown to be by others [8].





10



11

In summary, we and others have demonstrated many uses of cyclobutenediones as bioisostere frameworks for construction of medicinally useful agents. Additionally, new chemistry has be elucidated allowing for the ready introduction of cyclobutenediones into target structures.

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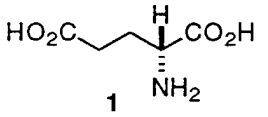
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SYNTHESIS AND CHARACTERIZATION OF PHOSPHONIC ACID-SUBSTITUTED AMINO ACIDS AS EXCITATORY AMINO ACID RECEPTOR ANTAGONISTS

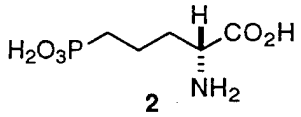
PAUL L. ORNSTEIN, M. BRIAN ARNOLD, NANCY K. ALLEN AND DARRYLE D. SCHOEPP
Central Nervous System Research Division, Lilly Research Laboratories, A Division of Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana, 46285, USA

Abstract Decahydroisoquinoline-3-carboxylic acids, substituted at C-6 with an acidic moiety such as a phosphonic, sulfonic or carboxylic acid or tetrazole, were prepared as antagonists of excitatory amino acid (EAA) receptors.

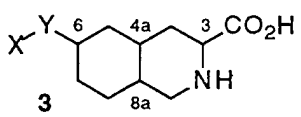
Glutamic acid (**1**) is the major excitatory neurotransmitter in the central nervous system, acting at a number of subclasses of excitatory amino acid (EAA) receptors. *N*-methyl-D-aspartic acid (NMDA) and 2-amino-3-(5-methyl-3-hydroxyisoxazol-4-yl)propanoic acid (AMPA) EAA receptors are coupled to ion channels, and signals are transduced through depolarizations resulting from changes in calcium and sodium ion concentrations.[1] It has been postulated that antagonists of NMDA and AMPA receptors may be useful therapeutic agents in the treatment of epilepsy,[2] cerebral ischemia,[3] head[4] and spinal cord trauma,[5] and chronic neurodegenerative disorders such as Alzheimer's[6] and Parkinson's disease.[7]



1



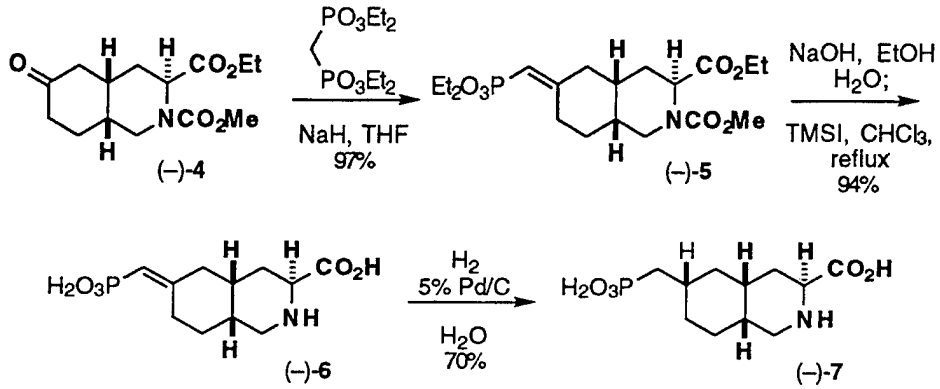
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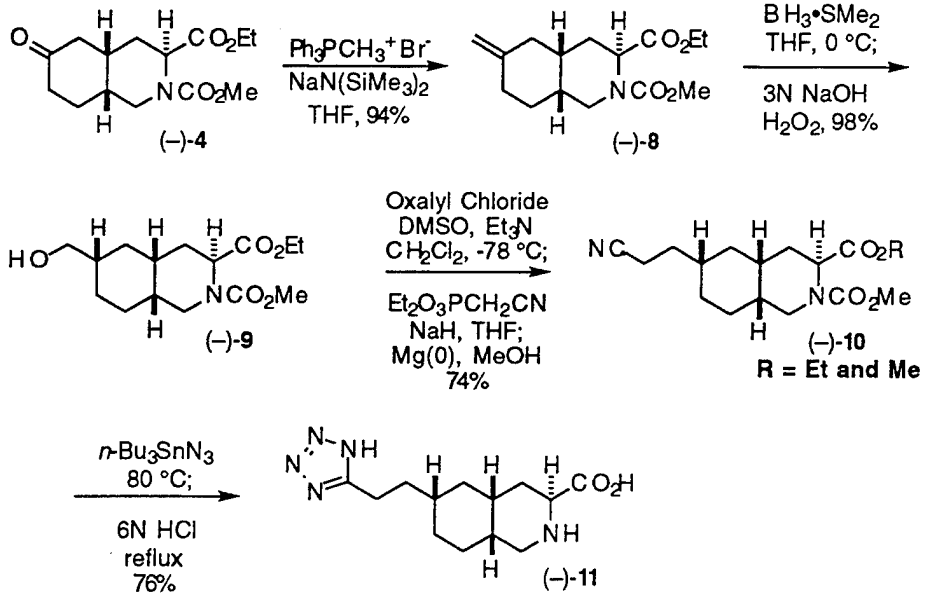
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Elongation of the chain connecting the two acidic moieties, conversion of the distal acid to the bioisosteric phosphonic acid, and inversion of the amino acid from *S* to *R* yielded the potent, selective and competitive NMDA antagonist 2*R*-2-amino-5-phosphonopentanoic acid (**2**, 2*R*-AP5).[8] A significant limitation of this compound and its congeners, however, was their lack of potency following systemic administration. It was therefore the goal of our medicinal chemistry research to identify novel structures that were more potent and afforded better bioavailability. We incorporated the AP5 substructure, which identified the minimum structural

requirements for NMDA antagonist activity, into a variety of cyclic systems. It was our hope that the conformational constraint of a cyclic system would provide a structure whose potency increased because the bioactive conformation was more readily attained. In the distal acid position, we incorporated the phosphonic acid, which provided a significant increase in potency and selectivity in the SAR of **2**. We also examined other acid bioisosteres (e.g., sulfonic acid and tetrazole) which we hoped would be as beneficial as a phosphonic acid. Of the cyclic systems that we investigated, a series of 6-substituted decahydroisoquinoline-3-carboxylic acids (**3**) were the most fruitful in providing potent, subclass selective EAA antagonists.



Scheme 1 Synthesis of the phosphonic acid-substituted NMDA antagonist (–)-7



Scheme 2 Synthesis of the tetrazole-substituted AMPA antagonist (–)-**11**

The structure activity studies of **3**[9,10,11] looked at a number of different features. We varied stereochemistry, preparing six of the eight possible diastereomeric pairs; examined the effects of varying the distal acid isostere X; and varied the chain Y that connects the acid X to the bicyclic nucleus, both in terms of length of the tether (one to four atoms) and substitution along the chain with heteroatoms (N, O and S). The syntheses of these amino acids were reported,[9-13] and the stereoselective syntheses of (–)-**7** (LY235959) and (–)-**11** (LY293558) are shown in Schemes 1 and 2, respectively, as representative examples from this series. The novel amino acids prepared were evaluated for affinity at NMDA and AMPA receptors using selective radioligand binding assays;[9,10,11] for antagonist potency in a cortical slice preparation;[9,10,11] and in vivo in mice versus NMDA-induced lethality and maximal electroshock induced convulsions.[9,10,11]

Of the different diastereomers prepared, compounds whose relative stereochemistry corresponded to **7** and **11** were the most potent.[9,10] When these amino acids were resolved, activity was found to reside in the isomer whose absolute stereochemistry corresponds to the isomer shown in Schemes 1 and 2 for (–)-**7**[11] and (–)-**11**,[10] respectively. With a single methylene spacer between the distal acid moiety and the bicyclic nucleus, compounds were selective NMDA antagonists.[9] With an ethylene spacer, compounds were AMPA antagonists.[10] One of the more interesting aspects of this SAR was evident when one examined the nature of the distal acid group relative to potency at either NMDA or AMPA receptors. Figure 1 shows a number of compounds from this SAR that are identical except for their distal acid substitution. For compounds with a methylene spacer, substitution with a phosphonic acid (**7**) at the distal acid position imparted high affinity and antagonist potency at NMDA receptors; the tetrazole (**13**) was nearly as potent an NMDA antagonist as its phosphonic acid substituted counterpart. Interestingly, the analogous compounds substituted with either a sulfonic acid (**14**, P.L. Ornstein, unpublished results) or a carboxylic acid (**16**) were significantly less potent as NMDA antagonists. We were surprised by this finding, considering that a sulfonic acid is similar in structure and acidity to a phosphonic acid, and a carboxylic acid is similar in structure and acidity to a tetrazole. For compounds with an ethylene spacer, the most potent AMPA antagonist activity was observed for the tetrazole-substituted compound **11**. The sulfonic acid-substituted compound **14** was less potent, the carboxylic acid compound **17** significantly less potent, and the phosphonic acid-substituted compound **12** was inactive (P.L. Ornstein, unpublished results). As in the NMDA SAR, no logical connection exists between activity and the nature of the distal acid moiety.

The phosphonic acid substituted amino acid 7 is a potent, selective NMDA antagonist that is active in animals following systemic and oral administration.[14] This compound also protects against excitatory amino acid-induced neuronal degeneration in animals,[14] and thus has the therapeutic potential to serve as a neuroprotective agent.

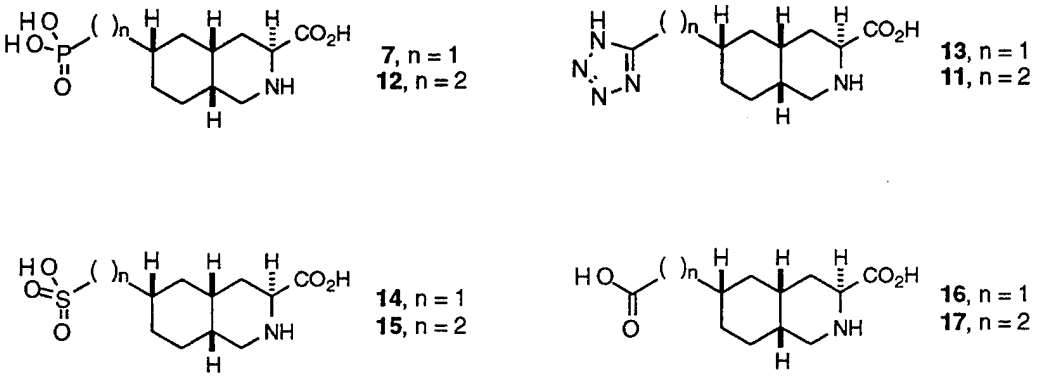


Figure 1 6-Substituted decahydroisoquinoline-3-carboxylic acid SAR

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PHOSPHONO SUBSTITUTED AMINO ACIDS AS SELECTIVE METABOTROPIC GLUTAMATE RECEPTOR ANTAGONISTS

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Abstract New phosphono substituted amino acid antagonists have been prepared and used to discriminate between different types of presynaptic metabotropic glutamate receptors (mGluRs) in the neonatal rat spinal cord that are activated selectively by L-2-amino-4-phosphonobutanoate (L-AP4) and (1S,3S)-1-aminocyclopentane-1,3-dicarboxylate ((1S,3S)-ACPD). (RS)-α-Methyl-4-phosphonophenylglycine (MPPG; K_D 9.2 μM), (S)-2-amino-2-methyl-4-phosphonobutanoate (MAP4; K_D 22 μM) and (RS)-α-methylserine-O-phosphate (MSOP; K_D 51 μM) were potent and selective antagonists of L-AP4-activated mGluRs. (RS)-α-Methyl-4-tetrazolylphenylglycine (MTPG; K_D 77 μM) and (RS)-α-methylserine-O-phosphate monophenylphospho ester (MSOPPE; K_D 73 μM) were moderately potent and preferential antagonists of (1S,3S)-ACPD-activated mGluRs. Structure-activity relationships are briefly discussed.

Key Words: metabotropic glutamate receptor (mGluR); mGluR antagonists; L-AP4; (1S,3S)-ACPD.

INTRODUCTION

It is widely accepted that (S)-glutamate is the predominant excitatory transmitter in the central nervous system, acting at a range of ionotropic and metabotropic glutamate receptors (mGluRs). Ionotropic glutamate receptors mediate their effects via ligand gated ion-channels and can be sub-divided into three main types named after the specific agonists which activate them, the N-methyl-D-aspartate (NMDA), (RS)-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate receptors. Phosphono analogues of longer chain congenors of glutamate (particularly the R forms) are well

hydantoins in 6N HCl. MSOP and MSOPPE were synthesized by a variation on the method of Fölsch and Mellander starting with α-methylserine.[9]

PHARMACOLOGY

The activity of the new compounds at reversing L-AP4- and (1S,3S)-ACPD-induced depression of the dorsal root-evoked monosynaptic excitation was investigated in the isolated hemisected neonatal rat spinal cord preparation.[5,6] These results together with apparent K_D values for previously reported antagonists are summarized in Table 1.

TABLE 1 Apparent K_D values for antagonism of test compounds of L-AP4- and (1S,3S)-ACPD sensitive presynaptic receptor sites in the neonatal rat spinal cord.

COMPOUND	K_D (μM) for antagonism of depression mediated by:	
	L-AP4	(1S,3S)-ACPD
(+)-MCPG	227 ± 12 (4)	479 ± 37 (5)
(RS)-MTPG	188 ± 9 (3)	77.2 ± 7 (7)
(RS)-MPPG	9.2 ± 0.3 (9)	113 ± 13 (3)
(S)-MAP4	22 ± 5 (5)	> 500
(RS)-MSOP	51 ± 6 (3)	> 700 (3)
(RS)-MSOPPE	221 ± 17 (3)	73 ± 3 (3)

The mGluR antagonists described above have no effect on postsynaptic mGluRs and only weak and variable effects on postsynaptic ionotropic receptors such as NMDA and AMPA receptors.

DISCUSSION

L-AP4-activated receptors were most potently antagonized by MPPG, which was also reasonably selective for these receptors, but less specific than (S)-MAP4 and (RS)-MSOP. MTPG and MSOPPE were somewhat selective for (1S,3S)-ACPD-activated mGluRs. The results indicate that both the open-chain and phenyl-spaced analogues can interact with the same sites on the L-AP4-sensitive receptor. The fact that MSOPPE is more selective for the (1S,3S)-ACPD activated receptor suggests that either two hydroxyl groups are necessary for interaction with the L-AP4 activated receptor, or that the O-phenyl group is too large and interferes with receptor interaction, or a combination

known as specific antagonists at the NMDA receptor[1] and together with antagonists of the AMPA/kainate receptors have received much attention as potential therapeutic drugs in a range of disease states including, traumatic head and spinal injury, stroke, epilepsy, spasticity, Parkinson's disease and Huntington's disease.[2]

In recent years the structure and function of mGluRs has come under intense investigation.[3,4] To date, molecular biologists have identified eight mGluRs which when expressed couple to second messenger systems through G proteins.[3,4] Group I receptors (mGluRs 1/5) are positively coupled to phospholipase C activity while group II (mGluRs 2/3) and group III (mGluRs 4/6-8) receptors are negatively coupled to adenyl cyclase activity. Recently the antagonist action of novel phenylglycine analogues on mGluRs has been reviewed.[4] The actions of (RS)-α-methyl-4-carboxyphenylglycine (MCPG), the first mGluR antagonist, were reported to be relatively non-specific for particular mGluR sub-types and therefore new analogues have been developed. To this end we recently reported the actions of (S)-2-amino-2-methyl-4-phosphonobutanoate (MAP4) and (2S,1'S,2'S)-2-(2-carboxycyclopropyl)alanine (MCCG) which are selective antagonists for different presynaptically located mGluRs that are activated specifically by L-2-amino-4-phosphonobutanoate (L-AP4) and (1S,3S)-1-aminocyclopentane-1,3-dicarboxylate ((1S,3S)-ACPD).[5] These mGluRs are considered to correspond to one or more receptors within group III and group II, respectively.[4] We have now developed new phenylglycine and open chain analogues of MCPG and MAP4, including (RS)-α-methyl-4-phosphonophenylglycine (MPPG), (RS)-α-methyl-4-tetrazolylphenylglycine (MTPG),[6] (RS)-α-methylserine-O-phosphate (MSOP) and (RS)-α-methylserine-O-phosphate monophenylphospho ester (MSOPPE), and compared their actions in neonatal rat spinal cord with those of the presynaptic mGluR antagonists previously reported.

CHEMISTRY

(S)-MAP4 was prepared by reaction of diethyl 2-bromoethylphosphonate and the cuprate derived from 5-lithio-(2R,5SR)-(-)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-methyl-pyrazine,[7] followed by hydrolysis of the intermediate firstly in 1N TFA in THF and then 6N HCl. (RS)-MTPG and (RS)-MPPG were synthesized by Bucherer-Berg reaction[8] on the appropriately substituted acetophenones followed by hydrolysis of the intermediate

of these factors. In contrast, the (1S,3S)-ACPD sensitive mGluR accommodates the O-phenyl group of MSOPPE suggesting that a) only one hydroxyl is necessary for receptor interaction and b) there may be a fairly large hydrophobic cavity in the receptor that the phenyl group can interact with. Using structural requirements for antagonism of the L-AP4 and (1S,3S)-ACPD activated receptors revealed in this and earlier studies it should be possible to design more potent and selective antagonists. Molecular modelling studies aimed at defining antagonist pharmacophores for these receptors are in progress and these, together with an on-going synthetic programme should lead to even more potent and selective mGluR antagonists in the future.

ACKNOWLEDGEMENTS

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DESIGN, SYNTHESIS AND BIOCHEMICAL APPLICATIONS OF ANALOGS OF PHOSPHATIDYLINOSITOL

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Abstract A general methods for synthesis of diverse precursors of phosphoinositides have been elaborated and applied towards synthesis of a variety of inositol phosphates, phospholipids, and their phosphorothioate, oxygen-labeled and stereoisomeric analogs. The obtained compounds have been used to study mechanism of phosphatidylinositol phospholipase C. The acquired mechanistic information was then applied for design and synthesis of inhibitors of this enzyme.

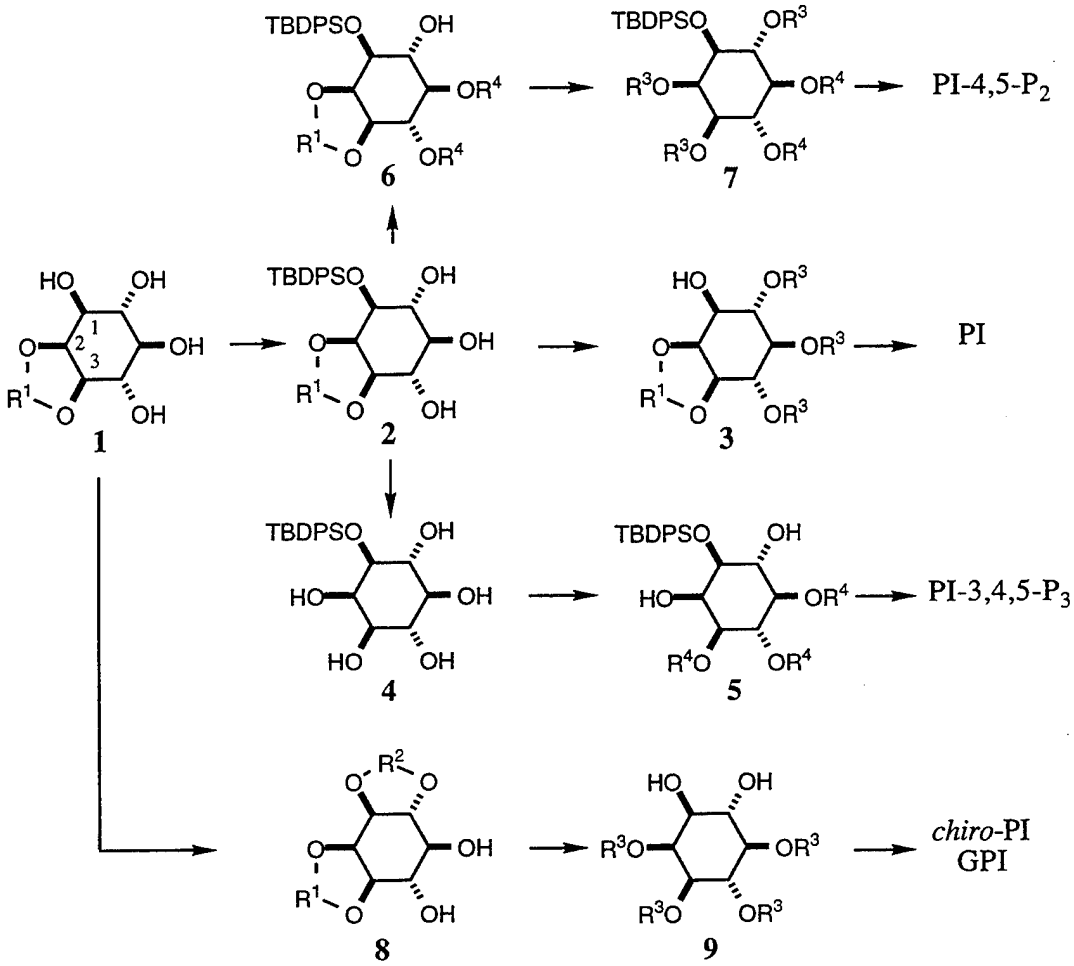
INTRODUCTION

Receptor-mediated cleavage of inositol phospholipids by phosphatidylinositol-specific phospholipase C (PI-PLC) is a key step in signal transduction of many hormones, neurotransmitters and growth factors [1]. Growth factors such as PDGF, EGF, FGF are known to increase levels of inositol trisphosphate second messenger by activation of PI-PLC-γ_1 [2]. On the other hand, insulin and TGF stimulate production of glycosylinositol phosphates (GIP), another family of putative second messengers known as insulin mediators, by activation of glycosylphosphatidylinositol-specific phospholipase C (GPI-PLC) [3]. One type of such insulin mediators have been found to contain the rare *chiro*-inositol instead of the typical *myo*-isomer [3]. Due to the central role of phospholipase C in signal transduction pathways the major thrust of our research is aimed at determining the mechanism of this enzyme [4,5], and design and synthesis of mechanism-based inhibitors as research tools for studying inositol-metabolism and as possible pharmacological agents against cancer, inflammation and hypertension. Furthermore, we work towards understanding the mechanism of transduction of insulin signal by investigating substrate properties of model *chiro*-phosphoinositides [6], and isolation and structure determination of *chiro*-inositol-containing phospholipids, precursors of the putative insulin mediators.

SYNTHESIS OF INOSITOL PHOSPHATES AND PHOSPHOLIPIDS

In view of our long-term interest in phosphoinositide metabolism it was essential to develop general methods enabling efficient synthesis of all naturally occurring inositol phosphates and phospholipids, and of some of their analogs. Our strategy has been to introduce highly versatile inositol intermediates [7] applicable towards synthesis of a variety of protected inositol precursors and further to synthesis of phosphomonoesters (inositol phosphates, IP), phosphodiesters (phosphatidylinositol, PI) or both (phosphatidylinositol phosphates, PIP) [4-9]. Several of our synthetic procedures are summarized in Scheme 1. Acetalization of inositol with D-camphor dimethyl acetal produces the pure diastereomer of 2,3-acetal **1** (30%) in a single step, not requiring chromatographic separations [10,11]. Further regioselective protection of the acetal **1** with tert-butyldiphenylsilyl (TBDPS) group at the 1-position produces a pivotal intermediate **2**, which upon exhaustive protection gives rise to the precursor **3** of phosphatidylinositol.

Scheme 1



R^1: bornanedi-2,2-yl; R^2: tetraisopropyldisiloxanedi-1,3-yl;
R^3: methoxymethyl; R^4: benzoyl

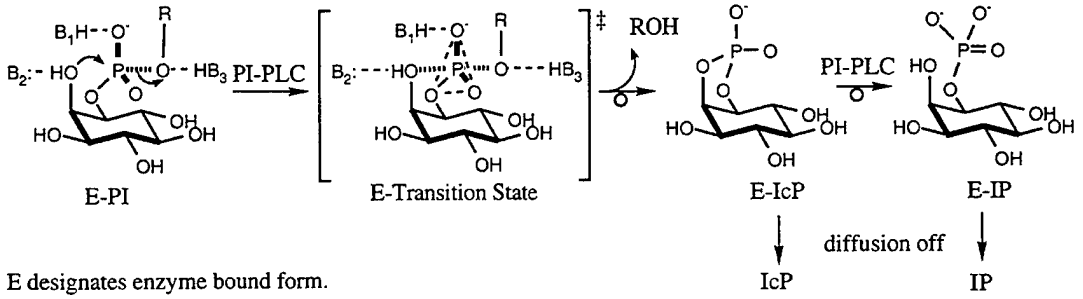
The deacetalization of the silyl derivative **2** affords the extremely versatile intermediate **4**, which upon selective tris-benzoylation gives rise to the precursor **5** of phosphatidylinositol 3,4,5-trisphosphate (PI-3,4,5-P_3). The respective monobenzoylation leads to a precursor of PI-3-P. On the other hand, benzoylation of the intermediate **2** produces selectively the 4,5-bisbenzoate **6**, which upon further deacetalization and protection gives a precursor **7** of PI-4,5-P_2. Silylation of the acetal **1** with 1,3-bissilyl dichloride occurs exclusively at the 1- and 6-positions to give the 4,5-diol **8** and a convenient access to the 1,6-diol **9** useful in syntheses of *chiro*-phosphatidylinositol and glycosylinositol phosphates. All the above shown intermediates and many other ones are generated in only 6-8 steps from inositol and have been used to produce almost every natural inositol phosphate and phospholipid [4-11]. An exemplary synthesis of an inositol phospholipid starting from the pentol **4** is described elsewhere in this volume in a related communication (see also ref. 9).

MECHANISM OF PHOSPHOLIPASE C

Despite significant sequence homology between mammalian and bacterial species of PI-PLC simultaneous vs. sequential formation of inositol 1,2-cyclic phosphate (IcP) and inositol 1-phosphate (IP) by these enzymes suggested different mechanisms. The origin of

this behavior was investigated by a stereochemical approach using P-chiral phosphorothioate and oxygen-isotope labeled analogs of PI as substrates [12]. PI-PLC from both mammalian and bacterial sources stereoselectively hydrolyzed the (Rp)-diastereomer of the phosphorothioate analog of PI to afford the 1,2-cyclic product with inversion of configuration at phosphorus. The bacterial enzyme further hydrolyzed IcP to IP with inversion of configuration [4]. Likewise, the mammalian enzymes produced IcP with inversion and IP with retention. These results can be best explained in terms of a unified mechanism presented in Scheme 2 [4].

Scheme 2

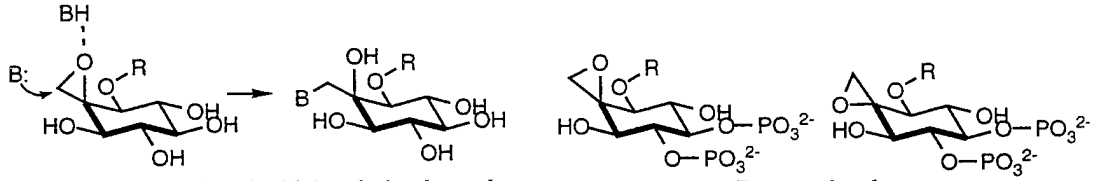


E designates enzyme bound form.

Formation of the pentacoordinated transition state with both the attacking 2-hydroxyl group and the diacyl glycerol oxygen leaving group occupying apical positions is preceded by deprotonation of the 2-hydroxyl group and protonation of the pro-*S* oxygen atom of the phosphate group in the case of all enzymes. The principal mechanistic difference between the enzymes is that the mammalian PI-PLC hydrolyzes the cyclic intermediate while it most likely still resides in the active site, while the bacterial enzyme releases the cyclic intermediate prior to the next hydrolytic step. Since the polar cyclic product is devoid of hydrophobic residue its active site binding upon return might not produce the catalytically competent enzyme conformation [13]. The presence of the hydrophobic side chain is important for efficient catalysis since the rate of hydrolysis is several times lower for short-chain PI [14], and several hundred times lower for short chain alkyl inositol phosphates, compared to natural PI. Furthermore, the mammalian PI-PLC binds the deacylated phosphatidylinositol 4-phosphate, but does not hydrolyze it [15].

Based upon the above postulated mechanism the replacement of the 2-hydroxyl group with the epoxide residue should confer inhibitory property to the analog of PI due to possible protonation of the axial oxygen of the epoxide and further epoxide opening by the enzymic base (Scheme 3). This amino acid residue would hence become alkylated causing irreversible inactivation of the enzyme. A series of compounds analogous to PI and PIP_2 have been synthesized, and their inhibitory properties towards PI-PLC are currently under investigation.

Scheme 3

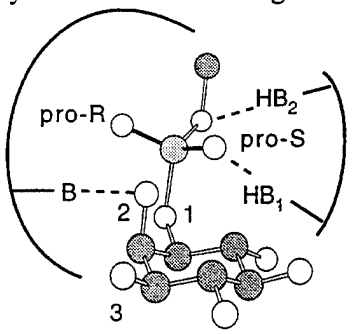


R = phosphatidyl, palmitoyl, octyl

R = octadecyl

MAPPING THE PHOSPHOLIPASE C ACTIVE SITE

In the absence of the three dimensional model of the active site the rational design of PI-PLC inhibitors can only rely on the mechanistic data and results of structure specificity studies. Significance of structural features of phosphatidylinositol for binding and catalysis can be summarized as follows [for a more detailed discussion see ref. 5]: (i) The presence of the charged phosphodiester group is not necessary for binding, since nonionic analogs bind with a similar affinity as PIP_2; [16] (ii) Protonation of the *pro*-S oxygen atom of the phosphoryl group is, however, essential for catalysis, since its replacement with sulfur causes a complete cessation of hydrolysis [12]; (iii) The presence of the 2-hydroxyl group is essential for catalysis, but not necessary for binding since the 2-deoxy analog of PI is an inhibitor of melanoma PI-PLC; (iv) The equatorial 3-hydroxyl group is essential for catalysis or binding, since its inversion causes 10^3-fold reduction of the cleavage rate [6]; likewise, PI 3-phosphates are completely resistant to PI-PLC; (v) The bridging oxygen of diacylglycerol moiety is essential for catalysis, since its replacement with sulfur causes 10-100 fold reduction in k_{cat} [17]; (vi) the exact structure of diacylglycerol and its configuration at the C-2 are insignificant, since both the single chain PI and the PI analog with a reversed configuration of the glycerol moiety are equally good substrates. In general, different main types of phospholipase C display various degrees of tolerance to substrate modifications at certain positions. Based on the findings above it should be possible to devise inhibitors with a narrow specificity towards these PI-PLC types.



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SYNTHETIC STRATEGIES BASED ON PHOSPHITE CHEMISTRY FOR INOSITOL PHOSPHATES AND PHOSPHOLIPIDS

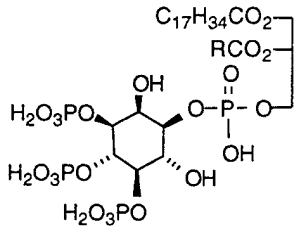
Yutaka Watanabe, * Tadashi Okazaki, Takashi Yamamoto and Shoichiro Ozaki
Department of Applied Chemistry, Faculty of Engineering, Ehime University,
Matsuyama 790-77, Japan

Abstract On the basis of the phosphite chemistry, new phosphorylation and glycosylation methodologies were developed. These methods were efficiently used for the syntheses of phosphatidylinositol 3,4,5-trisphosphate, and 2,6-di-*O*-mannopyranosylphosphatidylinositol.

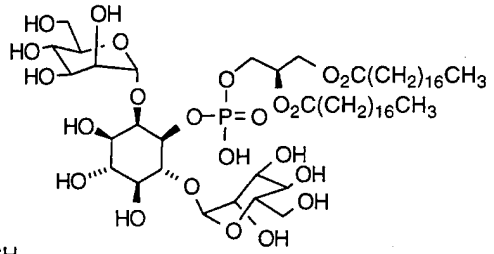
phosphorylation, glycosylation, inositol phospholipid, phosphite

INTRODUCTION

Recently, inositol phospholipids located within the plasma membrane have received much attention due to their biological interests in the intracellular signal transduction system.[1] In order to understand their physiological roles, chemical synthesis of them and analogs are very important. For the accomplishment of an efficient synthesis of inositol phosphate derivatives, new synthetic methodologies were necessary. From this standpoint, we have investigated a regioselective phosphorylation and glycosylation methodologies using the reducing and Lewis basic properties of phosphites. These synthetic methods were efficiently utilized for the synthesis of an analog **1a** of phosphatidylinositol 3,4,5-trisphosphate [PI(3,4,5)P3] and 2,6-di-*O*-mannopyranosyl-1-phosphatidyl-*myo*-inositol [2,6-(Man)2-PI]. These results are presented here.



PI(3,4,5)P3: R=$(CH_2)_2(CH_2CH{=}CH)_4(CH_2)_4CH_3$
1a: R=$(CH_2)_{16}CH_3$

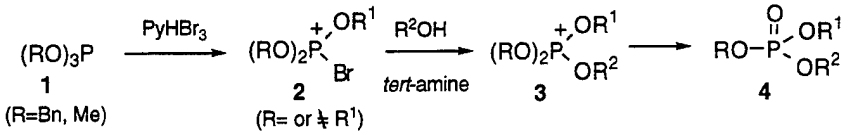


2,6-(Man)2-PI

SYNTHETIC METHODOLOGIES BASED ON PHOSPHITE CHEMISTRY

A Regioselective Phosphorylation Methodology

Treatment of trimethyl and tribenzyl phosphites **1** with pyridinium tribromide in the presence of an alcohol and a *tert*-amine furnished the phosphoric triesters **4** in high yields via Arbuzov-type decomposition of **3** (**Scheme 1**). Since phosphorous mixed triesters are readily available, mixed triester products **4** can be prepared.[2]

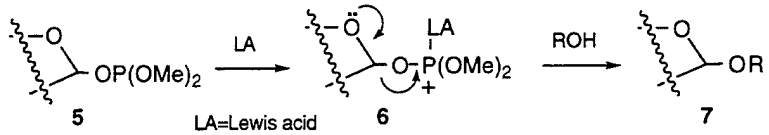


Scheme 1

This methodology was found to be effectively applicable to regioselective phosphorylation of 1,2-free inositol derivatives giving 1-O-phosphate as shown in the total syntheses (**Scheme 3** and **4**).

Glycosylation Using Glycosyl Phosphites

Finding[3] that a phosphite is protonated by 1*H*-tetrazole prompted us to investigate glycosylation using a glycosyl phosphite **5** (**Scheme 2**).[4] Lewis acids such as $ZnCl_2$-$AgClO_4$ and NIS-TfOH gave glycosides **7** in good yield. The same methodology using TMSOTf as the promoter was reported at the same period by other groups.[5] Furthermore, BF_3•OEt_2 was found recently to be efficient for β-selective glycosylation.[6]



Scheme 2

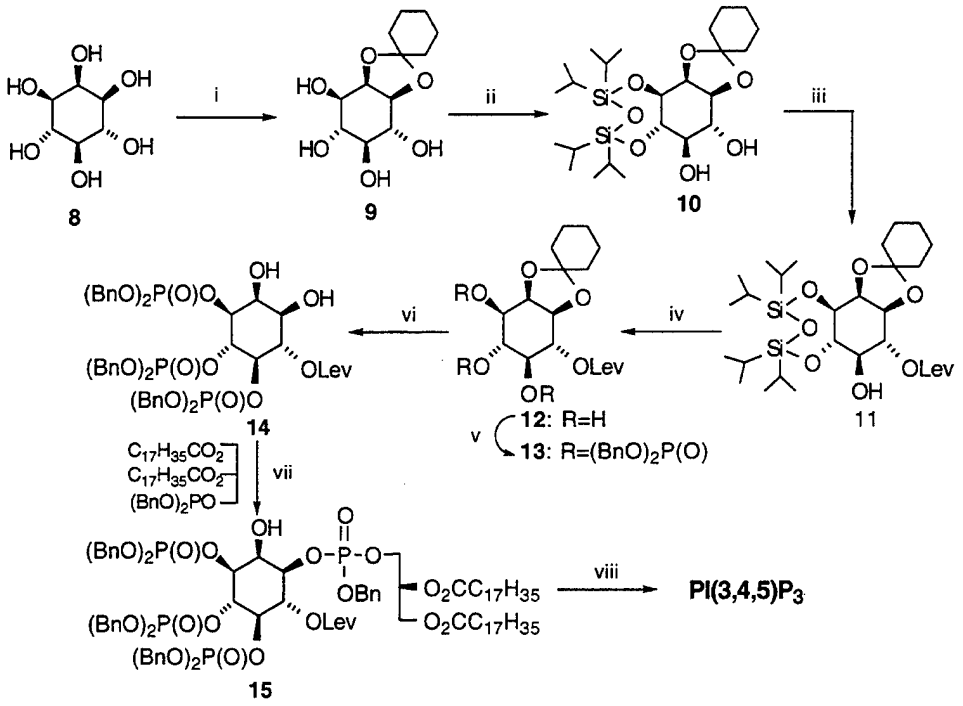
SYNTHESIS OF PHOSPHATIDYLINOSITOL DERIVATIVES

The tetraisopropyl-1,3-disiloxanyl group was found to be an ideal protecting group for the efficient synthesis of inositol phosphate derivatives.[7] This time, **10**, which can be smoothly derived from **9**, was used for the synthesis of the title compounds.

Synthesis of Phosphatidylinositol 3,4,5-trisphosphate

The disiloxanyl group in **10** functions not only to protect the hydroxyl groups at C-3 and -4 but also to prevent the reaction at C-5. Thus, 6-levulinate **11** was readily obtained.

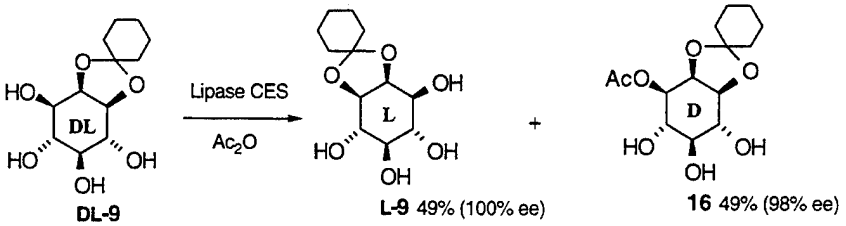
The ester was transformed to the 1,2-diol **14**, which was phosphorylated at C-1 followed by the final deprotection giving PI(3,4,5)P_3 (**Scheme 3**).[8]



i) Cyclohexanone, TsOH (97%); ii) i-$Pr_2Si(Cl)$-O-$Si(Cl)i$-Pr_2 (94%); iii) $CH_3CO(CH_2)_2CO_2H$, DCC, DMAP (84%); iv) $^nBu_4NF{\bullet}3H_2O$, $PhCO_2H$ (85%); v) $(BnO)_2PN^iPr_2$, Tetrazole then mCPBA (72%); vi) CF_3CO_2H, CH_2Cl_2 containing MeOH (83%); vii) $PyHBr_3$, lutidine (36%); viii) 1. H_2, Pd-C, 2. NH_2NH_2

Scheme 3

Optically active 1,2-cyclohexylidene-*myo*-inositol was enzymatically prepared via 3-acetate **16** (**Scheme 4**).[9] It was transformed to the pivotal intermediate **D-10**, from which chiral PI(3,4,5)P_3 was obtained (**Scheme 5**).[10]

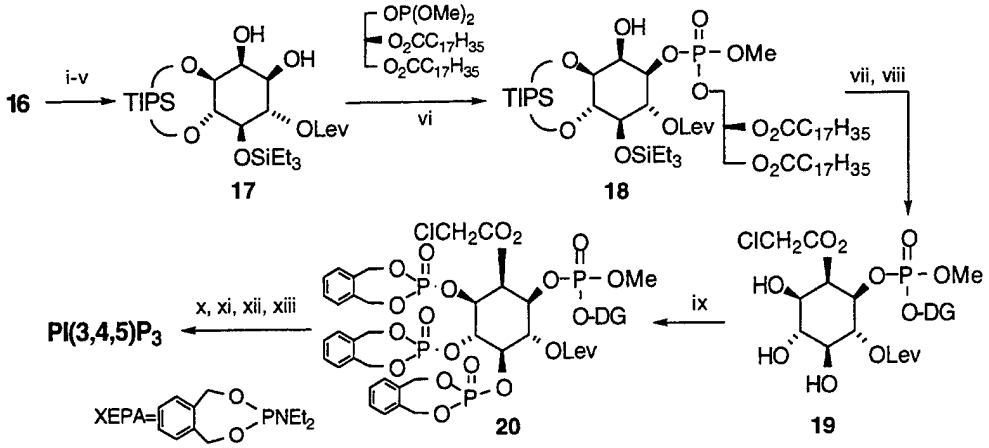


Scheme 4

Synthesis of 2,6-Di-*O*-mannopyranosyl-1-phosphatidyl-*myo*-inositol

The key intermediate **10** was regioselectively glycosylated at C-6 followed by, after removal of the cyclohexylidene group, regioselective phosphorylation of the resultant

triol to give the 6-*O*-tetrabenzylmannopyranosyl-1-*O*-phosphatidylinositol. Selective glycosylation of the product at C-2 and deprotection (desilylation, demethylation, and debenzylation) produced concisely 2,6-(Man)2-PI.



i) MeONa (92%); ii) TIPS-Cl_2 (94%) ; iii) $(Lev)_2O$, DCC (84%); iv) Et_3Si-Cl, (100%); v) TsOH, $(CH_2OH)_2$ (73%); vi) $C_5H_5NHBr_3$ (96%); vii) $(ClCH_2CO)_2O$ (100%); viii) 47% aq. HF (69%); ix) XEPA, tetrazole then mCPBA (89%); x) H_2, Pd/C; xi) $NH_2NHC(S)S^-Et^iPr_2NH^+$; xii) PhSH, Et_3N; xiii) NH_2NH_2(21%)

Scheme 5

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MODULATION OF THE INOSITOL 1,4,5-TRISPHOSPHATE RECEPTOR BY INOSITOL PHOSPHATES

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Abstract The mode of recognition at the binding site of the Ins(1,4,5)P_3 receptor was assessed by examining the structure-activity relationships of different Ca^{2+}-mobilizing inositol phosphates.

Key Words: the Ins(1,4,5)P_3 receptor; inositol phosphates; calcium mobilization; rat brain microsomes; calcium signaling

INTRODUCTION

The pivotal role of D-*myo*-inositol 1,4,5-trisphosphate [Ins(1,4,5)P_3] in intracellular Ca^{2+} signaling is well recognized. In the cytosol, Ins(1,4,5)P_3 and its metabolites undergo extensive metabolism by the sequential actions of specific phosphatases and kinases, from which a plethora of inositol phosphates are produced (Figure 1).

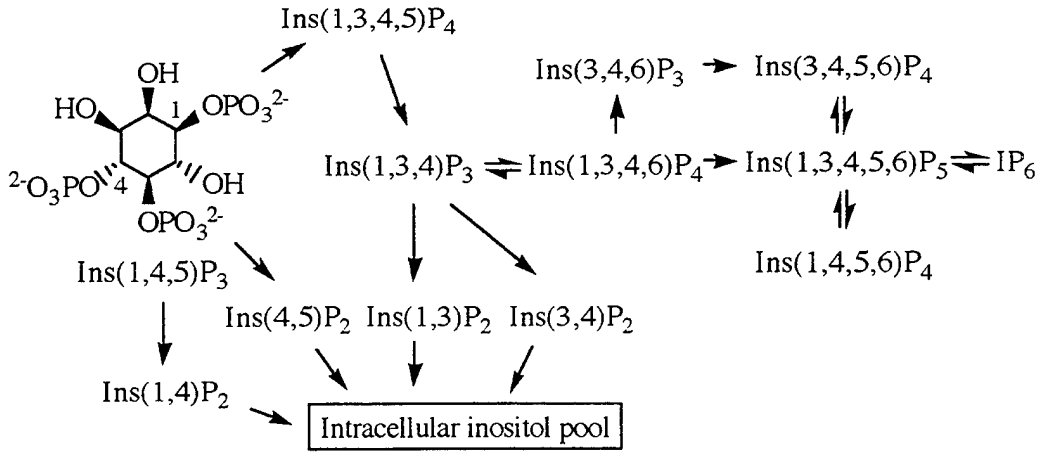


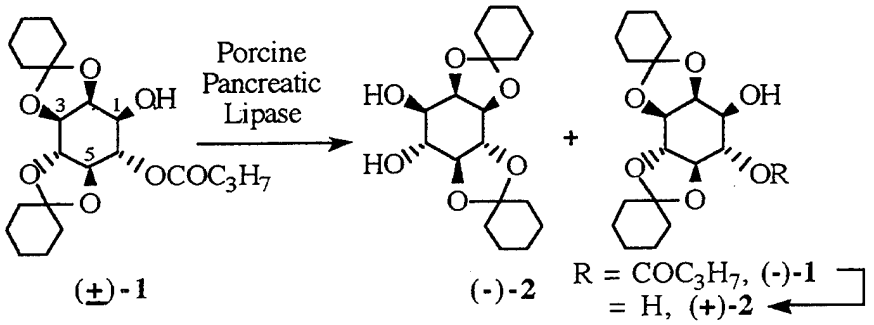
Figure 1 Metabolism of inositol phosphates

The rich diversity of phosphoinositols generated from such a complex metabolic network implies the physiological relevance of these molecules. Thus, examination of

the second-messenger role of inositol phosphates in Ca^{2+} signaling constitutes one of our research foci. In this account, we report the systematic synthesis of phosphoinositol congeners and their interactions with the Ins(1,4,5)P_3 receptor.

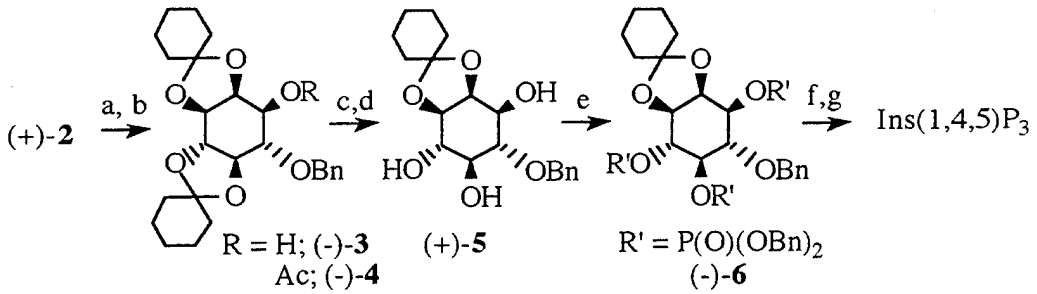
CHEMOENZYMATIC SYNTHESIS OF INOSITOL PHOSPHATES

Our key strategy employed a pair of enantiomerically active 1,2:5,6-dicyclohexylidene-*myo*-inositols (**2**) as common precursors to the target molecules, which was prepared by a facile enzymatic method. The 4-butyryl monoester [(±)-**1**] was subjected to enantiospecific hydrolysis by porcine pancreatic lipase, which gave both product [(-)-**2**] and substrate [(-)-**1**] fractions with satisfactory optical purity (e.e. ≥ 0.98) after recrystallization.



(±)-**1** (-)-**2**

The synthetic utility of **2** is illustrated by the example of Ins(1,4,5)P_3 synthesis.



a) *n*-Bu_2SnO, BnBr, CsF; b) Ac_2O, DMAP; c) TsOH/CH_2Cl_2; d) 1 *N* KOH/MeOH
e) $(BnO)_2P$-N(*i*Pr)$_2$, 1-*H*-tetrazole, MCPBA; f) Pd/C, H_2/95% EtOH; g) AcOH

Both enantiomerically active **2** allow the synthesis of eleven D-*myo*-inositol phosphates in fair yields, which included Ins(1,4)P_2, Ins(4,5)P_2, Ins(1,3,4)P_3, Ins(1,4,5)P_3, Ins(1,5,6)P_3, Ins(1,2,5,6)P_4, Ins(1,3,4,5)P_4, Ins(1,3,4,6)P_4, Ins(1,4,5,6)P_4, Ins(3,4,5,6)P_4, Ins(1,3,4,5,6)P_5.

INOSITOL PHOSPHATE-INDUCED CALCIUM RELEASE

Ca^{2+}-loaded rat brain microsomes were treated with individual inositol phosphates at 37 °C, and the released Ca^{2+} was monitored by bulk fluorimetry using Fura-2 as an indicator. Of the 12 phosphoinositols examined (the aforementioned 11 synthetic molecules and glycerophospho-D-*myo*-inositol 4,5-bisphosphate [GroPIns(4,5)P_2; purchased from Sigma], Ins(1,4,5)P_3, GroPIns(4,5)P_2, Ins(1,3,4,6)P_4, Ins(1,3,4,5)P_4, Ins(1,4,5,6)P_4, and Ins(4,5)P_2 exhibited Ca^{2+}-mobilizing activity in a dose-dependent manner (Figure 2), with apparent EC_{50} values of 0.13, 1.3, 4.4, 8.2, 11.2, and 60 μM, respectively. Other inositol phosphates including Ins(1,4)P_2, Ins(1,5,6)P_3, Ins(1,3,4)P_3, Ins(3,4,5,6)P_4, Ins(1,2,5,6)P_4, and Ins(1,3,4,5,6)P_5 failed to exert appreciable Ca^{2+} release from the microsomal preparation, even at concentrations up to 100 μM.

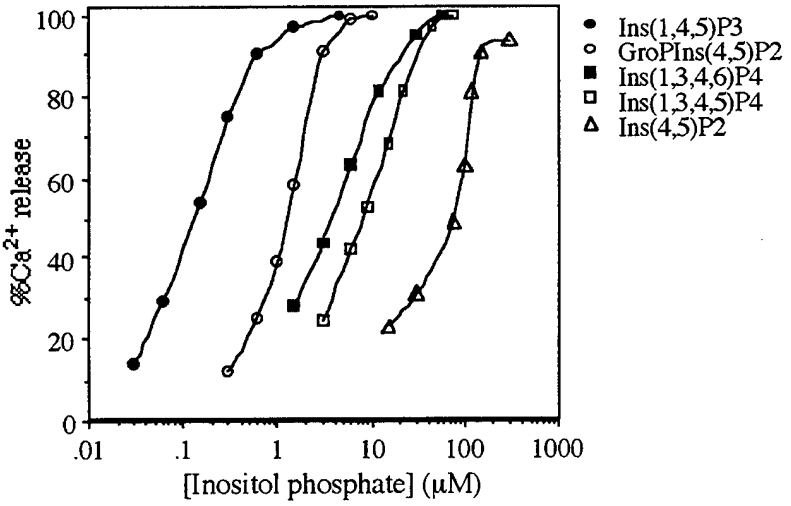


Figure 2 Inositol phosphate-induced Ca^{2+} release from rat brain microsomes.

BINDING AFFINITY OF INOSITOL PHOSPHATES WITH THE INS(1,4,5)P_3 RECEPTOR

To assess the binding of inositol phosphates to the Ins(1,4,5)P_3 receptor, displacement of specific [^{3}H]Ins(1,4,5)P_3 binding was carried out using rat cerebellar membrane preparations. According to the displacement curves (not shown), the mean dissociation constants (K_d) for individual inositol phosphates were determined as follows (n = 3): Ins(1,4,5)P_3, 0.028 μM; GroPIns(4,5)P_2, 0.92 μM; Ins(1,3,4,5)P_4, 1.4 μM; Ins(1,4,5,6)P_4, 2.1 μM; Ins(1,3,4,6)P_4, 2.2 μM; Ins(4,5)P_2, 24 μM; Ins(1,3,4,5,6)P_5, 40 μM; Ins(3,4,5,6)P_4, 56 μM; Ins(1,2,5,6)P_4, 57 μM; Ins(1,3,4)P_3, 146 μM; Ins(1,4)P_2, 217 μM; Ins (1,5,6)P_3, 454 μM. For the inositol phosphates capable of effecting Ca^{2+} mobilization, the relative potency of inhibiting [^{3}H]Ins(1,4,5)P_3 binding to the receptor paralleled the order of the EC_{50} values.

LIGAND RECOGNITION AT THE INS(1,4,5)P_3 RECEPTOR

Analysis of the structures of Ca^{2+}-mobilizing inositol phosphates indicates that all these molecules assume conformations sharing or mimicking the structural features of the 4,5-bisphosphate 6-hydroxy and 1-phosphate motifs of Ins(1,4,5)P_3 (Figure 3)

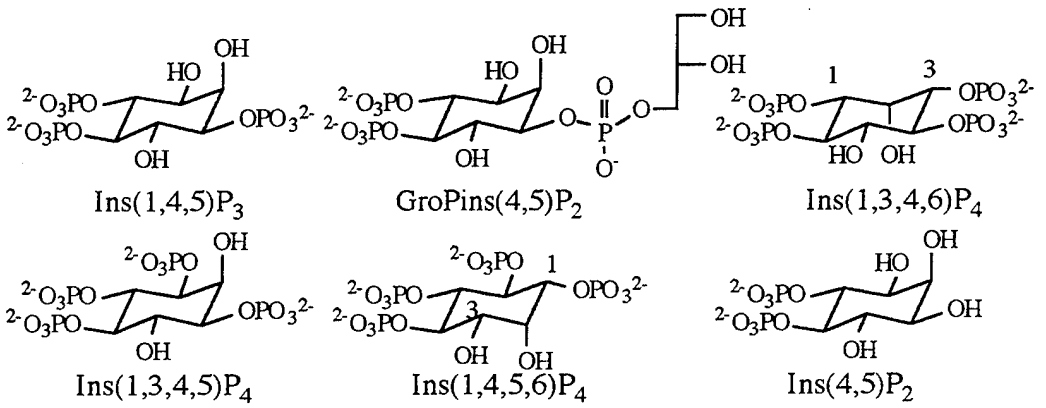


Figure 3 Structures of some inositol phosphates capable of eliciting Ca^{2+} release

On the basis of this finding, we propose a binding model to account for ligand recognition at the Ins(1,4,5)P_3 receptor (Figure 4). The binding site is presumably composed of two domains. The anchoring domain interacts with the 4,5-bisphosphate 6-hydroxy motif, attributing to the Ca^{2+}-mobilizing activity. The auxiliary domain exerts long-range electrostatic interactions with the 1-phosphate group, which enhances the binding affinity. The stereochemical requirement for this phosphate recognition is, however, less stringent. The biochemical implication of the cross-reactivity of the Ins(1,4,5)P_3 receptor with a number of inositol phosphates besides Ins(1,4,5)P_3 remains unclear.

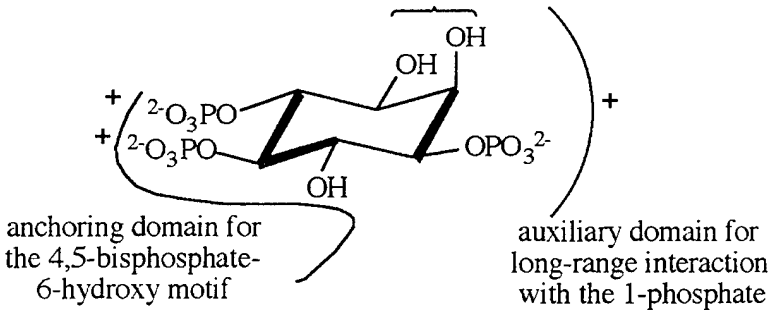


Figure 4. Ligand recognition at the Ins(1,4,5)P_3-binding site.

Reference

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SYNTHETIC MODULATORS OF THE POLYPHOSPHOINOSITIDE PATHWAY OF SIGNAL TRANSDUCTION

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Abstract Syntheses of regiochemically and structurally modified analogues of D-*myo*-inositol 1,4,5-trisphosphate are described to give second messenger mimics, enzyme inhibitors and receptor antagonists, demonstrating new leads for the design of agents to interfere with a key pathway of signal transduction.

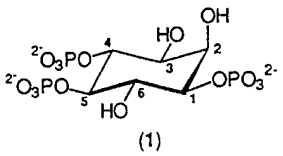
The second messenger D-*myo*-inositol 1,4,5-trisphosphate [Ins(1,4,5)P_3] **1** mobilizes intracellular Ca^{2+} as a response to phospholipase C activation by stimulation of an extracellular G-protein coupled receptor in many cell types.[1,2] Intensive biological interest has followed the discovery of the Ca^{2+} releasing activity of Ins(1,4,5)P_3 in 1983.[3] Additionally, chemical investigations have aimed at synthesis of inositol polyphosphates and understanding structure-recognition parameters at the Ins(1,4,5)P_3 receptor and other binding proteins.[4-6] The key feature for Ca^{2+}-mobilizing activity is the *trans* 4,5-bisphosphate motif of Ins(1,4,5)P_3. The synthesis of structurally-modified Ins(1,4,5)P_3 analogues offers the prospect of pharmacological intervention in this signalling pathway. We have approached this challenge in four different areas:

(a) Regioisomers of Ins(1,4,5)P_3 with Ca^{2+}-mobilizing activity

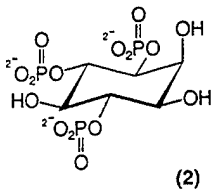
Although Ins(1,4,5)P_3 is the most well known mobilizer of intracellular Ca^{2+}, we reasoned that the regioisomeric *myo*-inositol trisphosphates D-Ins(1,4,6)P_3 and L-Ins(1,3,4)P_3 should also be D-Ins(1,4,5)P_3 mimics, although they do not formally possess the crucial 4,5-bisphosphate group. We thus synthesized both enantiomers of Ins(1,4,6)P_3 and Ins(1,3,4)P_3.[7,8] In Ca^{2+} mobilization neither synthetic L-Ins(1,4,6)P_3 **2** nor D-Ins(1,3,4)P_3 **3** [the naturally occurring metabolite of Ins(1,3,4,5)P_4] showed activity. By contrast, the enantiomers D-Ins(1,4,6)P_3 **4** and L-Ins(1,3,4)P_3 **5** were both relatively potent full agonists, thus abolishing some previous structure-activity dogma. L-Ins(1,3,4)P_3 also mobilises Ca^{2+} in *Limulus* photoreceptors.[8]

(b) Inositol phosphorothioates as enzyme inhibitors and receptor antagonists

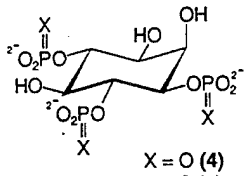
Inositol phosphorothioates are well established as analogues of Ins(1,4,5)P_3 with *inter alia* resistance against degradation by metabolic enzymes. We noted earlier that phosphorothioate substitution generally increases the affinity of an analogue for 5-phosphatase.[9] For design of potent and selective non-Ca^{2+}-mobilizing inhibitors of this



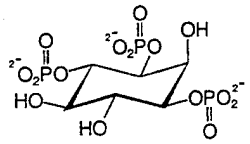
(1)



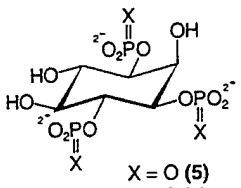
(2)



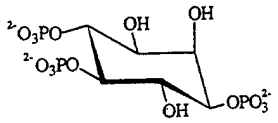
X = O **(4)**
X = S **(7)**



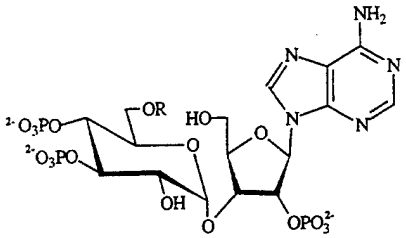
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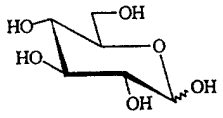
X = O **(5)**
X = S **(6)**



(1)

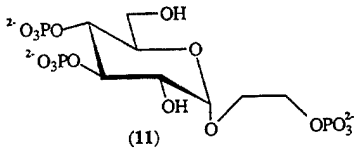


(8) R=H
(9) R=$COCH_3$

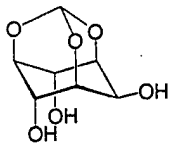


(10)

6 steps

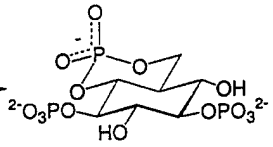


(11)

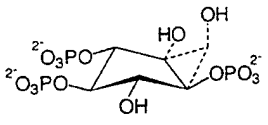


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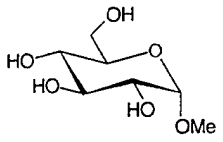
12 steps



(13)

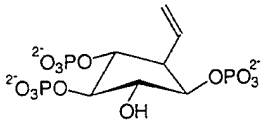


(14)



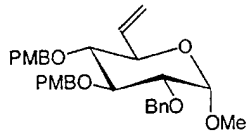
(15)

6 steps



(17)

4 steps



(16)

enzyme, we thus reasoned that phosphorothioate substitution of weak polyphosphate-based non-Ca^{2+}-mobilizing 5-phosphatase inhibitors should be appropriate. Indeed, the trisphosphorothioates of Ins(1,3,5)P_3, L-Ins(1,4,5)P_3 and L-*chiro*-Ins(1,4,6)P_3 are all sub-micromolar inhibitors with no Ca^{2+}-mobilizing activity or action on the other metabolic enzyme 3-kinase.[10,11] Trisphosphorothioate analogues **6** and **7** of L-Ins(1,3,4)P_3 and D-Ins(1,4,6)P_3 respectively proved to be low intrinsic activity partial agonists at the Ins(1,4,5)P_3 receptor[12] providing leads for small molecule antagonist design. Another trisphosphorothioate, L-*chiro*-Ins(2,3,5)PS_3, and its parent trisphosphate are moderate inhibitors of phosphoinositide 3-kinase[13] and represent new leads for development of inhibitors in this newly emerging signal transduction pathway.

(c) A carbohydrate polyphosphate mimic of Ins(1,4,5)P_3 and adenophostin A

Structural modification of Ins(1,4,5)P_3 has generally consisted of phosphate alteration or hydroxyl group deletion, reorientation, alkylation, or replacement by isosteres and other groups in the cyclitol ring.[4-6] Much success has been achieved in understanding structure activity profiles for Ins(1,4,5)P_3 analogues. The recently reported adenophostins A and B,[14] **8** and **9** respectively, isolated from *Penicillium brevicompactum*, are agonists with little apparent resemblance to Ins(1,4,5)P_3 and yet possess a Ca^{2+}-mobilizing potency some 100 fold *greater* than Ins(1,4,5)P_3. A structural rationalisation of this exceptional potency is presently lacking. The adenophostins are thus targets for chemical modification and we have made the first step in this direction with the synthesis of the polyphosphorylated carbohydrate derivative (2-hydroxyethyl) α-D-glucopyranoside 2',3,4-trisphosphate **11**.[15] Our route from D-glucose **10** employed a regioselective dibenzylation of allyl α-D-glucopyranoside, and elaboration to provide a key triol for phosphorylation. After deblocking and purification, trisphosphate **11** was found to release intracellular Ca^{2+}. Its potency was not comparable to that reported for **7** and was some 10 fold weaker than Ins(1,4,5)P_3. The adenosine motif is thus important for the extreme potency of the adenophostins and **11** represents the first synthetic carbohydrate polyphosphate mimic of Ins(1,4,5)P_3.

(d) Ins(1,4,5)P_3 mimics with extreme structural dissimilarity

Synthesis of conformationally restrained analogues has not yet been explored for Ins(1,4,5)P_3. We therefore decided to constrain one of the vicinal bisphosphates using a ring. Since binding affinity correlates most closely with the ionization state of the 5-phosphate,[16] the more cautious approach was to focus on position 4. Deletion of the 3-hydroxyl should be well tolerated, as 3-deoxy-Ins(1,4,5)P_3 is highly active.[6] We therefore synthesized the cyclic phosphate **13**, in which the phosphate group equivalent to the 4-phosphate of Ins(1,4,5)P_3 is tethered *via* a methylene group to the equivalent carbon of position 3. The hydroxyl group at the equivalent position 2 is equatorial rather than axial, but this is not significant, as D-*scyllo*-inositol 1,2,4-trisphosphate is almost equipotent with Ins(1,4,5)P_3.[17] The 3- and 6-OH groups of Ins(1,4,5)P_3 may hydrogen bond to the 4- and 5-phosphates respectively, and we therefore constrained the 4-phosphate in such a way as to mimic this conformation. An efficient synthetic route to **13** started from *myo*-inositol orthoformate **12** in some 12 steps.[18] Racemic **13** was examined for Ca^{2+}-mobilizing activity and behaved as a full agonist, although with

an EC_{50} around 40 fold higher than Ins(1,4,5)P_3. Thus, we have shown that a conformationally restricted analogue of Ins(1,4,5)P_3, even at the supposedly crucial 4,5-bisphosphate group, can retain activity, despite reduction of charge.

The fundamental requirement of a six-membered ring for Ins(1,4,5)P_3 activity has not yet been addressed. Since the 2- and 3-positions are surprisingly tolerant to modification,[4-6] we envisaged that a contracted structure such as **14** should also fulfil receptor recognition requirements. We thus synthesized a related "pentagon IP_3", (1*R*, 2*R*, 3*S*, 4*R*, 5*S*)-3-hydroxy-1,2,4-trisphospho-5-vinylcyclopentane **17**[19] with a *five-membered* cyclic core structure. Molecular modelling studies of **17** indicate a good overlay of essential recognition elements for activity with those of Ins(1,4,5)P_3. The 5-vinyl pyranoside **16** was synthesized from methyl α-D-glucopyranoside **15** in 5 steps. After zirconium mediated ring contraction, the major diastereoisomer was partially deblocked, phosphorylated and completely deblocked. The purified trisphosphate **17** was examined for Ca^{2+}-mobilizing activity and was a relatively potent agonist with an EC_{50} some 65-fold higher than Ins(1,4,5)P_3. We have thus demonstrated for the first time that Ins(1,4,5)P_3 receptor mediated Ca^{2+}-mobilization does not necessarily require a cyclohexyl (or equivalent) structural motif. Potent activity can be achieved with a smaller ring polyphosphate retaining key recognition elements of Ins(1,4,5)P_3.

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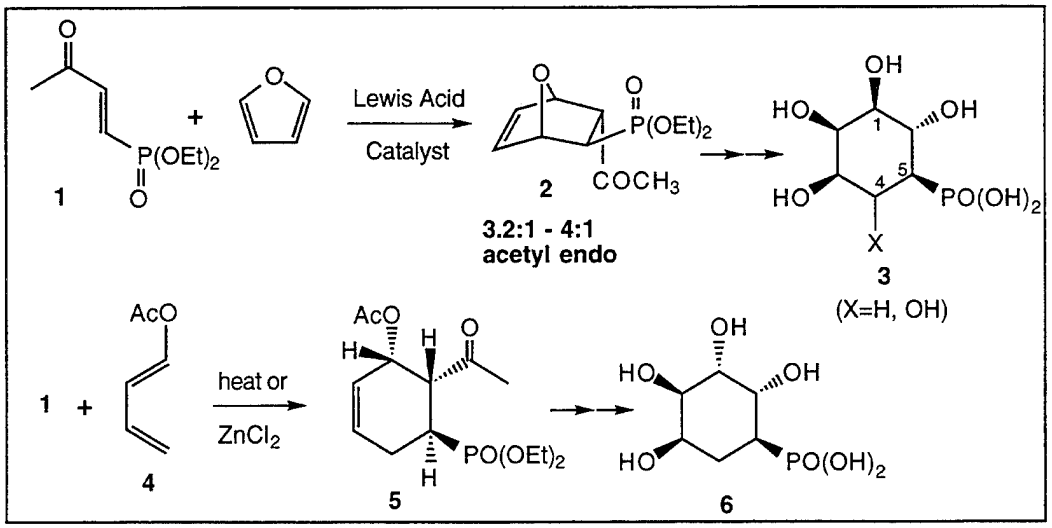
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DIELS-ALDER REACTIVITY OF A KETO VINYLPHOSPHONATE. EMPIRICAL AND THEORETICAL OBSERVATIONS. APPLICATION TO THE SYNTHESES OF PHOSPHONATE ANALOGUES OF *MYO*-INOSITOL.

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Montana State University, Dept. of Chemistry and Biochemistry, Bozeman, MT 59171

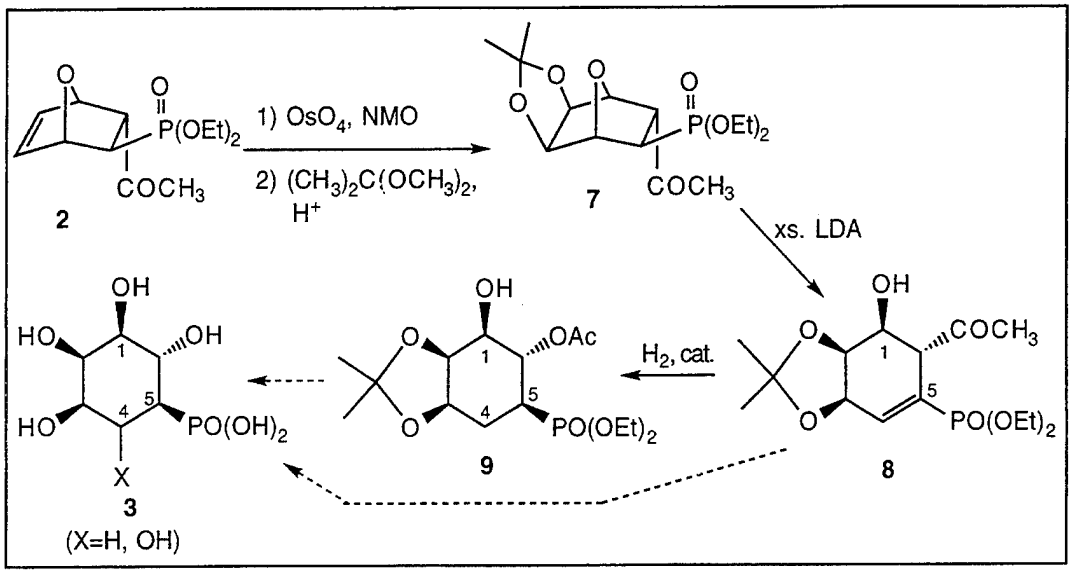
Abstract The Diels-Alder reactivity of the keto vinylphosphonate **1** with furan, cyclopentadiene and E-1-acetoxy-1,3-butadiene was investigated with and without Lewis acid assistance. The acetyl group directed in each case. LUMO molecular orbital coefficients were obtained via *ab initio* (3-21G*) calculations, and support the experimental data. The Diels-Alder products from the reactions with furan and 1-acetoxybutadiene are being carried on to phosphonate analogs of inositols.

We are currently investigating the Diels-Alder reactivity of the keto vinylphosphonate **1** with various dienes, the ultimate targets being phosphonate analogues of *myo*-inositol phosphates. *Myo*-inositol phosphates are key players in cellular signal transduction, and are second mesengers in a large array of cellular processes.[2] Two routes to the phosphonate inositol analogues are being pursued: (a) via a Lewis acid catalyzed Diels-Alder reaction of **1** with furan, and (b) via a Diels-Alder reaction of **1** with (E)-1-acetoxy-1,3-butadiene (**4**).



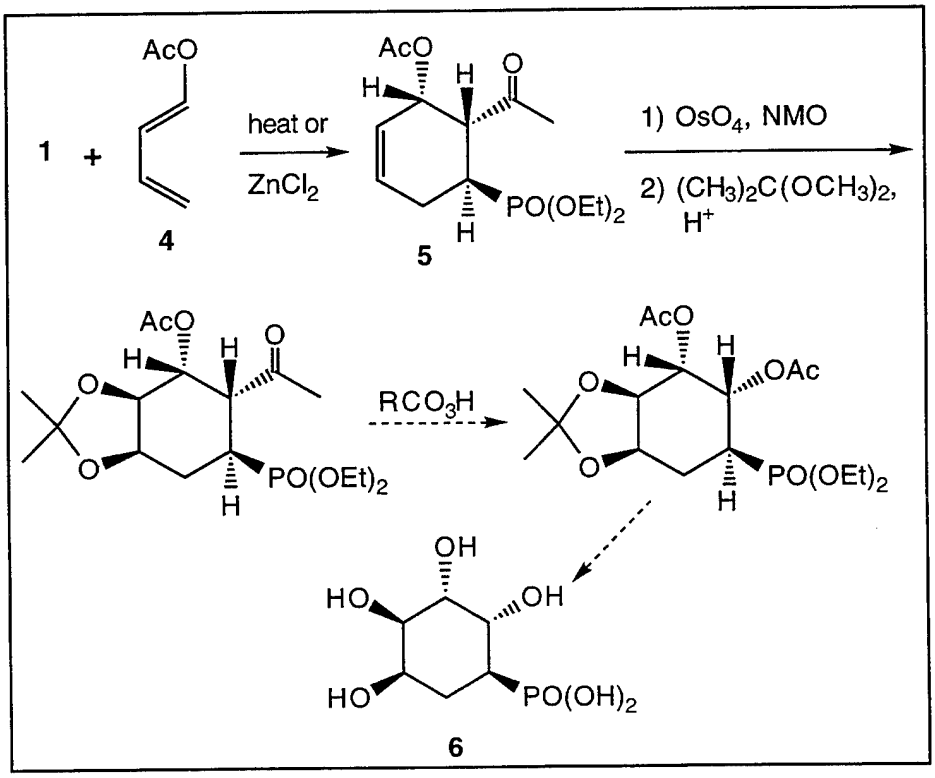
Keto vinylphosphonates have seen limited use a dienophiles, presumably due to the lack of ready availability of these compounds. Our keto vinylphosphonate **1** was easily prepared utilizing our pentacovalent oxaphospholene methodology.[3] To our knowledge, there have been no studies on the effects of Lewis acids on the Diels-Alder reactivity of keto vinylphosphonates analogous to **1**.[4] Therefore, we first investigated the use of the keto vinylphosphonate **1** with and without Lewis acid assistance in the Diels-Alder reactions with cyclopentadiene and furan. The Lewis acids studied to date are $ZnCl_2$, $LiClO_4$, Et_2AlCl, $Eu(fod)_3$ in diethyl ether or CH_2Cl_2. *We found that the acetyl group directed under all the conditions used.* Two or more equivalents of the Lewis acids had to be used in order to see any affect on the ratios. Lower reaction temperatures also helped to increase the endo:exo ratios. For cyclopentadiene, the ratios ranged from 2.5:1 (no Lewis acid) to 6.7:1; and for furan, the ratios were 3.2:1 ($ZnCl_2$) to 4.0:1. The lanthanide Lewis acid, $Eu(fod)_3$, has given the best acetyl endo : exo ratios to date (6.7:1 with cyclopentadiene, 4:1 with furan). Spectroscopic (IR, ^1H, ^{13}C, ^{31}P NMR) confirmation that the first equivalent of Lewis acid was complexing with the phosphoryl oxygen (P=O) was obtained using 1 equiv. of $ZnCl_2$ in $CDCl_3$.

The acetyl endo furan adduct, **2**, was carried on in the synthesis of the inositol phosphonate analog **3**. Osmylation of the alkene, followed by protection of the diol, proceeded in good yields. Attempts at inducing a Baeyer-Villiger reaction on the acetyl group at this point gave only starting material. We also tried to open the bridge using acetyl bromide, dry HBr, or $FeCl_3/Ac_2O$. None of these conditions produced any products, and only starting material was recovered. However, we found that upon

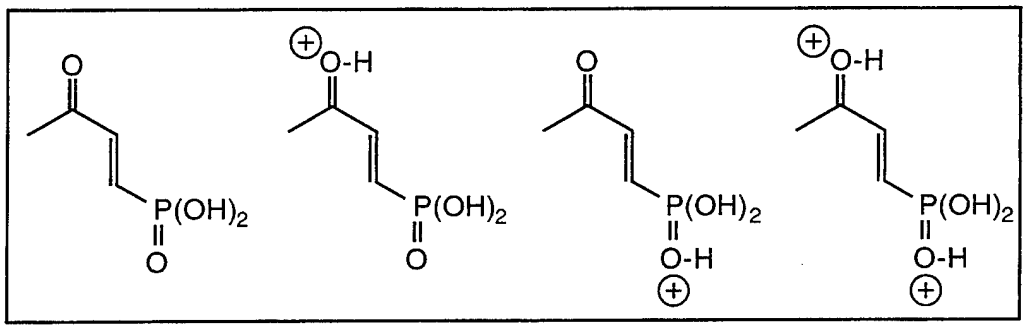


treatment with 2.2 eq. of LDA, we could deprotonate α to the phosphonate and effect a ring opening of the bridge to form the vinylphosphonate, **8**, in 80% yield, but only 30% conversion. Attempts to push the reaction produced aromatized by-products. Hydrogenation of **8** produced the expected isomer in quantitative yield. We are currently at this stage of the synthesis, and plan to pursue other methods for opening the oxygen bridge.

In contrast to the non-polarized dienes above, Diels-Alder reaction of **1** with E-1-acetoxy-1,3-butadiene, **4**, produced only one regio- and stereo-isomer, **5**, under thermal or Lewis acid ($ZnCl_2$) assisted conditions. Its structure was determined to be as shown via 2-D COSY, HETCOR and J-Resolved experiments. This regio- and stereo-isomer (acetyl directing endo) is in contrast to that reported by Darling using the same diene, but where the phosphonate group was replaced with a diphenyl phosphine oxide.[5] They reported isolation of only one product where the phosphine oxide had directed in the exo mode. Our Diels-Alder adduct, **5**, is being carried on to (±)-1-epi-4-deoxy-5-phosphono-*myo*-inositol **6** (also called (±)-3-deoxy-4-phosphono-*dl*-inositol) as shown. Osmylation and protection of the diol have proceeded in good yields. We are currently at this stage of the synthesis.



To further investigate the effects Lewis acids have on the Diels-Alder reactivity of keto vinylphosphonates analogous to **1**, we have also performed theoretical (*ab initio* RHF/3-21G*) calculations using a model Lewis acid (H^+) and the phosphonic acid analogue of **1** (see figure below). The resulting LUMO levels of these model dienophiles exhibited a lowering of the relative energies upon going from non-protonated, to mono-protonated (either carbonyl or phosphoryl oxygens) to di-protonated at both the carbonyl and phosphoryl oxygens, as expected. The molecular orbital coefficients varied as expected with the complexation, and supported the empirical data.



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MECHANISM AND INHIBITION OF INOSITOL MONOPHOSPHATASE

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Abstract The design and synthesis of inhibitors of inositol monophosphatase (IMPase, E.C. 3.1.3.25) based on natural substrates and lead compounds discovered by screening is discussed. The physiologically relevant form of the enzyme and a likely mechanism have been deduced from structure-activity relationships, site-directed mutagenesis experiments, X-ray crystallography and molecular modelling.

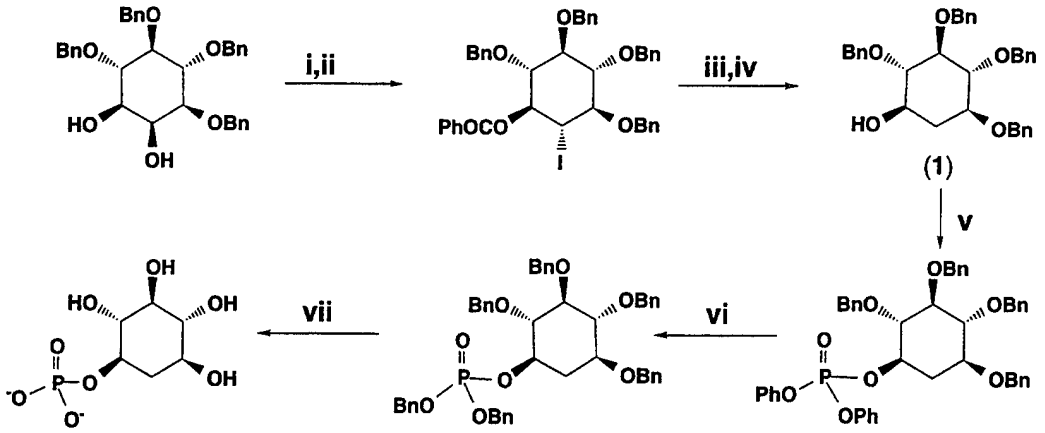
INTRODUCTION

Lithium is the major drug treatment for bipolar disorder, despite a poor side effect profile and narrow therapeutic window. The hypothesis that the phosphatidylinositol (PI) cell signalling system and in particular IMPase are the site of action for the beneficial effects of lithium has found significant support and has been reviewed elsewhere[1]. On this basis, a selective organic inhibitor of IMPase might be expected to treat bipolar disorder while showing less side effects than the unselective agent lithium.

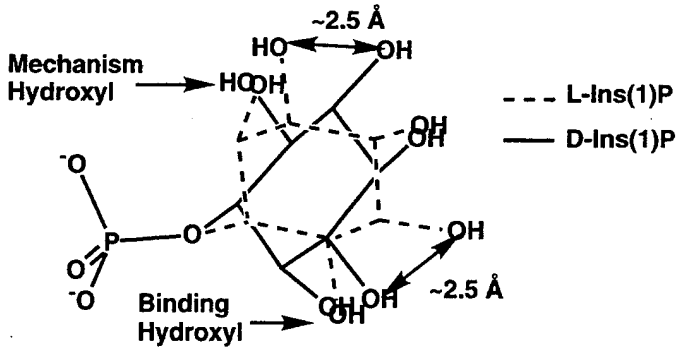
INHIBITORS

Both D- and L-inositol-1-phosphate (D- and L-Ins(1)P) are hydrolysed at equal rates by IMPase, yet the two compounds differ only in the stereochemistry of the two hydroxyl groups flanking the phosphate group. If the phosphate and the inositol ring bind in similar orientations in both enantiomers, it appears likely that neither the 2- nor the 6-hydroxyl should bind to the enzyme since they do not superimpose in such an overlay. (±) 2- Deoxyinositol-1-phosphate was therefore prepared as shown in scheme 1, while (±) 6-deoxyinositol-1-phosphate was prepared analogously using cyclohexylidene groups to provide differential protection. In the latter case, it was not necessary to transesterify the phosphate group with benzyl alcohol before removal of all the protecting groups by treatment with silica followed by hydrogenation over platinum[2].

Surprisingly, *both* were found to be competitive inhibitors ($IC_{50} \approx 70\mu M$), demonstrating that both flanking hydroxyl groups were needed for substrate activity. Resolution of the enantiomers of 2-deoxyinositol-1-phosphate was achieved *via* the camphanic acid ester of racemic (**1**). Homochiral (**1**) was then treated as before to give enantiomerically pure 2-deoxyinositol-1-phosphate. The (+) enantiomer, corresponding to D-Ins(1)P, was a weak substrate, while its antipode was a competitive inhibitor (K_i 50μM). This suggested that the relative binding modes of the two substrates might be as suggested in the lower part of scheme 1, leading to the idea that the 3 and 5 hydroxyl groups might play no part in binding. In this picture, one flanking hydroxyl group (the 2-OH of L-Ins(1)P and the 6-OH of D-Ins(1)P) was necessary for catalysis to take place, while the other conferred good binding properties.

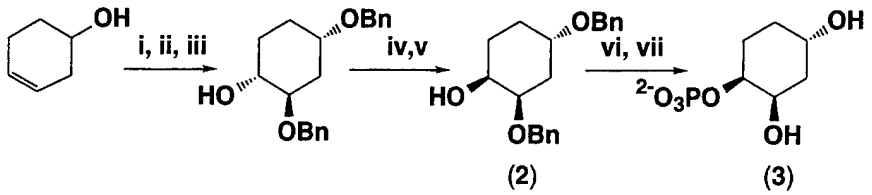


i : Bu_2SnO / MeOH / PhCOCl ii : I_2 / PPh_3 / Imidazole iii : Bu_3SnH / AIBN
iv : NaOH / MeOH v : $(PhO)_2POCl$ / Et_3N vi : NaOBn / THF vii : H_2 / Pd / C



SCHEME 1 Synthesis of 2-deoxyinositol-1-phosphate, and deduced binding modes.

In keeping with this, the 3,5 dihydroxy and 4-hydroxy cyclohexane-1-phosphates were inactive, while (**3**), synthesized[3] as in scheme 2 and resolved by separation of the camphanate esters of compound (**2**), was a good inhibitor (IC_{50} 3μM). The 4-hydroxy group could not be removed without a drastic loss in binding. From these results, similar overlays with other substrates, notably 2'-AMP, could be generated, and suggested that bulky hydrophobic substituents at the 6-position might enhance binding and/or improve physical properties. A number of such compounds were prepared[4] following a similar route to that used previously, with optimum IC_{50}'s of 40nM.

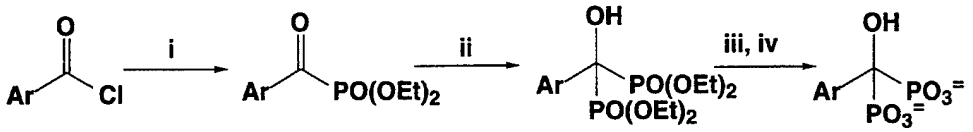


i : $VO(acac)_2$, ButOOH ii : NaH, BnBr iii : BnOH, Al_2O_3, PhMe, ↓↑ iv : Swern oxidation
v : L-selectride vi : $[(BnO)_2PO]_2O$ vii : H_2 / Pd/C

SCHEME 2 Synthesis of 3,5,6-trideoxy-D-Ins(1)P.

In these cases, the phosphorylation was more conveniently achieved with N,N-diethyl-dibenzylphosphoramidite followed by oxidation with *m*-CPBA and hydrogenolytic removal of the protecting groups.

Hydroxymethylene-bisphosphonic acid was identified as a weak (IC_{50} 280 μM) inhibitor of the enzyme. Affinity was improved by substitution with an aryl group, synthesized according to Scheme 3, which led to sub-micromolar compounds[5].

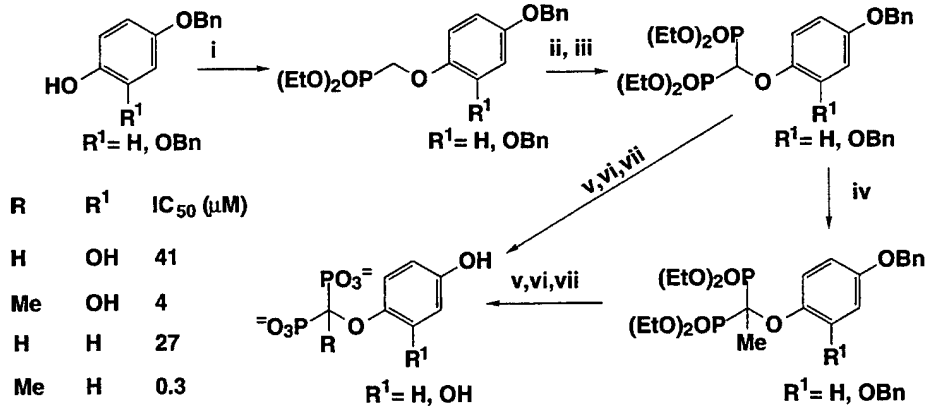


i : $(EtO)_3P$ ii : $HPO(OEt)_2$, nBu_2NH, Et_2O iii : Me_3SiBr iv : H_2O

SCHEME 3 Synthesis of arylhydroxymethylenebisphosphonates

The introduction of the second phosphonate unit required the use of di-^{n}butylamine, triethylamine giving the opposite regiochemistry of addition across the carbonyl group.

The methylenebisphosphonate unit could also be linked through oxygen to the trideoxyinositol moiety and served as a good replacement for phosphate providing new inhibitors which were stable to hydrolysis[6]. Replacement of the phosphate permitted replacement of the inositol ring with a simple phenol[7]. The synthesis of some of these compounds is illustrated in Scheme 4. Further optimisation could be achieved by simple modification of the synthetic scheme to introduce larger groups at **R** providing compounds with $IC_{50} \approx 80$ nM. However, L-690,330 and a prodrug derived from it proved sufficient to establish that an organic inhibitor of IMPase would produce similar effects on the PI cycle in cells and in whole animals to those seen with lithium[8].



i : NaH, $TfOCH_2PO(OEt)_2$ ii : LDA iii : $ClPO(OEt)_2$ iv : NaH, MeI v : Me_3SiBr vi : H_2O vii : H_2 / Pd/C

SCHEME 4 Synthesis and properties of phenolic bisphosphonate inhibitors.

MECHANISM

Several crystal structures have been obtained of the enzyme in inhibited and active

forms[9]. We have blended the structures in the presence of substrate and the inhibitory metal Gd^{3+} and in the presence of the catalytically viable metal Mn^{2+}.[10] Initial studies enabled the identification of appropriate sites for site-directed mutagenesis which later assisted in confirming the validity of the model. Molecular dynamics was used on models containing a variety of different metal ion combinations to remove strain and provide a sampling of conformations available to the enzyme. A model containing Gd^{3+} together with two Li^{+} ions reproduced many of the observations for the metal environment seen in the crystal, while a model containing two Mn^{2+} ions was consistent with a large body of mutagenetic and kinetic evidence[10,11]. Analysis of potential nucleophiles revealed three possibilities. Phospho-enzyme intermediates have already been demonstrated not to form a part of the IMPase mechanism[12], leaving two water molecules which could play the role of the nucleophile. We prefer that located on the first metal site identified, which also forms interactions with Glu70, and which would be able to apically attack the phosphorus atom in a manner similar to that deduced for the structurally homologous enzyme fructose bis-phosphatase[13,14].

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SYNTHESIS AND PROPERTIES OF 2-AMINO-2-ARYLETHYLPHOSPHONIC ACIDS AND DERIVATIVES

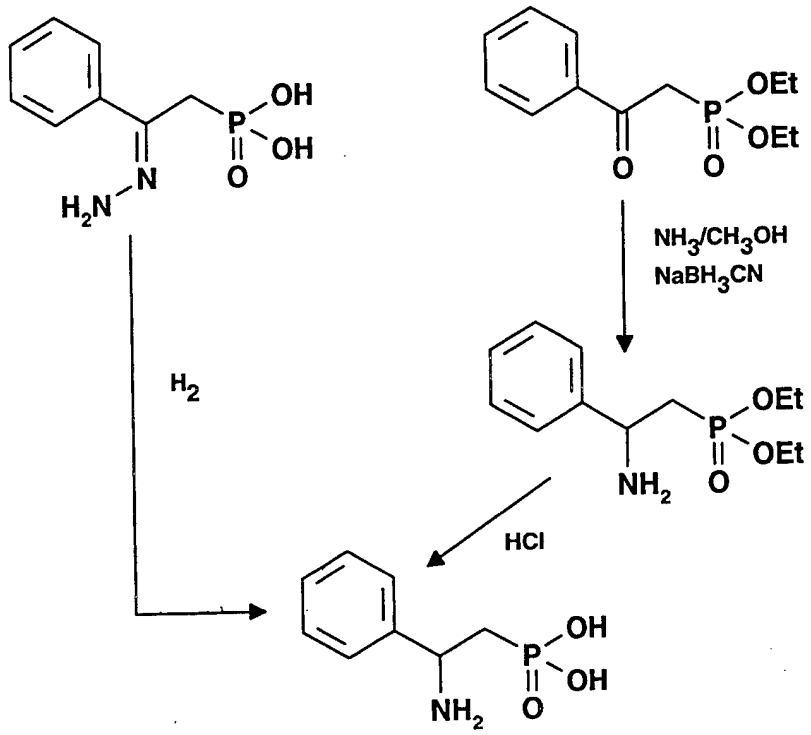
LUDWIG MAIER AND PETER J. DIEL
CIBA-GEIGY AG, Agricultural Division, CH-4002 Basel, Switzerland

ABSTRACT 2-Amino-2-arylethylphosphonic acids, **6a** to **6q** have been prepared from the corresponding 2-acetoxyimino- or 2-methoxy imino-2-arylethylphosphonates, **3** or **4**, by hydrogenation using Raney-Ni as a catalyst, followed by hydrolysis with HCl. **3** and **4** were obtained from the corresponding aryl-bromomethyl-ketoxime-O-acetates, **1**, or aryl-bromomethyl-O-methylketoximes, **2**, by an Arbuzov reaction with triethylphosphite.
Several of the 2-amino-2-arylethylphosphonic acids **6** show activity against Botrytis cinerea and Cercospora. Among the more active compounds were **6a**, **6b**, **6g** and **6k**, whereby **6b** and **6k** gave full protection against Botrytis cinerea (on apple) down to 60 ppm. The same compounds show also a weak inhibition of anthocyanin synthesis in vivo.[1]

Key words: 2-Amino-2-arylethylphosphonic acids; 2-amino-2-arylethylphosphonates; 2-acetoxyimino-2-arylethylphosphonates; 2-methoxyimino-2-arylethylphosphonates; Reduction of oximes; biological activity.

INTRODUCTION

A few years ago we reported on the synthesis and properties of 1-amino-2-arylethylphosphonic acids.[2] It was shown that several compounds of this type are strong inhibitors of PAL and anthocyanin synthesis and are also quite active botryticides. It seemed of interest to prepare the 2-amino-2-arylethylphosphonic acids and compare their biological activity with that of the 1-amino-2-arylethylphosphonic acids.
In the literature are already described some of these compounds. Thus Mastalerz et al.[3] obtained the unsubstituted 2-amino-2-phenylethylphosphonic acid, **6a**, by reduction of the hydrazon, and Varlet et al.[4] synthesized several compounds of this type by reductive amination of the corresponding keto-compounds (Scheme I)



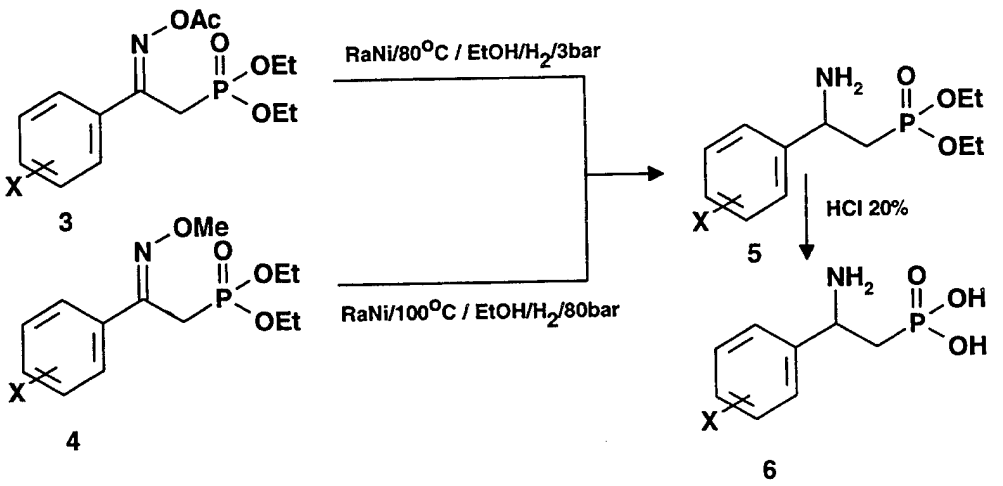
6a

Scheme I

Both methods need β-ketophosphonates as starting materials which are not so readily available. In the following we describe a new preparative procedure and also report on the biological activity of this type of compounds.

RESULTS AND DISCUSSION

To avoid the use of β-ketophosphonates we started with oxime acetates **1** or oxime ethers **2** of aryl-bromomethylketones which can be easily prepared. Treatment of these with triethylphosphite yields the 2-aryl-2-acetoxyiminoethylphosphonates **3**[5] and 2-aryl-2-methoxyiminoethylphosphonates **4** in high yield (Scheme II).



Scheme II

Reduction of **3** with hydrogen in ethanol at 80°C and 3 bars and of **4** at 100°C and 80 bars in the presence of Raney-Ni as catalyst produced **5** in reasonable to good yields. It was observed that in general the reduction of **4** gave higher yields of **5** than that of **3**, e.g., reduction of **4k** ($X=CH_3$) yielded **5k** in 79.6% yield, whereas reduction of **3k** ($X=CH_3$) gave **5k** in only 51.5% yield. **4n** ($3,4\text{-}Cl_2$) and **4o** ($X=2,4\text{-}Cl_2$) were reduced to **5n** and **5o**, respectively, with zink in formic acid[6], in order to avoid dehalogenation.

Hydrolysis of 2-amino-2-arylethylphosphonates **5** with 20% HCl under reflux afforded 2-amino-2-arylethylphosphonic acids, **6**, (Scheme II) in good yields. Since the difluormethoxysubstituent in **5l** was cleaved with HCl, **5l** was converted to **6l** by dealkylation with trimethylbromosilane followed by hydrolysis with methanol.

BIOLOGICAL ACTIVITY

Like 1-amino-2-arylethylphosphonic acids[2] several of the 2-amino-2-arylethylphosphonic acids **6**, described in this paper, also show activity against Botrytis cinerea (on apple and cercospora (on peanuts). Among the more active compounds were **6a**, **6b**, **6g** and **6k**, whereby some of the compounds (**6b** and **6k**) gave full protection against Botrytis cinerea down to 60 ppm. In addition, the same compounds show a weak inhibition of anthocyanin synthesis in vivo (3.4% by 1 mM).

ACKNOWLEDGEMENT

We wish to thank Ciba-Geigy's Central Function Research for the hydrogenation experiments and the combustion analyses and Mr. H. Spörri and C. Devonas for experimental help. We particularly want to thank Professor N. Amrhein for providing the anthocyanin synthesis inhibition constants.

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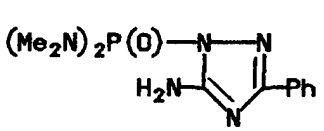
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AN APPROACH TO THE DEVELOPMENT OF ORGANOPHOSPHORUS FUNGICIDES

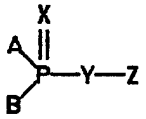
HARRY R. HUDSON AND MAX PIANKA
School of Applied Chemistry, University of North London, Holloway Road, London, N7 8DB, U.K.

Abstract Phosphoramidates, phosphorodiamidates, phosphoric triamides, aminophosphonic acids, guanidinophosphonic acids, and phosphonopeptides are discussed as fungicides with potential for application in agriculture.

Following the discovery of systemic fungicidal activity in triamiphos (1) and the development of this compound under the name Wepsyn by Philips-Duphar,[1] a large number of organophosphorus compounds, mainly ester and amide derivatives of phosphoric or thiophosphoric acid (2), were investigated as potential fungicides.[2] Of these, four compounds



(1)



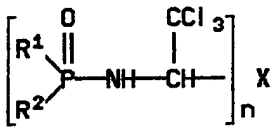
(2)

A, B = RO or R_2N
X, Y = O or S
Z = heterocyclic, benzyl, etc.

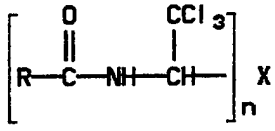
(iprobenfos, edifenphos, pyrazophos, and fosetyl) are currently available for commercial use.[3] There is still much active research in this area, with numerous papers each year reporting new fungicidal organophosphorus compounds.

We have followed two lines of investigation, the first dealing with novel phosphoramidates, phosphorodiamidates, and phosphoric triamides, and the second with aminophosphonic acids, guanidinophosphonic acids, and phosphonopeptides.

Our approach in the first series of investigations was to prepare phosphorus-containing analogues (3) of known fungicidal carboxamide derivatives (4), in which an *N*-(1-substituted-2,2,2-trichloroethyl) group is present.[4] A well known example is triforine (4, R = H, X = piperazine-1,4-diyl, n = 2).[3] The phosphoramidates (3, R^1 = R^2 = EtO) were obtained[5] by condensation of diethyl phosphoramidate with chloral, replacement of hydroxy in the so-formed adduct with chlorine



(3)



(4)

n = 1 or 2

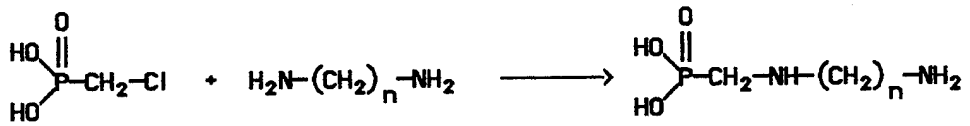
to give the tetrachloro compound $(EtO)_2P(O)NHCH(CCl_3)Cl$ (5), elimination of hydrogen chloride to give the imine $(EtO)_2P(O)N=CHCCl_3$ (6), and addition to the latter of a nucleophilic species e.g. imidazole, triazole, morpholine, piperazine, *N*-formylpiperazine, thioethanol, or various carboxamides or phosphoramides. Derivatives containing dithiocarbamate substituents (3, $R^1 = R^2 = EtO$, X = Me_2NCS_2, Et_2NCS_2, n = 1) or the ethyl xanthate group (3, $R^1 = R^2 = EtO$, X = $EtOCS_2$, n = 1) were obtained by direct reaction of the corresponding sodium dithiocarbamate or potassium ethyl xanthate with the tetrachloride (5).

Phosphoramides (3, $R^1 = R^2 = Me_2N$, X = NHCOR, n = 1) were obtained by a sequence of reactions involving the initial preparation of an imine derived from a carboxamide, i.e. $RCON=CHCCl_3$,[6] followed by the addition of *N,N,N',N'*-tetramethylphosphoric triamide. The product derived from chloroacetamide, X = $NHCOCH_2Cl$, was a useful intermediate in which the chlorine atom could be replaced by nucleophilic reagents, e.g triazole, dithiocarbamate, xanthate, and other thio derivatives.

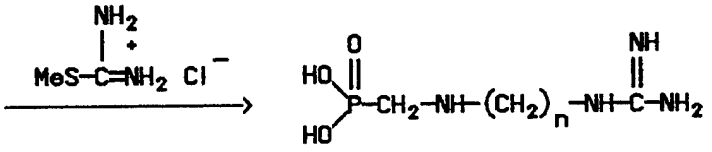
Among the diethyl phosphoramidates (3, $R^1 = R^2 = EtO$), the most active were the dithiocarbamate and ethyl xanthate derivatives which, at 500 ppm, gave 99 - 100% control *in vitro* of *Fusarium*, *Helminthosporium*, and *Ophiobolus* species. Under similar conditions, the triazole, hydroxyethylthio, imidazole, and *N*-formylpiperazinyl derivatives, gave *ca.* 90, 90, 50 and 50% control, respectively. Other compounds of this class were less active. An imidazole derivative in which both an ethoxy and a dimethylamino group were attached to phosphorus (3, $R^1 = EtO$, $R^2 = Me_2N$, X = imidazolyl, n = 1), showed higher activity than the corresponding diethyl analogue *in vitro*.

Tested as seed dressings at 400 ppm against *Drechslera teres* the most active compounds (3, $R^1 = R^2 = EtO$, X = Me_2NCS_2, Et_2NCS_2, $EtOCS_2$, imidazolyl, NHCOMe, $NHCOCCl_3$, 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxamido, n = 1; 3, $R^1 = R^2 = Me_2N$, X = NHCHO, NHCOMe, $NHCOCH_2Cl$, n = 1), gave 50 - 75% of the control shown by guazatine.

Our second series of investigations was based on the known activity of guanidines as fungicides[3] and the biological importance of phosphonic acids.[7] A series of compounds was therefore prepared (Scheme 1) by condensation of chloromethylphosphonic acid with α,ω-diamines, and conversion of the terminal amino group to guanidino.



(7)

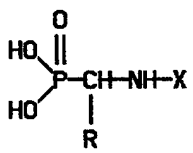


(8)

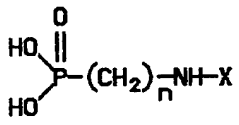
SCHEME 1

Fungicidal activity of the guanidines varied with chain length, and reached a maximum for the decamethylene derivative (8, n = 10), which at 500 ppm gave 100% control *in vitro* of *Piricularia oryzae*, *Botrytis cinerea*, *Septoria nodorum*, and *Drechslera sativa*, and > 50% control of *Rhizoctonia solani* and *Fusarium avenaceum*.[8] Activity against *D. sativa* and *S. nodorum* was also demonstrated for the ω-amino compounds (7), albeit at a lower level.

The above results led us to investigate the fungicidal potential of simple α- and ω-aminoalkanephosphonic acids (9, 10) and the corresponding guanidino compounds (11, 12), all of which were prepared by known methods.[7] Biological testing was directed mainly towards possible use of these compounds as seed-dressings for the replacement of organomercurials in the control of *Drechslera* spp. and other pathogens of cereal crops[9] and it was noted that the amino



[9, X = H; 11, X = C(:NH)NH_2]



[10, X = H; 12, X = C(:NH)NH_2]

compounds were generally more active than the guanidino analogues. The α-amino series (9, R = Me, Et, Pr^n, Bu^n, n-C_7H_{15}) all gave 75 - 100% control of *D. sativa* or *D. teres* when tested *in vitro* at 500 ppm. In field trials, the use of α-aminopropanephosphonic acid (9, R = Et) as

a seed dressing agent at 400 ppm gave 95 - 100% control of *D. teres*, *D. avenae*, *D. graminea*, and *Ustilago avenae*, and 70 - 80% control of *Septoria nodorum*, *Ustilago hordei*, and *Tilletia caries*. Laboratory tests, using seeds infected with *D. teres*, showed the α-amino compounds (9) to be more active then those of the the ω-amino series (10) and that optimum activity in both types of compound occurred for the C_3 structure. Activity was less in the branched-chain derivatives.

A number of peptide derivatives of α-aminopropanephosphonic acid were also prepared by a standard synthetic procedure[10] and it was shown that the *N*-(*L*-ala)- and *N*-(*L*-ala-*L*-ala)-peptides had similar activity to that of the parent aminophosphonic acid. Peptides containing a glycyl residue were slightly less active. Those in which a *D*-alanyl residue was attached directly to the nitrogen atom of the aminophosphonic acid residue showed little or no activity.

Further studies are necessary in order to determine mechanisms of action for the above types of compound and to provide more detailed information on structure-activity relationships which may lead to compounds of improved performance. The low mammalian toxicity and environmental acceptability of α-aminopropanephosphonic acid (ampropylfos)[11] indicate that compounds of this type provide a promising area for further investigations.

We are grateful to KenoGard AB and the University of North London for financial support and biological testing.

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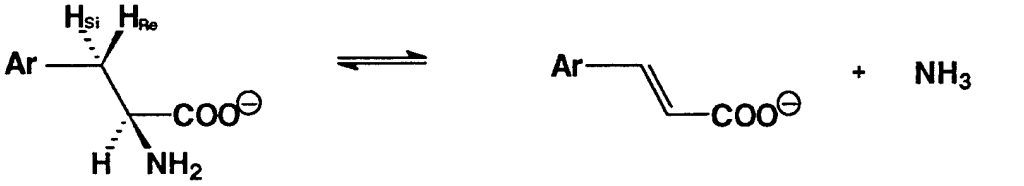
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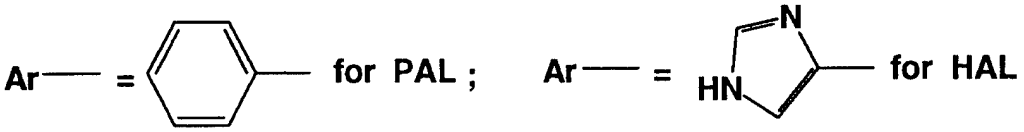
PHOSPHONIC ANALOGUES OF PHENYLALANINE AND HISTIDINE AS STRONG INHIBITORS OF PHENYLALANINE AND HISTIDINE AMMONIA-LYASES

JERZY ZON
Institute of Organic Chemistry, Biochemistry and Biotechnology; Technical University; 50 370 Wroc³aw, Poland

Abstract Syntheses of phosphonic analogues of phenylalanine (**5**) and histidine (**7**) as well as their biological activities as phenylalanine and histidine ammonia-lyases inhibitors have been discussed.

Both phenylalanine ammonia-lyase (PAL) (the common enzyme in plants) and histidine ammonia-lyase (HAL) (the enzyme occurs in bacteria) catalyze the anti-elimination of ammonia to give (E)-cinnamic acid and (E)-urocanoic acid, respectively.

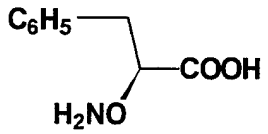




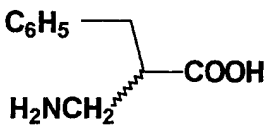
It was pointed out a similarity of both enzymes based on the common carbanion intermediates [1-2], the presence of dehydroalanine in the active sites [3-5] and amino acids homology [6, 7].

We would like to present the synthesis of 2-aminoindan-2-phosphonic acid (**5**) [8] and racemic 1-amino-2-imidazol-4'-ylethylphosphonic acid (**7**) [9], as well as to discuss their biological activities as PAL [8,10] or HAL [11] inhibitors.

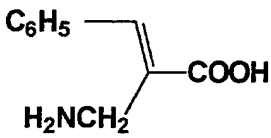
Inspired by the strong inhibition of PAL by (S)-2-aminooxy-3-phenylpropanoic acid (**1**) [12,13], we have synthesized (±)-2-aminomethyl-3-phenylpropanoic acid (**2**) and (E)-2-aminomethyl-3-phenylpropenoic acid (**3**) as potential PAL inhibitors [14].



1

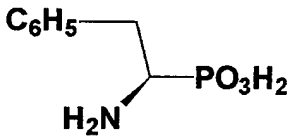


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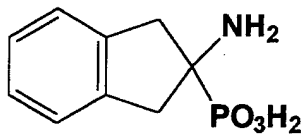


3

The analogue **3** is much better inhibitor than **2**, and inhibits PAL less strongly by two orders of magnitude than **1** [14]. We have assumed that some active conformation of aminooxy acid **1** better fits into PAL's active site than that of amino acid **3**. The compound **3** very weakly inhibits *in vivo* PAL activity although does not inhibit *in vitro* phenylalanine transamination activity as well as phenylalanine hydroxylase [14]. We have concluded that the analogue **3** is not delivered to the active site of PAL due to factors such as poor uptake and transport. Then, we have turned our attention to the phosphonic analogues of phenylalanine. Inhibitory activity of (R)-1-amino-2-phenylethylphoshonic acid (**4**) has already been known [15,16]. On the other hand, we considered the cyclic analogues of phenylalanine as a very interesting models to study, due to their fixed conformation. In this context we undertook the synthesis of 2-aminoindan-2-phosphonic acid (**5**) [8].

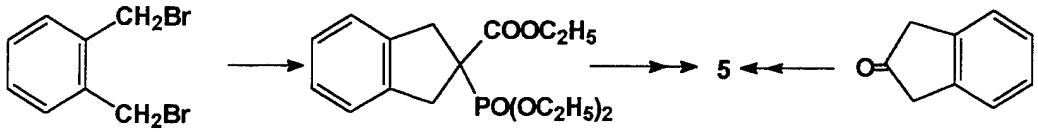


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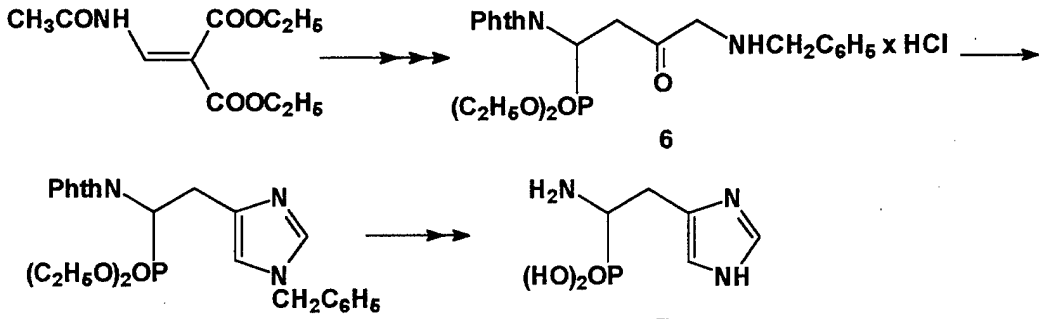
5

2-Aminoindan-2-phosphonic acid (**5**) was obtained by two independent synthetic routes from 1,2-bis(bromomethyl)benzene and triethyl phosphonoacetate or 2-indanon [8].

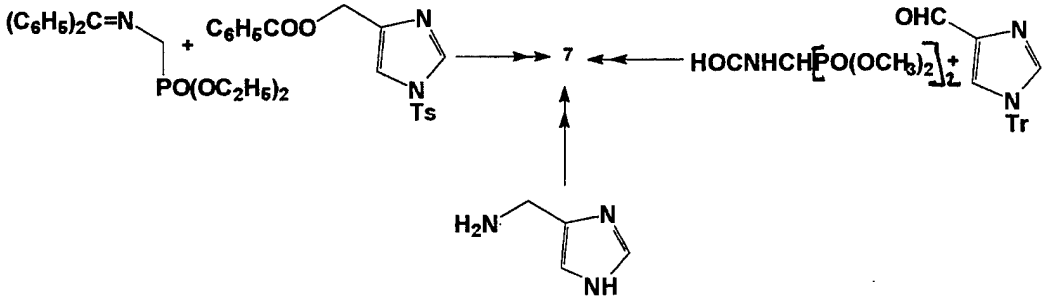


Synthesis and evaluation of a few compounds related to **5** provided evidence that both the amino group and the phosphonic group as well as the benzene moiety of the indan backbone are required for the effective inhibition of PAL [8]. 2-Aminoindan-2-carboxylic acid is poorer substrate for PAL than (±)-2-amino-3,4-dihydronaphthalene-2-carboxylic acid [10]. We assume that the fixed conformation of **5** [17] is between a flexible one for **1** and completely flat one for cinnamic acid. We think that this allows the better understanding what is the active conformation of (**1**).

The idea of similarity of histidine ammonia-lyase and phenylalanine ammonia-lyase has encouraged us to evaluate (±)-1-amino-2-imidazol-4'-ylethylphosphonic acid (**7**) as a HAL's inhibitor [11]. Merrett et al. [9] have reported synthesis of phosphonic analogue of histidine from diethyl acetamidomethylenemalonate. They introduced the imidazole ring using compound (**6**) as the appropiate precursor.

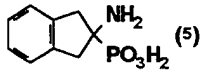


Then, other methods for the synthesis of (±)-1-amino-2-imidazol-4'-ylethyl-phosphonic acid using imidazole containing precursor have been worked out [18-20].



Phosphonic cyclic analogue of phenylalanine (**5**) is strong inhibitor of PAL [8] and phosphonic analogue of histidine (**7**) is strong inhibitor of HAL [11]. In contrary, racemic 3-phosphonoalanine, the phosphonic analogue of aspartic acid, is weak inhibitor (Ki/K_m = 0.2) of aspartate ammonia lyase [21]. Inhibitory activities of some selected compounds are presented in Table I.

TABLE I Inhibitory activities of phosphonic and some other analogues [8, 11, 13, 15 and 22].

PAL's inhibitors	K_i/K_m	HAL's inhibitors	K_i/K_m
(S)-$C_6H_5CH_2CH(ONH_2)COOH$ (1)	0.0003		
 (5)	0.002		
(R)-$C_6H_5CH_2CH(NH_2)PO_3H_2$ (4)	0.03		
(±)-$C_6H_5CH_2CH(NH_2)PO_3H_2$	0.06	(±)-$C_3H_3N_2CH_2CH(NH_2)PO_3H_2$ (7)	0.002
(±)-$C_6H_5CH_2CH(NHNH_2)COOH$	0.06	(±)-$C_3H_3N_2CH_2CH(NHNH_2)COOH$	0.02

It is worthy of mention that *in vivo* inhibition of PAL by the compound **5** is superior to that of either **1** and **4** [8]. We think that the mechanism of the strong PAL and HAL inhibition by the both phosphonic analogues involves ionic and hydrogen bond interaction between the phosphonic groups with the guanidine group of the enzyme arginine.

The strongest inhibition *in vivo* of phenylalanine ammonia-lyase by 2-amino-indan-2-phosphonic acid (**5**) among inhibitors, was used to some studies on different aspects of phenylpropanoid compounds biosynthesis in plants [23-30].

Futher study of a inhibitor with more or less fixed conformation as well as of an inhibitor containing an additional photoreactive group are in progress.

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HERBICIDALLY ACTIVE DERIVATIVES OF AMINOMETHYLENEBIS-PHOSPHONIC ACID - MODE OF ACTION AND STRUCTURE - ACTIVITY RELATIONSHIP

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Abstract: (N-pyridylamino)methylenebisphosphonates exhibit strong herbicidal activity which may be reversed by supplementation of the growth media with aromatic amino acids.They appeare to be the inhibitors of aromatic amino acids biosynthesis acting as inhibitors of DAHP synthase the first enzyme of shikimate pathway. Over 40 analogues of these acids were synthesized in order to determine the structure-activity relationship.

INTRODUCTION

The disclosure of glyphosate (N-phosphonomethylglycine), in 1971, instituted a milestone in a rational design of herbicides and pointed out an aromatic amino acids biosynthesis pathway as a particularly attractive target of such an approach.[1] This discovery initiated also the extensive research concerned with the design, synthesis and evaluation of physiological properties of hundreds, or perhaps thousands of glyphosate derivatives, homologues and analogues. Obviously, it is difficult to improve on a

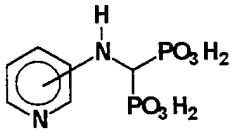
Using bacterial (*Escherichia coli*, *Micrococcus luteus*, *Sarcina lutea* and *Bacillus cereus*) and plant models (cell cultures of *Nicotiana plumbaginifolia*, and whole *Lepidium sativum* plants) we have found the reversal of the toxic action of the bisphosphonates by the combination of phenylalanine, tyrosine and tryptophan. Since nearly identical effects were observed in the case of N-phosphonomethylglycine (used as positive control) the shikimate pathway should be considered as a site of action of (N-pyridylamino)methylenebisphosphonic acids. Further studies indicated that these acids did not inhibit EPSP synthase, the target enzyme for glyphosate. They appeared, however, to be the strong inhibitors of DAHP (3-deoxy-*D*-arabinoheptulosonate-7-phosphate) synthase partially purified from *Nicotiana plumbaginifolia* suspension cultured cells. DAHP synthase is the first enzyme of the shikimate pathway. At milimolar concentrations Co^{2+}-dependent, cytosol localized enzyme form was inhibited by the tested compounds. This inhibition was nearly completely relieved by the increase of cobalt ion concentration. This suggests that the inhibition could be due to the chelating properties of these phosphonates. They also significantly reduced the activity of the other isoform of DAHP synthase - plastidal Mn^{+2}-stimulated. A kinetic analysis showed that compoud **2** was an uncompetitive with respect to phosphoenolpyruvate, but competitive with respect to other substrate - erythrose-4-phosphate. The studies also ruled out the possibility that an inhibition simply bases upon metal chelation.

In order to determine structural features of aminomethylenebisphosphonates responsible for their herbicidal action over 40 derivatives of aminomethylene-bisphosphonic acids were synthesized and screened for their herbicidal activity on *Lepidium sativum* and *Cucumis sativus*. The structural changes introduced were as follows: (1) modification or substitution of pyridyl moiety, (2) replacement of pyridyl fragment of herbicide by aromatic or another heteroaromatic one, (3) replacement of N-pyridyl by aliphatic or heteroaliphatic moiety, (4) replacement of aminomethylene-bisphosphonate fragment of the molecule by iminodi(methylphosphonate). Although some of the synthesized compouds (for example, compounds **3**, **4**, **5**, **6**, **7**, **8** and **9**) exerted strong herbicidal activity, being equipotent or even stronger than the parent compounds **1**, it is not possible to draw any meaningful relations on structure-activity relationship for them.

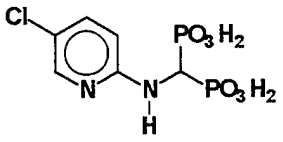
compound that is as simple as glyphosate and exhibits such a powerful activity. Indeed most of the analogues are less active than the herbicide itself. However, these efforts were not totally unsuccessful and resulted in discoveries of numerous highly active compounds. These include, at least, herbicidal phosphinothricin, introduced simultaneously in Germany and Japan,[2] N-pyridyl derivatives of aminomethylenebisphosphonic acid being developed in Japan,[3] as well as phosphonic acid analogues of morphactins first synthesized in our laboratories.[4] Among these compounds (N-pyridylamino)methylenebisphosphonic acids (compounds **1**) are of special interest since the structure of aminomethylenebisphosphonic acid, which posses two strongly acidic groups and positively charged amino group, closely resembles N-phosphonomethylglycine. Glyphosate has long been postulated to act as transition state analogue for the putative tetrahedral intermediate formed transiently during reaction catalyzed by EPSP (5-enoylpyruvylshikimate-3-phosphate) synthase, the sixth enzyme of shikimate pathway.[5] One may thus speculate that pyridyl fragment of compounds **1** resembles nearly flat cyclic part of this intermediate while aminomethylene-bisphosphonic moiety, similarly as glyphosate, mimics the tetrahedral fragment of the intermediate. In order to check this speculation we undertook the studies on the mode of herbicidal action of these compounds.

RESULTS AND DISCUSSION

(N-pyridylamino)methylenebisphosphonates strongly inhibited the growth of five plant species (*Fagopyrum esculentum* Munch., *Lepidium sativum* L., *Cucumis sativus* L., *Triticum aestivum* L. and *Zea mays* L.) being equipotent or even stronger than glyphosate. These effects were additionally supported by studies on the influence of aminomethylenebisphosphonates **1** on the growth characteristics of plant cell suspension cultures of *Nicotiana plumbaginifolia, Daucus carrota, Zea mays* and *Oryza sativa.*

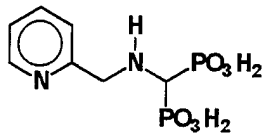


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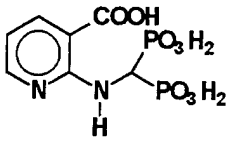


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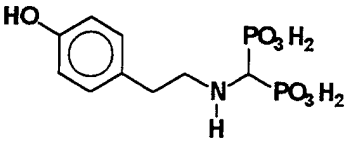
Powerful inhibition of the *Fagopyrum esculentum* anthocyanin production by all the compounds **1** indicate that aromatic acids biosynthesis pathway may be the site of action of these compounds.



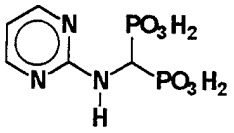
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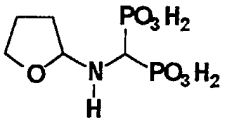
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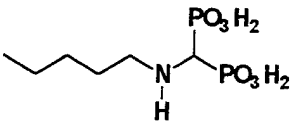
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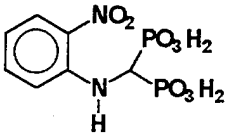
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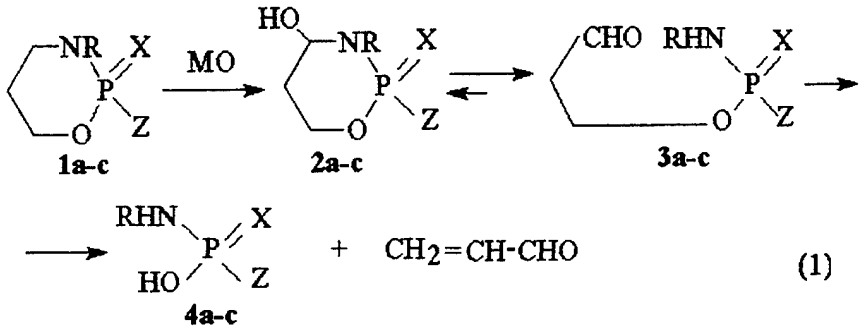
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SYNTHESIS, BIOLOGICAL ACTIVITY AND MECHANISM OF ACTION OF 1,3,2-OXAZAPHOSPHORINANE DERIVATIVES

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R.I. VOLKOVA, G.F. MAKHAYEVA, S.A. ROSLAVTSEVA,
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Abstract The title compounds were obtained by the reaction of the corresponding phosphorodichloridates with 3-aminopropanol-1 in the presence of an organic base or under phase transfer conditions, and by some other methods. They are highly active nematocides and sinergists to permethrin with low toxicity to mammals. Some peculiarities of mechanism of action of the compounds were established.

The searching for selective pesticides among the derivatives of 1,3,2-oxazaphosphorinane is founded on the new hypothesis, based on the well-studied metabolism of cancerolitic cyclophosphamide (**1a**) [1] (equation 1).



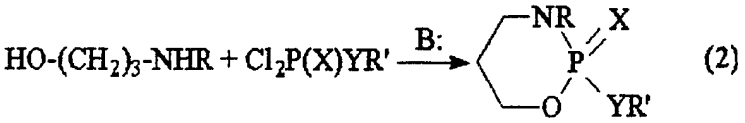
a: R = H, X = O, Z = $N(CH_2CH_2Cl)_2$; **b**: R = H, Alkyl, Ph, X = S, Z = YR';

c: R = H, Alkyl, Ph, X = O, Z = YR'; Y = O, S; R'= Ar, Alkyl.

We suggested, that thioderivatives **1b** with typical for insecticides leaving groups (Z= =YR') insted of the nitrogen mustard residue of **1a** would undergo analogous metabolic transformations. In this case oxydative desulfuration (activation) of **1b** to **1c**, involving the formation of cholinesterase inhibitors, should occur faster in arthropoda,

whereas hydroxylation to **2b,c** under the action of monooxygenases, leading eventually to the detoxication products **4b,c** is more typical for mammals. The differences in the rates ratios of these metabolic reactions in arthropoda and mammals could be a factor of selectivity.

The most general method of synthesis of the title compounds is presented by the equation (2):



(2)

where B: - Et_3N or aqueous NaOH (CH_2Cl_2, phase transfer conditions). Some of monothioderivatives were obtained by the reaction of tetramethylammonium salt of 2- oxy-2-thio-1,3,2-oxazaphosphorinane [2] with alkyl halides (only S-products were formed) and with alkyl chlorocarbonates (O- and S-isomers in the ratio 5:1 were obtained). Dithioderivatives (**1b**; Z = SR'), where R' is a substituted alkyl group, were synthesized by the reaction of 2-chloro-2-thio-1,3,2-oxazaphosphorinane with sodium mercaptides.

Most of the compounds **1b** have a low toxicity for mice (LD_{50} 1000-3500 mg/kg, orally) and possess a weak insecticidal activity - only the compound **1b** (R = H, Z = SPh; LC_{50} 0.002%) as aphicide against black been aphids is at the llevel of malathion (LC_{50} 0.002%). As acaricides the compounds are more active, but only **1b** (R = H, Z = 2,4,5-$Cl_3C_6H_2O$; LC_{50} 0.002%) and **1c** (R = H, Z = PrS; LC_{50} 0.006%) against spider mites are near the level of parathion-methyl (LC_{50} 0.001%). Many of the compounds **1b,c** are active nematocides at the level of ethaphos and geterophos: potato stalk nematodes - LC_{50} 0.00016-0.00083% (ethaphos, LC_{50} 0.00015%); rice aphelenchoides - LC_{50} 0.00027-0.00034% (ethaphos, LC_{50} 0.00021%); lucerne cystogenous nematodes (**1b**; R = i-Pr, Z = 3-$NO_2C_6H_4O$) - LC_{50} 0.00039% (geterophos, LC_{50} 0.00039%). The compounds, where Z = 3-$NO_2C_6H_4O$ (**1b**, R = H, LD_{50} >1000 mg/kg; **1b**, R = i-Pr, LD_{50} 625 mg/kg and **1c**, R = i-Pr, LD_{50} 260 mg/kg) are active against gall nematodes in soil, providing 88% reduction of gall formation at the concentration 0.096 g/kg of soil, that is at the level (84-99%) of considerably more toxic geterophos (LD_{50} 30 mg/kg).

Some peculiarities of the compounds **1b,c** biological action were also observed. In toxicological experiments on mice the compounds show a typical clinical picture of

poisoning by cholinesterase inhibitors. However, the oxones **1c** possess an extremely low, compared to acyclic analogs, ability to inhibit human acetyl cholinesterase (AChE) and american cockroach cholinesterase (ChE). Some of the compounds **1c** are active inhibitors of american cockroach carboxyesterase (CE). For the compounds **1c** (R = H) Z and rate constants of inhibition (k_2, $M^{-1}.min^{-1}$) for AChE, ChE and CE are given: 4-ClC_6H_4O, $6.7.10^1$, $1.2.10^1$, $1.1.10^4$; 3-$NO_2C_6H_4O$, $2.4.10^2$, no inhibition, $5.4.10^4$; 4-$NO_2C_6H_4O$, $3.7.10^3$, $1.4.10^3$, $2.2.10^4$ (paraoxon, $3.7.10^5$, $4.3.10^5$, -); $EtSCH_2CH_2S$, $7.3.10^1$, no inhibition, $6.3.10^2$ (isosistox, $6.4.10^3$, -, -). A low anticholinesterase activity of the compounds **1c** was explained by one of us on the basis of the molecular mechanics calculations [3]. It was shown to be caused by steric hindrances, indused by the cyclic part of molecule, to a nucleophilic reaction of inhibitors with serine hydroxyl group.

However, a low inhibitory activity of the oxone **1c** (R = H, Z = 3-$NO_2C_6H_4O$) does not explain its high toxicity (LD_{50} 55 mg/kg) compared to that of the corresponding thione **1b** (LD_{50} >1000 mg/kg). It means, that this oxone can transformate *in vivo* to a more active cholinesterase inhibitor. This bioactivation was confirmed by the interaction of this oxone with the mixture of AChE and mice liver monooxygenase (MO) in the absence and in the presence of coenzyme NADPH. The results are given in Fig. 1

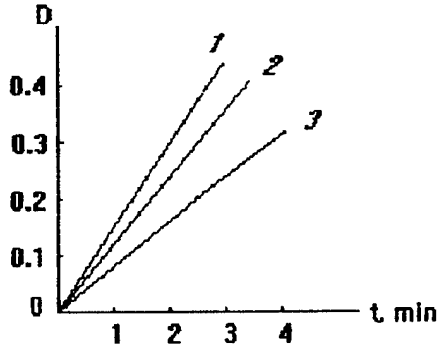


FIGURE 1. The Ellman kinetics of acetyl thiocholine iodide hydrolysis.

(the Ellman kinetics of acetyi thiocholine iodide hydrolysis, which is measured by an increase in optical density (*D*) over time (*t*)), where the line *1* presents an initial activity of AChE and MO mixture. The decreas of AChE activity in this mixture after 27 min incubation with the oxone (line *2*) is due to inhibition only by this compound because in the absence of NADPH MO is inactive. In the presence of NADPH the residual activity

is significantly lower (line *3*). It is a direct evidence of the formation of a more active inhibitor, which is very likely to be the compound **3c** (R = H, Z = 3-NO_2- C_6H_4O).

Since the compounds **3c** by analogy with the corresponding metabolite of cyclophosphamide **3a** can be unstable, we synthesized closely related in structure, but stable model compounds $H_2N(EtO)P(O)Z$ (**5**). They are actually considerably more active inhibitors of AChE, ChE and CE, than their cyclic analogs (Z and k_2 for AChE, ChE and CE are given): 4-ClC_6H_4O, $2.4.10^4$, $7.0.10^2$, $7.5.10^5$; 3-$NO_2C_6H_4O$, $4.4.10^5$, $1.1.10^5$, $1.3.10^7$.

Furthermore, the thione **1b** (R = H, Z = 3-$NO_2C_6H_4O$) does not desulfurate to the oxone **1c**, and suppresses desulfuration of insecticide dichlorone - $(EtO)_2P(S)SCH_2Cl_2$, that is the thiones **1b** inhibit MO. Hence, a low toxicity of thiones **1b** may be partially due to self-inhibition of desulfuration (activation), and a high toxicity of the oxones **1c** is due to metabolic convertion to more active AChE inhibitors.

Due to the ability of the compounds **1b** to inhibit MO, and their metabolites **1c** and **3c** - to inhibit CE - the both enzymes, detoxicating pyrethroids in insects, the thiones **1b** can be synergists to these preparations. In fact, the compounds **1b** in the mixture with permethrine (10:1) was shown to possess a high synergetic activity towards houseflies and german cockroaches with synergy coefficients (SC) being close to that of piperonyl butoxide (PB) conserning houseflies (**1b**, SC 1.2-2.4; PB - 2.1) and considerably higher conserning cockroaches (**1b**, SC 1.5-5.2; PB - 1.1).

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^{31}P NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY OF CELLS AND TISSUES

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Abstract Phosphorus-31 magnetic resonance spectroscopy is an excellent technique for biological studies due mainly to its non-invasive nature. We describe some illustrative applications on phospholipid metabolism and hormone effects of breast cancer cells, and on skin metabolism and pharmacodynamics.

Key Words: Phosphorus-31 NMR, breast cancer, skin, pharmacodynamics, cells

INTRODUCTION

Phosphorus (^{31}P) is the most prominent nucleus studied by nuclear magnetic resonance (NMR) spectroscopy both *in vivo* and *in vitro*. ^{31}P NMR spectroscopy has been established as an excellent non-invasive procedure for studying the metabolism of some biological compounds of fundamental functional and structural importance, as well as a precise method to measure intracellular pH and membrane permeability.

In this article, we summarize recent work on the application of ^{31}P NMR spectroscopy to the metabolism of different cells and tissues in our laboratory, as examples of the multiple applications of this powerful technique. We will start with the results of our investigations to evaluate the biochemical status and physiological processes in perfused intact breast cancer cells, continuing with our *in vitro* measurements on epidermis with ^{31}P NMR spectroscopy as a basis for developing a mechanistically relevant topical corticosteroid bioequivalence technique.

^{31}P NMR SPECTROSCOPY OF BREAST CANCER CELL LINES

NMR studies of cellular metabolism can be performed with cellular extracts, cell suspensions, and perfused intact cells. Cellular perfusion is much preferred for NMR studies since metabolic processes can be continuously monitored (not possible with extracts), and cells can be studied for prolonged periods during perfusion under physiological conditions (very limited experiments are warranted with cell suspensions). There are now enough methods that an appropriate one can be adjusted to almost all cell types and experimental conditions. Comparisons and utilities of these methods have been recently reviewed[1].

During perfusion, substrates and nutrients are continuously furnished, and waste products removed, while stable pH levels and temperature of 37 ^{o}C are maintained. Perfusion is done with the cell's growth medium, at an appropriate flow rate, using a peristaltic pump. In ^{31}P NMR experiments, a phosphate-free medium is used in order not to interfere with intracellular pH determination, since its signal appears very close to the intracellular Pi resonance. A high density of cells ($2\text{-}3\times10^{8}$) must be present within the receiving coil since phosphorus NMR spectroscopy (or, generally, magnetic resonance) has low sensitivity. Thus it is difficult to perform a series of NMR studies of normal cell lines, e.g. with normal breast cells, since they grow very slowly in culture. In all experiments that are expected to last several days sterility must be maintained, and this should be considered in selecting the appropriate perfusion method. This can be accomplished by either using large capacity filters, or closed systems.

Two perfusion methods has been developed in our laboratory. The first method, which was introduced by Foxall and Cohen[2], is based on the properties of low-temperature gelling agarose. Cells are embedded in agarose threads prepared by extrusion of a cell suspension in a liquid gel through a cooled capillary tube. Since the cells are inside the matrix, the porosity of the matrix and the ease of nutrients diffusion are of critical importance. Penetration of molecules (smaller than albumin) has been determined. Attachment to the gel is not essential, so that both anchorage-dependent and -independent cells can be studied. However, due to the limited growth of anchorage-dependent cells in agarose threads, this method is not optimal for studies of cellular proliferation. The second method developed in our laboratory, based on a basement membrane (Matrigel), overcomes this obstacle.[3] Cancer cells grow in the Matrigel, and are morphologically identical to their *in vivo* counterparts. Most of our results have been obtained with agarose threads, although perfusion with cells embedded in Matrigel will establish a model tumor, most suitable for metabolic and pharmacological studies.

Initial experiments were performed to make peak assignments of the ^{31}P spectra. Cell extracts were used since better spectral resolution is obtained over intact cell threads allowing easier identification. Comparisons between normal and neoplastic breast cancer cells, and among different drug resistant breast cancer cell lines, have been done using ^{31}P NMR spectroscopy, with both extracts and agarose thread cell perfusion. These studies help delineate the differences in control of metabolic pathways between cells types.

Phospholipid metabolism has been extensively studied in our laboratory by ^{31}P NMR of perfused human breast cancer cell lines. Notable are the effects of substrates and inhibitors on specific enzymatic processes, such as ethanolamine kinase, which in the presence of extracellular ethanolamine resulted in the formation of PE (FIGURE 1). The effect of hemicholinium-3 in perfusate resulted in the reduction of the concentration of phosphocholine (PC). These studies showed that the second step in the process of phospholipid biosynthesis is rate limiting.

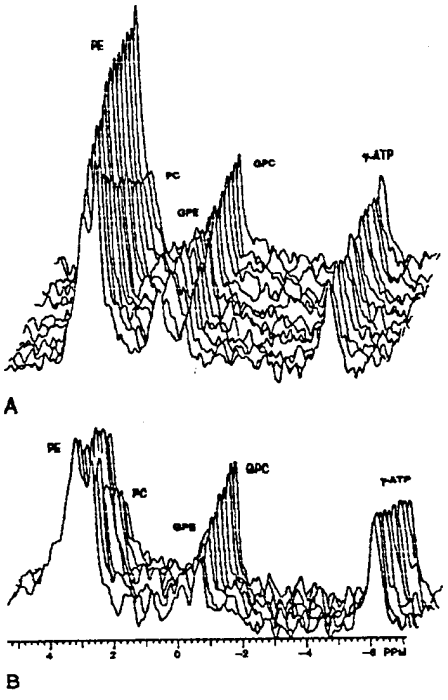


FIGURE 1 A. Effect of ethanolamine (2 mM) on the ^{31}P spectra of perfused breast cancer line (MDA-231) at 37 ^{o}C. B. Effect of hemicholinium-3, a specific inhibitor of choline kinase. Abbreviations are: phosphoethanolamine (PE), phosphocholine (PC), glycerophosphoethanolamine (GPE), and glycerophosphocoline (GPC).

Our efforts have also been directed to determine the effects of drugs and hormones on breast cancer cells. These results indicate that ^{31}P NMR can be used to measure the efficacy of an anti-neoplastic agent. A series of human breast cancer cells that vary in their estrogen and antiestrogen responsiveness was used to investigate their hormone growth dependence and the effects of tamoxifen. We observed no metabolic changes clearly associated with the metastatic phenotype. On the other hand, estrogen treatment produces no consistently significant changes in any of the cell lines, while a estrogen independent and estrogen responsive cell line responded to tamoxifen treatment by significantly increasing all spectral resonances (FIGURE 2).[4] This may reflect a tamoxifen-induced change to a more differentiated or apoptotic phenotype, or an attempt by the cells to reverse the inhibitory effects of the drug.

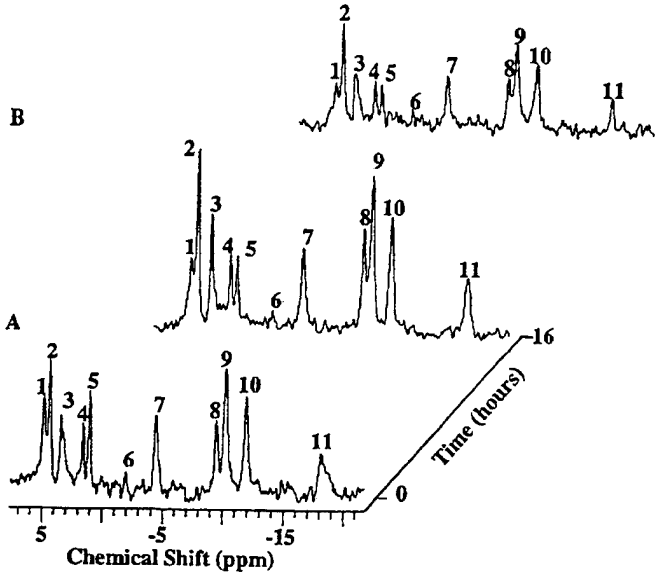


FIGURE 2. ^{31}P spectra of MIII breast cancer cells. **A.** baseline spectrum, and after 16 hr perfusion the cells were perfused for two hours with Tamoxifen (0.5 μM). **B.** Difference spectrum.

^{31}P NMR SPECTROSCOPY OF SKIN

We have recently measured the pharmacodynamic effects of dexamethasone on viable epidermis by following intracellular phosphate metabolism using ^{31}P NMR spectroscopy.[5] Changes to the concentrations of phosphate-containing metabolites in response to exposure to dexamethasone were an indication of the drug effects on the skin. In addition to demonstrating the applicability of determining pharmacodynamic relationships in epidermis for the modeling of drug effects in the skin during their absorption, this work can serve as a basis for developing a mechanistically relevant topical corticosteroid bioequivalence technique.

Strips of viable, enzymatically separated miniature swine epidermis were cut and placed into a 10 mm NMR tube and perfused with phosphate-free balanced salt solution during the experiment. The effect of the drug, dexamethasone, was measured on the epidermis by measuring changes in the concentrations of phosphate metabolites by NMR spectroscopy while exposing it to different drug concentrations. The concentrations of these metabolites remain constant in untreated epidermis for 18 or more hours of perfusion. The metabolites acting as sources of biochemical energy (NTPs and phosphocreatine (PCr)) showed consistent decreases in peak heights during drug perfusion with a return to baseline peak heights after 3 to 5 hr of washout. The decrease in PCr peak intensity was the change best correlated with drug dose. A log-linear dose-response relationship was observed (FIGURE 3).

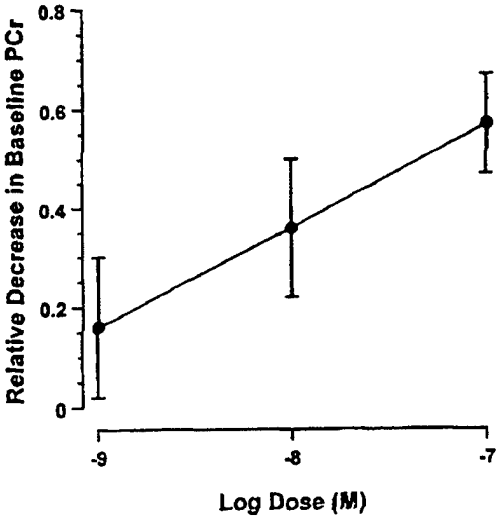


FIGURE 3. Log dose-response relationship for dexamethasone effect on reduction of epidermal phosphocreatine (PCr) levels

The data obtained from the NMR dose-response experiments was used to estimate parameters for an indirect model of pharmacodynamic effect. The model is based on the assumption that dexamethasone acts to reduce the production of PCr in the skin as described by the equation:

$$\frac{dPCr}{dt} = k_{in}\left(1 - \frac{C_{Epidermis}}{IC_{50} + C_{Epidermis}}\right) - k_{out}\ C_{PCr}$$

In this model, a basal rate of production of a PCr is expressed by the rate constant , k*in*, and a basal rate of elimination of PCr is expressed by the rate constant, k*out*. The drug effect is dependent on its concentration in the skin and the IC50. The IC50 is defined as the concentration of drug required to inhibit the production of PCr by 50%. The parameters, k*in*, k*out*, and IC50, were estimated by a simultaneous fit of the model to tissue concentrations of PCr, determined by the NMR spectroscopy dose-response experiments.

Dexamethasone exerts a reproducible and reversible effect upon phosphate metabolites within the epidermis. A dose-response relationship between dexamethasone and PCr was significant and reproducible. The correlation of dose of dexamethasone to PCr levels in epidermis could function as a surrogate pharmacodynamic endpoint for anti-inflammatory or antiproliferative action. The observation of an epidermal pharmacodynamic response by ^{31}P NMR spectroscopy and its incorporation into a pharmacodynamic model is an initial attempt at cellular level cutaneous pharmacodynamic modeling. Measurement of the dose-response relationship *in vitro* or *in vivo* through NMR techniques could function as a mechanistically relevant measure of topical corticosteroid bioequivalency.

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P-31 NMR STUDY OF POLYPHOSPHATES IN YEAST CELLS

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Abstract It was found that the chain length of polyphosphates (poly P), which are presented in various cell compartments, depends strongly on the growth stage and cultivation conditions of yeast cells. It was newly revealed, that only the chain length of poly P increased, while the amount of poly P remained constant during the poly P biosynthesis in cells.

Key Words: P-31 NMR study on polyphosphates, yeasts.

INTRODUCTION

Numerous studies on the structure and properties of polyphosphatases and polyphosphatkinases, in fact, contain no information about depolymerases, that cleave poly P to more short groups, which, in turns, are substrates to polyphosphate-specific enzymes [1]. As possible criteria of the enzyme activity, quantitative and qualitative levels of poly P in a cell may be estimated by P-31 NMR-spectroscopy.

In this work, we studied some specific features of the poly P accumulation and assumed that the chain length of poly P was dependent on the growth stage of culture.

MATERIALS & METHODS

P-31 NMR-spectra were recorded on a 'Bruker' (AM-400) instrument, D_20 was added for lock-signal.

To isolate fractions of poly P, Saccharomyces cerevisiae (BKM Y-1173) cells were treated as described in [2]; five poly P fractions were obtained. The cell culture were grown in phosphate-free and phosphate-containing media.

Samples were collected on the 4, 11, 13, and 15 hours of the culture growth.

The chain length (n) was estimated for each fraction over the culture growth. Poly P chain length was determined by the ratio of intensities of signals attributed to the central, preterminal, and terminal residues in the poly P molecule.

RESULTS & DISCUSSION

We varied cultivation conditions that manifested themselves in changing amount and chain length of each poly P fraction (Fig. 1-3). Fig. 1 shows that, after replacement of the yeast cells from a complete medium (point A) on a phosphate-free medium, the cells continued to grow and their biomass increased 4-fold over 7 h (point B); while, poly P was, in fact, completely consumed. Within 7 h of starvation, only 5% of all poly P were found in cells. After further replacement of the yeast culture to a complete phosphate-containing medium, the rapid accumulation of poly P (phenomenon of 'overcompensation') was observed, and the total poly P content increased more than two-times after 2 h (point C). Table 1 shows that, the poly P fractions 3 and 4 are maximally accumulated and content rose 4.5 and 8.5-fold, respectively, as compared to that at the point A.

Experimental data suggests that, under various cultivation conditions, the different poly P fractions are not uniformly consumed, or accumulated due various compartmentalization within the cell; and therefore, each poly P fraction has its own pathway of biosynthesis (Table 1).

In the case of phosphate starvation (point A), a mostly significant decrease in the poly P chain length was observed for the poly P fractions 3 and 4, unlike the poly P fraction 2, for which a sharp increase in the chain length was observed (Fig. 3). Note,

TABLE 1.
Quantitative changes in polyP fractions during different cultivation conditions.
The content of polyP fraction in the culture (point A) is taken as 100 %.

poly P fractions	Cultivation conditions			
	Complete medium (+P), 4 hours	Starvation (-P), 7 hours	Complete medium (+P), 2 hours	Complete medium (+P), 4 hours
	A	B	C	D
$HClO_4$, 0°C	100	2.4	138.6	121.1
$NaClO_4$, 0°C	100	5.3	206.6	143.0
NaOH, pH 8-9, 0°C	100	1.18	465.5	464.1
NaOH, pH 12, 0°C	100	9.1	82.2	97.4
$HClO_4$, 90°C	100	48.8	851.8	1235
Σ poly P	100	4.8	223.3	211.1

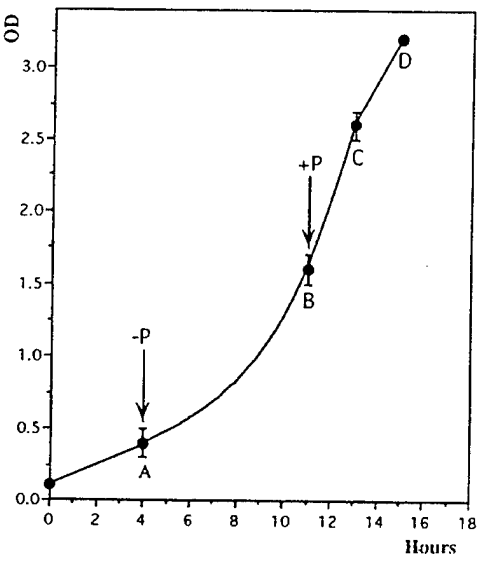


FIGURE 1 Biomass growth.

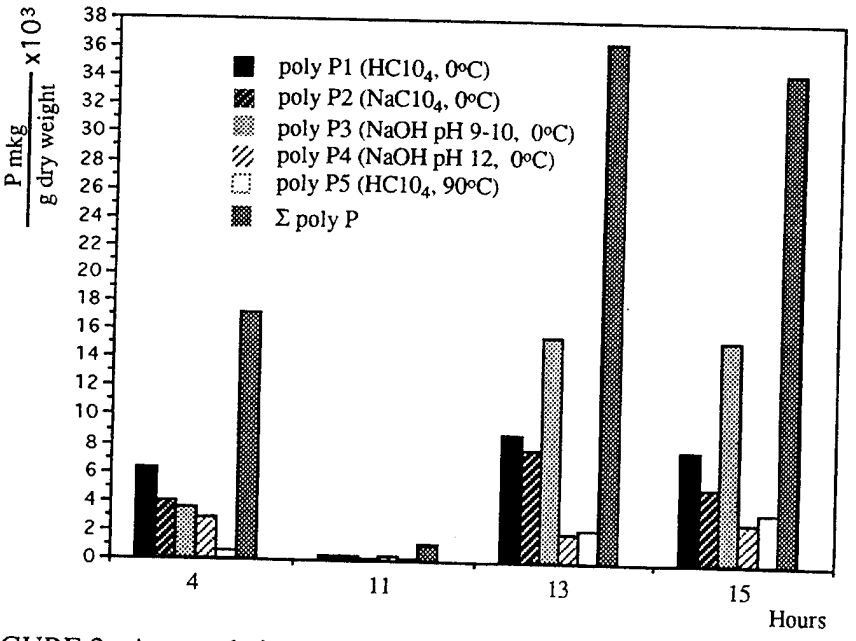


FIGURE 2 Accumulation of poly P fractions during culture growth.

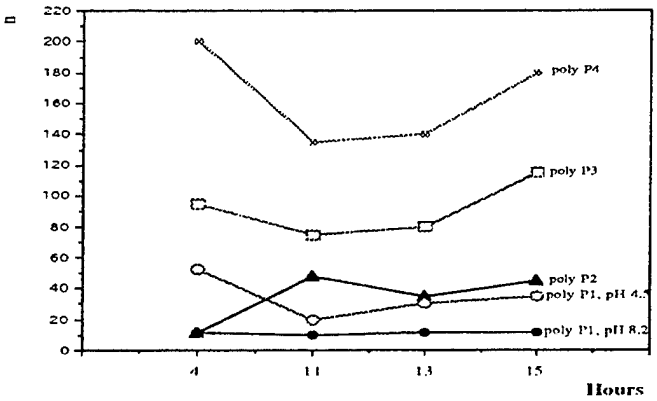


FIGURE 3 Changes in the chain length during cell cultivation.

within 2 h of the culture growth in the phosphate-containing medium, the chain length remained constant; whereas, their content sharply increased. Within 7 h of the cultivation (point B), the chain length began to grow, except the poly P fraction 2, whose chain length rose only within 4 h of the culture growth (point C).

Thus, the 'overcompensation' phenomenon involves two stages; the first one is followed by significantly increasing of short-length poly P amount; while, at the second stage the amount of long-chain poly P increased. The data obtained are considered with respect to the action of enzymes responsible for synthesis and hydrolysis of poly P. Likely, within the first hours of overcompensation, the accumulation (or activity) of polyphosphate-synthesizing enzymes and the consumption of poly P proceed simultaneously, yielding the short-length poly P. Then, after the culture growth in a phosphate-containing medium, when the enzyme biosynthesis sharply lowered, the poly P chain length increased, without considerable accumulation of poly P. To confirm this assumption, further experiments must be performed, because the synthesis of polyphosphatases is known to be not induced by phosphate starvation of some fungi [3].

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Making the Most of Inventive Discoveries in the Phosphorus Chemistry Field: Implications of a Probability Model of Invention

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Abstract A probability model of invention is discussed. The model is used to show how to identify the scope of invention, and support claims commensurate with this scope.

INTRODUCTION

To make the most of an inventive discovery, an inventor needs to be able to recognize the full scope of an invention, and know how to support claims commensurate with this scope. This paper presents a probability model of invention which can guide an inventor on these issues.

THE MODEL

We start with the premise that an invention contains novel information. By applying this premise to some simple probability notions, we are led to two conclusions that will be developed in the course of the paper: (i) an invention is patentable (nonobvious) if the novel information suggests further improvements; and (ii) the scope of the invention includes the invention and its suggested improvements.

To illustrate the probability model with an example from the field of phosphonate compounds, consider an invention for a competitive NMDA (N-methyl-D-aspartate) receptor antagonist compound[1]. One of the first NMDA antagonist compounds discovered was D-α-AA (D-α-aminoadipic acid), an analog of L-aspartate acid that contains an additional two methylene groups in its α-carbon side chain. The information contained in this invention is that "increasing the size of the α-carbon side chain by two methylene groups converts the NMDA agonist L-aspartate to an NMDA competitive antagonist."

How can this information be used? Before the inventive discovery, the logical

search space for finding an NMDA receptor antagonist is the space containing all possible L-aspartate analogs (excluding known agonists, such as L-glutamate and NMDA). Once the D-α-AA discovery is made, however, the search for new antagonists is logically confined to those L-aspartate analogs having side chains with additional methylene groups in the side chain (FIGURE 1). The constrained search leads to the identification of two additional NMDA antagonists, D-α-AP (D-α-aminopimelic acid) and D-α-AS (D-α-aminosuberic acid) containing 3 and 4 additional methylene groups, respectively, in the side chain.

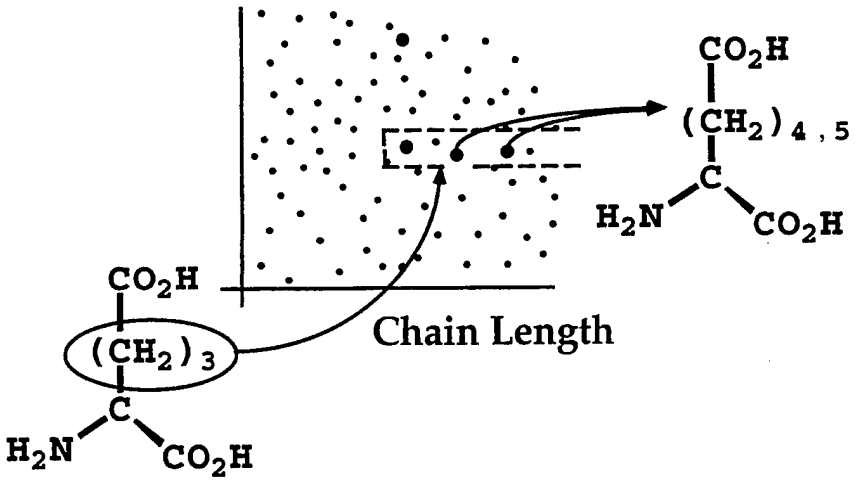


FIGURE 1 What D-α-AA suggests

The D-α-AA discovery has converted a relatively low-probability event-- identifying D-α-AP or D-α-AS as an NMDA antagonist-- to a high probability event. We can say that the parent discovery has "suggested" the improvements by confining the search for improvements to a narrow region of the total search space-- namely the space of L-aspartate analogs with additional methylene groups in the α-carbon side chain. The ability to suggest further improvements not previously suggested provides a simple test for patentability, i.e., nonobviousness.

Note that under this test, the improvements D-α-AP and D-α-AS would not be independently patentable, because they don't suggest further modifications not already suggested by D-α-AA.

The scope of the D-α-AA invention would encompass all improvements

suggested by the compound. It is therefore useful to ask whether D-α-AA suggests other analogs, for example, AP-5 (D-2-amino-5-phosphonopentanoic acid), a second-generation NMDA antagonist that differs from D-α-AA in the substitution of a δ phosphono group for a δ carboxy group (FIGURE 2). Although D-α-AA does suggest confining the search space to analogs with extended α-carbon chains, there is nothing about the D-α-AA discovery to specifically guide the search among L-aspartate analogs to the chain-terminal acid group, or to a phosphono group in particular. For this reason, the discovery of D-α-AA as an NMDA antagonist hasn't significantly increased the probability of finding the δ carbon phosphono analog over any other analog containing three-methylene side chains. Thus, D-α-AA cannot be said to suggest AP-5, and AP-5 would not be within the scope of the D-α-AA invention.

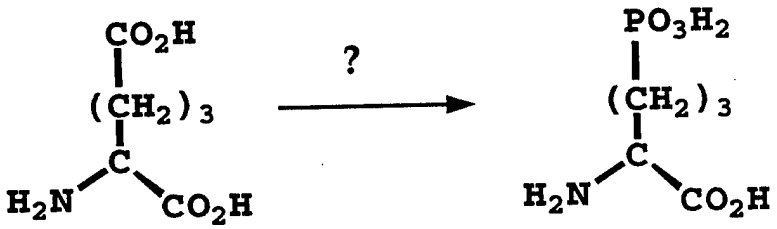


FIGURE 2 First-to-second generation NMDA antagonists

In summary, the scope of invention will include the invention itself and the improvements suggested by the invention, i.e., improvements for which constraints imposed by the invention convert a low-probability discovery event to a high-probability one. Now, to obtain claims whose scope is commensurate with the scope of the invention, the inventor must further establish a reasonable basis for predicting that the suggested improvements are enabled, that is, can be made and used.

To illustrate the latter point, the cyclic phosphono NMDA antagonist CGS 19755 (FIGURE 3) would logically suggest any R-group substitution that preserves the basic features of the invention of a piperidine ring with an "α" carboxy group and a phosphono R-group attached to the ring. The range of these substitutions would represent the scope of the invention, i.e., improvements whose discovery is significantly enhanced by the parent discovery.

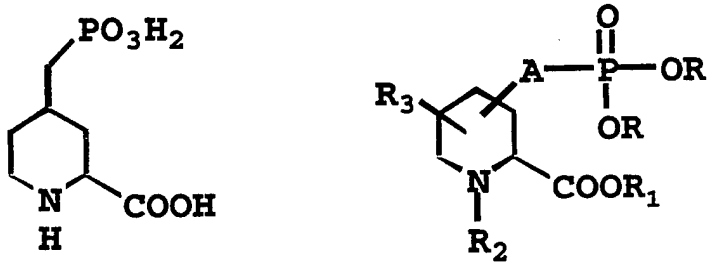


FIGURE 3 Scope of an invention

To support claims of this scope, the inventor must show, by selected examples, that various combinations of R-groups within the scope of the invention can be synthesized and retain NMDA antagonist activity[2].

OTHER IMPLICATIONS OF THE MODEL

The invention model discussed above establishes a link between nonobviousness and claim scope, which may be useful in examining various stretegies employed in medicinal chemistry research. SAR and pharmacophore modeling studies are designed to yield information that can be used to predict the structure of novel, high-activity compounds. If the modeling information is highly predictive, the information will lead to the discovery of such compounds with high probability. In this case, the information is inventive, and the scope of the invention includes the suggested high-activity compounds. By the same token, a weakly predictive model will not significantly enhance the probability of finding high-activity compounds, and the modeling information will be of limited patent value.

We can contrast SAR or pharmacophore modeling with small-molecule combinatorial library screening, which has the inherent capability of generating highly predictive information, because of the large number of data points considered. In fact, this approach, perhaps for the first time, may allow inventors to claim novel compounds in terms of search constraint information, rather than structural features.

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THE FIRST NOOTROPS AMONG NON-ANTICHOLINESTERASE ORGANOPHOSPHORUS COMPOUNDS. STUDY OF STRUCTURE-NEUROTROPIC ACTIVITY RELATIONSHIPS OF NITROGEN-CONTAINING PHOSPHORYLACETIC ACID DERIVATIVES.

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ABSTRACT. New series of nitrogen-containing phosphorylacetic acid derivatives (I-V) were synthesized. The antidepressant,neuroleptic,sedative,anxiolytic,antialcoholic and nootropic effects of new compounds(I-V) were studied. Efficiency of neurotropic action depends on the presence both phosphoryl and acyl fragments of molecule. A novel preparation(I-B) has been discovered as having high potential of nootropic activity.The receptor binding studies and investigation of nootropic and antidepressant actions mechanism of hydrazids(I) were conducted.

INTRODUCTION.

A new series of active neurotropic and non-anticholinesterase compounds studied by us belong to phosphorylacetic acid derivatives. The first representative of these series is diphenylphosphinylacetic acid hydrazid, named PHOSENAZID [1]. Initially PHOSENAZID was proposed for medical application as a "day-time" tranquillizer with marked vegetotropic activity and antiepileptic action. When examined more closely it displayed a specific antialcoholic action and properties of nootrope and adaptogene. That makes possible to apply PHOSENAZID for correcting the disturbances of mental function resulting from hypoxia,intoxication,acute and chronic alcoholism,and for reducing the delay in children's mental development [2].

SYNTHESIS.

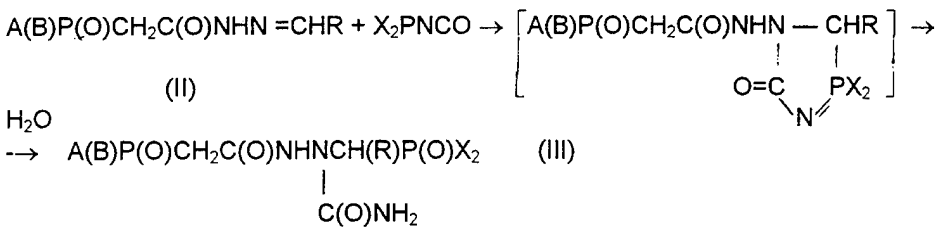
To screen the neurotropic activity and to develop general strategy for phosphorus-containing drug design we have synthesized numerous phosphorylacetic acid and aldehyde derivatives(I-V) combined by common formulas $ABP(O)CH_2C(=X)Y$.

	I	II	III	IV	V
X	O	O	O	O	NN^+HR_2
Y	NHNHR	NHN=CHR	NHN(R)C(O)R'	$O^-[N^+H_3R]$	H

Unsubstituted phosphorylacetic acid hydrazids formed the main part of the compounds(I). They were obtained by an interaction of phosphorylacetic acid esters and hydrazine [3]. In hydrazid group the substituent R was introduced via the reaction between unsubstituted hydrazids(I) and chloral or phosphonchloral [4].

Hydrazons(II) were easily formed by interaction of phosphorylated hydrazids (I) and aldehydes [5].

To obtain the compounds(III) we used both well-known acylation of hydrazids(I) and original reaction of [2+3]-cycloaddition with participation of isocyanatophosphine [6].



The salts(IV) were obtained on the basis of mono- or dibasic phosphorylacetic acids prepared by alkaline or acid hydrolysis of their esters. In cation moiety these salts contained ethyl esters of neuroactive amino acids such as glycine, alanine, etc. Phosphorylethylidene hydrazins' salts(V) were produced by the reaction of phosphorylacetic acid aldehydes and hydrazine salt [7].

TOXICITY AND NEUROTROPIC EFFECTS.

The acute toxicity data showed that in studied series(I-V) effect manifestation depended on electron influence of the substituents at both phosphorus and acetic acid fragment. The highest toxicity was observed in unsubstituted hydrazids(I). In these series the values of lethal doses (DL_{50}) increased as the number of alkoxylic groups at phosphorus grew.

TABLE 1. Acute toxicity of hydrazids(I).

DL_{50} mg/Kg	A=B= 4-ClPh	A=B= Ph	A=B= 4-FPh	A=Me_2NPh B=OC_2H_4Cl	A=B= OC_2H_4Cl
	300±25.7	315±24.8	810±41.6	960±35.0	2500±86.2

Any changes at hydrazid fragment of compounds (I-III) led to decrease of their toxicity. As it can be seen from table 2 the major part of hydrazons(II),some phosphorylated semicarbazides (III) and salts(IV) were practically non-toxic. A passage from the structure of phosphorylacetic acid derivatives(I-IV) to one of phosphorylethylidene hydrazins' salts(V) considerably increased toxicity of the latter.

TABLE 2. Acute toxicity interval of compounds(I-V)

	I	II	III	IV	V
DL_{50} mg/Kg	300÷2500	970÷5000 and more	850÷5000 and more	1500÷4500	400

The neuropharmacological action estimation of each series was made on models characterising a wide variety of their neurotropic effects. The antidepressant, neuroleptic, sedative, anxiolytic, antialcoholic and nootropic properties of new compounds (I-V) were investigated.

Analysis of the obtained data showed versatility and high neurotropic activity of compounds(I-III),which molecule contained a chain of $>P(O)CH_2C(O)NHN<$ atoms.

The great number of active substances was observed in the unsubstituted hydrazids(I). At that, the phosphinate (I-B) with arylic and β-chlorine ethoxylic group at phosphorus had optimum activity. The phosphine oxides with two arylic groups possessed also a wide spectrum of action. The neurotropic effects of hydrazons(II) were present too but in a less marked form, and some representatives of semicarbazides(III) were as active as hydrazids(I).

Thus, in studied series(I-III), the neurotropic action efficiency depended on the presence of both phosphoryl and hydrazid fragments in molecule. The lack of hydrazid moiety in the salts(IV) as well as passage to the structure of phosphorylethylidene hydrazins' salts (V) led to reduced activity In the series(IV) the structural change caused appearance of neuroleptic effect, when the hydrazid derivatives(I-III) didn't have them.

PHOSENAZID(I-A), hydrazid(I-B) and their analogues was shown to display nootropic effects [8]. In our experiments, hydrazid (I-B) was the most active compound among studied. Their antihypoxic and antiamnesic effects exceeded those of classical nootrope PYRACETAM. In distinction from PYRACETAM hydrazid(I-B) prevented hyperfermentemia and normalized metabolic changes in blood of animals under hypoxia.

STUDY OF MECHANISM.

Potent active hydrazids(I-A) and (I-B) possessed variety of effects specifying their nootropic action. In experiments in vivo and in vitro these compounds displayed membrane-stabilising activity and antioxidant property. The studied hydrazids(I) were found to increase the level of nuclear acids in cerebral cortex of rats.

One of the original characteristics of the investigated mechanism was choline-sensibilising action of hydrazids(I) discovered by the synaptic effects studies. This action and the ability of hydrazids(I) to ease up the process of signal transmission in cholinergic synapses evidenced their properties to restore the disturbed memory

and to improve training. It makes also possible to forecast positive results when treating Alzheimer's disease.

It's important that hydrazids(I-A) and (I-B) do not influence the state of synaptic acethylcholynesterase, which proves the absence of their anticholinesterase action.

There is another peculiar feature of the studied hydrazids, namely, a dose-dependent character of their effects manifestation. Thus,the membrane-stabilising action was getting greater when the preparation dose was diminished to 1/1000 DL_{50}. The mechanism of hydrazids (I-A) and (I-B) antidepressant activity changes also depending on the doses. At relatively large dose (1/10 DL_{50}) the antidepressant effect is apparently connected with the ability of the compounds to inhibit the monoaminooxidase ferment. However, at small doses (1/100-1/1000 DL_{50}), this activity was perhaps the consequence of their nootropic action. Moreover, the hydrazid(I-B) antidepressant effect is displayed in a wide range of doses and developed much earlier than with the tricyclic antidepressants.

The receptor binding studies showed that at doses of 1-100 micromolar, there was no marked affinity of hydrazids(I) at wide variety of receptors (sigma, adenosine, GABA, 5-HT, muscarinic, nicotinic, CCK, opiod, neurokinin NK1) or at Ca, K or Na channels. From the receptorscan, the main lead is an apparent action of the compounds(I) at the glycine site of the NMDA complex. Such an action could result in both neuroprotection and memory enhancement.

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CHEMICAL AND BIOCHEMICAL STUDIES ON THE CONVERSION OF ALKYLATING AGENTS TO PHOSPHOROTHIOLATES AND THEIR SUBSEQUENT SEQUESTRATION BY CHOLINESTERASES

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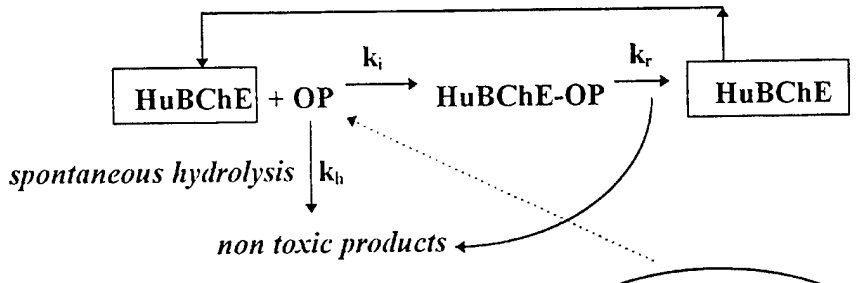
Abstract In endeavor to develop a universal, mild decontamination solution of vesicants and nerve agents, we have examined the possibility of transforming bis(β-chloroethyl)sulfide (sulfur mustard; HD) to an organophosphorus (OP) compound that will have a significant preference for inhibition of human butyrylcholinesterase (HuBChE) compared with acetylcholinesterase (AChE).

Key Words Human butyrylcholinesterase, sulfur mustard, nerve agents, inhibition, reactivation, hydrolysis.

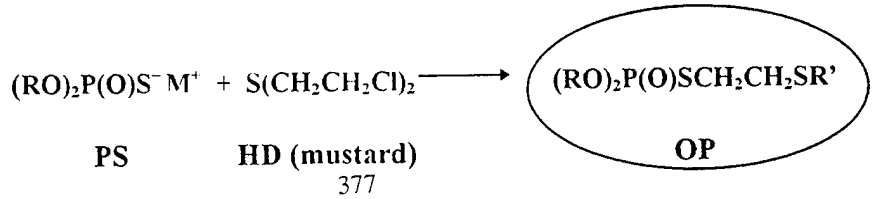
INTRODUCTION

A new strategy for the development of a universal bio-detoxification solution of alkylating agents (e.g., mustards) and anti-AChE poisons (e.g., nerve agents), is based on a mixture of, a) human butyrylcholinesterase (HuBChE), b) suitable reactivator of the phosphoylated enzyme , and c) phosphorothiolate salt that rapidly transforms mustards to non toxic anti-HuBChE compounds. Reactions **a** and **b** depict the chemical and biochemical principles that underlie this approach. The presence of HuBChE together with suitable reactivator permits the reuse of the reactivated enzyme to catalytically hydrolyze both mustards and nerve agents.

a.



b.



EXPERIMENTAL PROCEDURES

The dicyclohexylammonium salt of $(n\text{-PrO})_2P(O)SH$ (**I**) was prepared according to a general procedure described by Pelchowicz and Leader [1] and recrystalized from ethyl acetate (mp 158°C). δ ^{31}P 52.3 ppm ($CDCl_3$; quintet, $J_{P\text{-}O\text{-}CH}$ = 7.6 Hz).

Isolation of products of reaction of I with mustard in aqueous solution.
Bis(β-chloroethyl)sulfide (HD; 20 mg, 126 μmol) was delivered dropwise from a micropipetor to a stirred solution of **I** (100 mg, 260 μmol) in 40 ml water at ambient temperature. The suspended droplets gradually dissolved with the concomitant appearance of a light precipitate. The mixture was allowed to stand overnight with continuous stirring at room temperature. The precipitate was filtered off and the major components in solution extracted into ethyl acetate and chromatographed on silica gel column using chloroform as the eluent.

NMR spectra were determined with a GN 300WB NMR instrument (General Electric) at 300 (^1H) and 121.65 (^{31}P) MHz. ^1H and ^{31}P NMR chemical shifts were assigned to TMS and trimethyl phosphate, respectively. MS was performed on a VG 70SEQ hybrid mass spectrometer, using the 'in beam' probe introduction technique.

Inhibition and reactivation of cholinesterases. The bimolecular rate constants of the inhibition of HuBChE and fetal bovine serum acetylcholinesterase (FBS-AChE) was determined as described before [2]. Inhibitor's stock solutions (0.4 mM) were made in CH_3CN, and the actual concentration was determined by measuring the amount of thiol released in 0.1 N NaOH [3]. Enzyme solution was made in 50 mM phosphate buffer pH 8.0. Reactivation of OP-ChE conjugates was initiated by dilution of the inhibited enzyme into 0.1 M of 2-(hydroximinomethyl)-1-methylpyridinium methanesulfonate (P2S), or mono-isonitrosoacetone (MINA) in phosphate buffer, pH7.30-7.95, at 25°C.

RESULTS AND DISCUSSION

Elucidation of the structure of $(n\text{-PrO})_2P(O)S$-mustard adducts.
The reaction of **I** with mustard gave two major products (**II** and **III**) in high yield. Purification to homogeneity was achieved by column chromatography. The front peak was identified as the bis-phosphoryl mustard **II** followed by the mono-phosphoryl adduct **III**.

$$(CH_3CH_2CH_2O)_2P(O)SCH_2CH_2SCH_2CH_2SP(O)(OCH_2CH_2CH_3)_2$$
$$a \quad b \quad b \quad a$$
II

$$(CH_3CH_2CH_2O)_2P(O)SCH_2CH_2SCH_2CH_2OH$$
$$a' \quad b' \quad c \quad d$$
III

FIGURE 1. Structures of bis- (**II**) and mono-(**III**) phosphorylated mustard.

Thus, ^{31}P NMR chemical shifts of **II** (δ, 24.16 ppm) and of **III** (δ, 24.44 ppm), is consistent with alkylkation of the P-SH moiety of the starting material **I** (δ, 52.3 ppm).

The analysis of the ^{1}H NMR spectra revealed essentially similar chemical shifts and line multiplicity for both compounds with one major difference: the multiplicity of one set of the two methylene lines assigned to protons ***a*** and ***b*** in the symmetric molecule **II**, was reduced in **III**, as expected, to a first order triplets (Fig. 2, hydrogens ***c*** and ***d***).

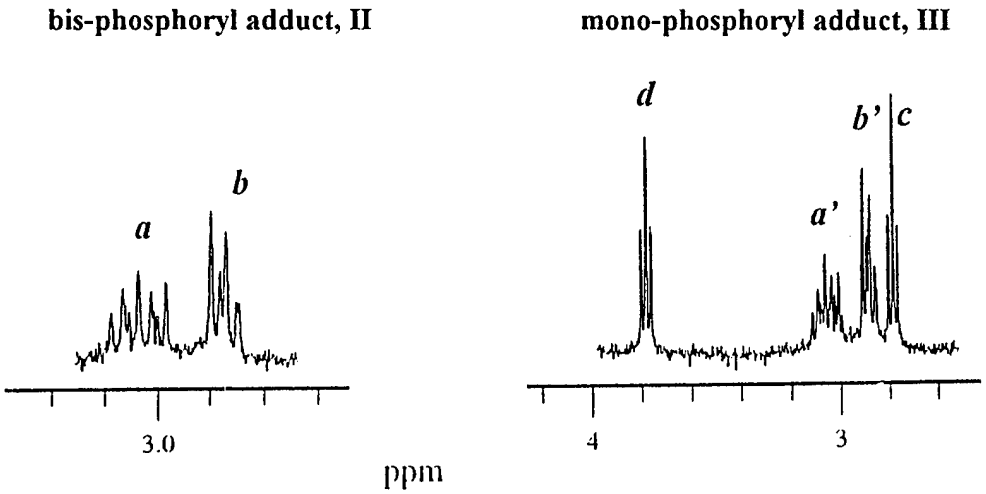


FIGURE 2. Excerpt from ^{1}H NMR spectra of **II** and **III**. Lines assignment is in accordance with Fig. 1.

MS (CI) showed strong quasi-molecular ions $[M+H]^+$ of m/z of 483 and 303 for **II**, and **III**, respectively. When either **II** or **III** were transferred to 2% NaOD, the ^{31}P NMR signal shifted upfieled (δ, -2.24 ppm), suggesting that the phosphorothiolates were hydrolyzed to the mono-acid $(CH_3CH_2CH_2O)_2P(O)OH$. All these observations are consistent with the proposed structures of **II** and **III**.

Inhibition and reactivation of HuBChE and FBS-AChE.

The bimolecular rate constants of the inhibition of HuBChE and FBS-AChE by **II** and **III** are summarized in Table I.

TABLE I

Bimolecular rate constants of the inhibition of ChEs by **II** and **III**

(k_i, $x10^6$ $M^{-1}min^{-1}$)

Phosphorylated mustard	HuBChE	FBS-AChE	k_{HuBChE}/k_{AChE}
II	69	3.1	22
III	3.8	0.11	35

The potency of the bis-phosphoryl adduct **II** in inhibition of HuBChE and AChE is 18- and 28-fold higher, respectively, than that of **III**, due to structural differences in the S-alkyl side chain. It appears that the second phosphoryl moiety enhances the inhibition relative to **III** by a decrease of approximately 1.9 kcal/mol in energy barrier. This is

attributed to more productive interactions of **II** compared with **III**, with amino acids at the entrance to the catalytic gorge. Either inhibitor phosphorylated HuBChE faster than AChE. This selectivity is likely to arise from differences in the amino acid residues that are lining the active site gorge of HuBChE and AChE [4, 5]. The release of constraint in the active site of HuBChE due to replacement of aromatic with aliphatic side chains, suggest that bulky alkyl groups of OP inhibitors are accommodated by HuBChE more comfortably than by AChE.

Reactivation of HuBChE inhibited by **II** and **III**, provides evidence that the same OP-HuBChE conjugate was obtained irrespective of the S-alkyl moiety. More than 93% of the phosphorylated enzyme by either inhibitor, were reactivated by 0.1 M P2S at $t_{1/2}$ 5.6 to 5.8 min.

To demonstrate the feasibility of hydrolysis of OPs catalyzed by use of HuBChE-reactivator mixture, molar excess of **III** over HuBChE was added to enzyme solution containing 0.1 M of either P2S or MINA (Fig. 3A). Despite the large stoichiometric excess of **III** over the enzyme, the inhibition of HuBChE at steady state did not exceed 70%. Since the hydrolysis of **III** was < 1%/h, the recovery of enzyme activity suggests that reaction ***a*** is essentially correct. The time course of enzyme activity shown in Fig. 3A indicates that the overall detoxification rate of a given organophosphoyl-bound moiety, depends on the nature of the reactivator. From the data shown in Fig. 3B it is also evident that the efficacy of the proposed mixture can be enhanced by selecting suitable PS salt.

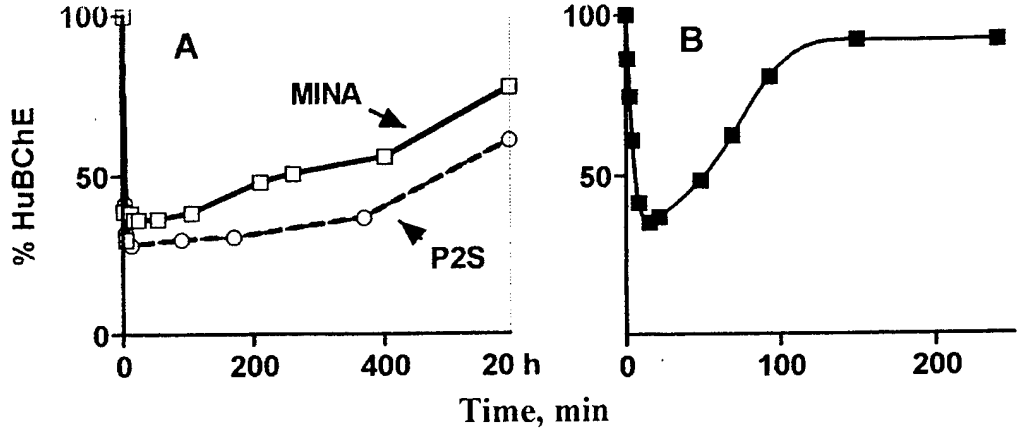


FIGURE 3. Time course of enzyme activity of HuBChE-reactivator solutions following the addition of stoichiometric excess of OPs. Panel A, **III** to HuBChE ratio = 15 (pH 7.95, 25°C). Both reactivators were at 0.1 M; Panel B, reactivator: 0.1 M P2S; $CH_3P(O)(OC_2H_5)SCH_2CH_2N(isoPr)_2$ to HuBChE ratio = 8 (pH 7.3, 25°C).

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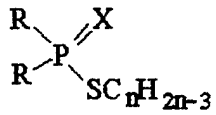
PHOSPHORYL- AND THIOPHOSPHORYL THIOALKYNES

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Abstract Syntheses of S-alkynyl derivatives of phosphorus monothioacids with the triple bonds in the α, β, and γ positions are described. Compounds of the type $R_2P(O)SC{\equiv}CR'$ show unusually high anticholinesterase ability ("acetylenic effect").

Key words:thioalkynes, thiophosphorus acid, bromoacetylene.

This communication is devoted to alkynyl esters of thio- and dithiophosphorus acids of the general type



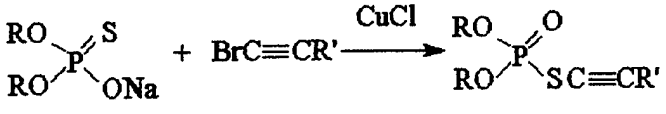
where X is O or S and R is alkyl or alkoxyl.

The triple bond can be located in the α-, β-, or γ-positions relative to the sulfur atom. Earlier this type substances have little been studied but there was reason to look for interesting physiologically active compounds among them. All the literature data indicated the prosperity of the compounds with the triple bond in the β-position relative to the heteroatom, and we performed the synthesis and investigation of physiological action of phosphorylated 2-butynes[1] but all the compounds obtained exhibit a moderate anticholinesretase activity.

We synthesized also the substances with the γ-position of the triple bond relative to the sulfur atom but they appeared to be even less interesting.

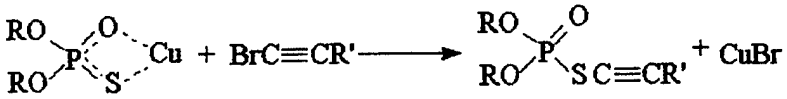
The comparison of the physiological activity, for example, anticholinesterase action, of the compounds studied reveals the following order: compounds with the triple bond in the γ-position have K_{II}s about $10^3 M^{-1}min^{-1}$, those of the butyne derivatives are in the range from 10^4 to 10^5 $M^{-1}min^{-1}$, K_{II}s of propargyl thiol esters slightly exeed $10^5 M^{-1}min^{-1}$. This matching pointed to the advisability of the synthesis and investigation of acetylene thioesters with the triple bond in the α-position

First attempts to alkylate monothiophosphorus acid salts with bromoacetylene, by analogy with the well-known alkylation reaction, were not successful: the reaction did not proceed at all[2]. An attempt to perform the synthesis by the reaction of free acids with bromoacetylene in the presence of pyridine gave also the negative result. At the same time, the Khodkieviez and Cadiot reaction[3] is known where the copper catalyst revives the substitution of bromoacetylene. In our case, the alkylation of the alkaline thiophosphoryl salt was successful when using copper (I) chloride as a catalyst:



(60-80%)

as well as the reaction of a free acid with bromoacetylene and pyridine in the presence of copper (I) chloride. Unlike the Khodkieviez and Cadiot reaction, an equimolar amount of copper (I) chloride was necessary rather than catalytic. That means that the reaction runs through the copper (I) salt of phosphorus thioacid. Indeed, the copper salt reacts readily with bromoacetylene to give the expected thiophosphoryl derivative:



(60-85%)

In doing so, three questions arise as follows: What is the structure of the copper salt of thiophosphorus acid? What is the difference between the reactivity of this salt and that of alkaline metal salts and why they differ? What is the mechanism of the reaction between the copper salt of thiophosphorus acid and bromoacetylenes?

X-ray analysis answered the first question[4]. Copper diethylthiophosphate is tetrameric: copper atoms form a tetrahedral (irregular) cluster. All the bond distances in the complex are typical of covalent (coordination) bonds. Hence, the copper salt is built

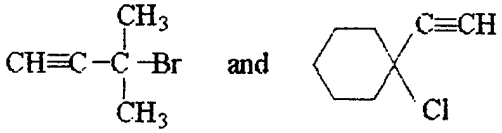
up in the covalent fashion while alkaline metal salts are ionic. This is the answer to the second question.

In order to answer the third question about the mechanism of alkylation of copper (I) thiophosphates, we studied a number of reactions of such copper salts with various alkynyl halides parallel with alkyl halides.

Above we considered reactions with bromoacethylenes. They react with copper (I) salts but do not react with potassium salts. On the contrary, alkyl halides alkylate potassium salts but they do not react with Cu(I) salts.

However, bromoalkynes with the bromine atom in the alkyl part of the molecule react with potassium salts and do not react with copper (I) salt: whereas 1,4-dibromobutyne reacts with both potassium and copper (I) salt but in different fashions. The bromoalkynyl derivatives obtained differ in their ability to react with trimethylamine. The former reacts with trimethylamine to form ammonium derivatives but the second does not react with trimethylamine.

Significantly that both potassium and copper (I) salts react with propargyl bromide. Since the propargylic bromine atoms are sure to exchange with potassium salts according to the mechanism of heterolitic substitution of the S_N2 type, it is reasonable to suppose that copper (I) salts react in the same manner. However, if the S_N2 reaction is inhibited by sterical hindrances, the potassium salt stops reacting but the copper (I) salt continues. For example, the compounds



react only with the copper (I) salt. The problem was solved by NMR and ESR studies[5], which show that we are dealing with the redox transfer of one electron leading to the formation of the free radical $^{\bullet}C{\equiv}CPh$. The free radical formed attacks the sulfur atom in the copper salt to give the reaction products.Both stages are most likely to proceed into the solvent cage. When leaving the cage, the $^{\bullet}C{\equiv}CPh$ radicals are dimerized to form diphenyldiacetylene $PhC{\equiv}C\text{-}C{\equiv}C\text{-}Ph$ (in our case, 10-15%).

Biochemical experiments on the inhibition of cholinesterases of various origin revealed that the majority of these substances appeared to be anticholineaterases of a great strength with inhibition constants ($K_I M^{-1} min^{-1}$) being tens, hundreds, millions times higher than those of corresponding saturated compounds. We termed the ratio

between the constants of acetylene and saturated compounds (that is $K_{II,acet.}/K_{II,sat}$) the "acetylenic effect" ("AE").

The comparison of anticholinesterase action of $(MeO)_2P(O)SC{\equiv}C\text{-}C_6H_{11}$-c with $(MeO)_2P(O)SCH_2\text{-}CH_2\text{-}C_6H_{11}$-c gives AE of two millions; $K_{II} = 2.0.10^8 M^{-1}min^{-1}$. On butylcholinesterase, AE = $1.5.10^6$ and $K_{II} = 2.2.10^9 M^{-1}min^{-1}$. For cholinesterase of fly heads, AE = $2.7.10^6$ and $K_{II} = 3.0.10^8 M^{-1}min^{-1}$. The presented values are the highest among all obtained but for other compounds, they are also very high.

Unusually high "thionic effect" of α-acetylenic compounds should be specially pointed out consisting in the fact that while changing the P=O group in acetylene compounds for the P=S group, the toxicity is changed very little for arthropoda but sharply decreases for mammals.

The possible mechanisms of the acetylenic and thionic effects are discussed.

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BIOLOGICAL PROPERTIES OF DODECA(THYMIDINE PHOSPHATES) CONTAINING 5-(*o*-CARBORAN-1-YL)-2'-DEOXYURIDINE

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Abstract 5-(*o*-Carboran-1-yl)-2'-deoxyuridine containing dodecathymidylic acids (**2-7**) manifested increased lipophilicity, resistance to digestion by calf spleen phosphodiesterase, and snake venom phosphodiesterase. They were substrates for T4 polynucleotide kinase, primers for *E. coli* polymerase I, human α DNA polymerase, and HIV-1 reverse transcriptase. They also form heteroduplexes that are substrates for *E. coli* RNase H.

INTRODUCTION

Polymers and biopolymers such as boronated oligophosphates and oligonucleotides, are novel radiosensitizer for boron neutron capture therapy (BNCT) of cancers. Carboranyl containing oligonucleotides were designed as boron rich carriers for BNCT, and also as antisense agents for antisense oligonucleotide technology (AOT). They were produced from the monomer 5-(*o*-carboran-1-yl)-5'-dimethoxytrityl-2'-deoxyuridine-3'-[*N,N*-diisopropyl-β-cyanoethyl]phosphoramidite in an automated DNA synthesizer.[1] The physicochemical characteristics of model 12-mers (**2-7**) containing 5-(*o*-carboran-1-yl)-2'-deoxyuridine (CDU) were studied.[2] Herein, we report the biological properties of oligonucleotides **2-7** containing one or more CDU residues at different locations within the oligonucleotide chain.

RESULTS

Synthesis of 5-(o-carboran-1-yl)-2'-deoxyuridine containing dodecathymidylic acids (2-7). The synthesis of oligonucleotides **2-7** has previously been reported.[2] All compounds were characterised by UV, HPLC and ESI-MS.

Resistance to bovine spleen phosphodiesterase II (BSPDE). Pronounced effect of CDU modification on the oligonucleotide stability in the presence of phosphodiesterase II, 3'-exonuclease from calf spleen (BSPDE) was observed. The resistance increased in the order $d(T)_{12}$ (1) < $d(T)_{10}$CDUd(T) (5) ~ $d(T)_9(CDU)_2$d(T) (6) < CDUd$(T)_{11}$ (2) ~ d(T)CDUd$(T)_{10}$ (3) ~ $^{5'}$CDUd$(T)_9$CDUd(T) (7).

Resistance to snake venom phosphodiesterase (SVPDE). The presence of CDU at the 3'-end of oligonucleotides effectively improved their stability towards snake venom phosphodiesterase (SVPDE) from *Crotalus durissus terrificus*. The oligonucleotide resistance towards enzymatic hydrolysis of internucleotide phosphodiester linkages increased in the following order: unmodified **1** < **5** ~ **7** << **6**. The fraction of nonhydrolyzed oligonucleotide after 10 min was 2.5, 44, 38, and 80 %, respectively.

Phosphorylation by T4 polynucleotide kinase. The phosphorylation experiments with T4 polynucleotide kinase showed that CDU-oligonucleotides **1-7** were efficiently phosphorylated at their 5'-ends by the enzyme. The efficacy of the 5'-end phosphorylation was comparable to the phosphorylation of unmodified, standard oligonucleotide $d(T)_{12}$ (**1**).

Priming the DNA polymerization. CDU-modified oligonucleotides **2-7** and unmodified dodecathymidylic acid **1** were tested for their ability to serve as a primers for DNA polymerases. Four different enzymes were studied, namely human polymerase α and β, *E. coli* bacterial polymerase I, and human immunodeficiency virus type-1 (HIV-1) reverse transcriptase (RT). All oligonucleotides **1-7** functioned as primers for polymerases studied, except for human polymerase β.

Induction of RNase H activity. CDU-modified oligonucleotides **2-7** formed RNA-DNA heteroduplex substrates for *E. coli* RNase H with a poly rA template of 400-600 bases in length. These heteroduplexes were digested by RNase H in a fashion comparable to the digestion of the unmodified duplex formed by dodecathymidylic acid **1**.

DISCUSSION

The enzyme SVPDE successively hydrolyzes 5'-mononucleotides from deoxyribooligonucleotides with free 3'-OH groups. The digestion of the DNA proceeds in the 3'->5' direction.[3] In contrast, BSPDE requires a free 5'-hydroxyl terminus, and digestion proceeds in the opposite 5'->3' direction. The nucleolytic activity of both enzymes towards oligonucleotides is substantially decreased by nucleic base modification for single stranded as well as double

stranded substrates.[4,5] The presence of two CDU residues at the 3'-end of the oligonucleotide substantially increased the oligomer stability towards 5'-exonucleolytic enzymes, such as phosphodiesterase I from snake venom (SVPDE).[2] The observed higher stability of **6** compared to **5** may be due to the slow hydrolysis of two internucleotide linkages beyond the modified base 5'-CDUpCDU-3' and 5'-TpCDU-3' or very slow cleavage of the phosphodiester linkage beyond modified dimer 5'-TpCDUpCDU-3' or trimer 5'-TpTpCDUpCDU-3'. A substantially pronounced effect on the oligonucleotide stability was observed for the 3'-exonuclease from calf spleen (BSPDE), which truncated the oligonucleotides from the 5'-end. It appears that the presence of one CDU residue at the 5'-end as in **2** or **7** protected the oligonucleotide against digestion. For oligomers **3-6** it is likely that the nucleolytic hydrolysis of the oligionucleotides proceeded fast until the first CDU residue or nucleoside directly preceding the CDU was reached.[5,6]

A variety of nucleic acid compounds can be phosphorylated in the polynucleotide kinase reaction provided they have a nucleotide bearing a free 5'-hydroxyl group with a phosphoryl group at the 3'-position.[7] As anticipated, phosphorylation of CDU-containing oligonucleotides with T4 polynucleotide kinase was shown for all oligonucleotides **2-7**. The efficacy of phosphorylation was comparable to the unmodified oligonucleotide **1**. Similarly results were obtained for the oligonucleotide **2** bearing a CDU modification at the 5'-end. The data demonstrate that CDU-oligonucleotides can be labeled at the 5'-end which is of practical importance.

CDU-modified oligonucleotides **2-7**, and unmodified dodecathymidylic acid **1** were tested for their priming activity in DNA polymerisation process catalyzed by four different DNA polymerases: human polymerase α and β, *E. coli* polymerase I and human immunodeficiency virus type-1 (HIV-1) reverse transcriptase (RT). It was found that all oligonucleotides **1-7** were primers for the polymerases used although with different efficacy, except for human polymerase β. In general, the ability for priming the DNA synthesis changed in order **2** ~ **3** $\geq$ **1** > **4** ~ **5** ~ **6** ~ **7**. Elongation of CDU-modified oligonucleotide primers, using poly dA template, in the presence of human polymerase β did not occur. This is consistent with the enzyme requirement for the presence of phosphate at the template 5'-end in the short gap (less than 6 nucleotides) filing process.[8] Indeed, oligonucleotide **1-7** were used in fourfold excess (per base) relative to the template, which favors formation of short gaps.

RNase H recognizes RNA-DNA hybrids as a substrate and cleaves only the RNA in endonucleolytic manner. At least four base pair heteroduplex stretches are necessary for the substrate recognition. All CDU-modified oligonucleotides **2-7** RNA-DNA heteroduplexes with a 400-600 bases poly rA template were found to be substrate for RNase H. Despite the finding that the melting temperatures (T_m) of duplexes with CDU-oligonucleotides varied from 15°C to 29°C, the efficacy of poly rA template digestion seems independent of the T_m of the duplex formed with CDU-oligonucleotide.[2]

Based on the physicochemical and biological properties of these carboranyl containing oligonucleotides, we are currently designing oligomers that could be targeted against overexpressed genes in cancer and in virally infected cells. We also are developing methodologies for the synthesis of the oligonucleotides containing the carboran-1-yl modification within the internucleotide linkage.[9,10]

ACKNOWLEDGMENTS

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ISOLATION AND HPLC SEPARATION OF POLYUNSATURATED SPECIES OF RAT BRAIN ACYL-CoA PRODUCED DURING DECAPITATION - ISCHEMIA

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Abstract Acyl-CoA is a crucial metabolic intermediate for the incorporation of fatty acid into membrane phospholipid. The rat brain long chain acyl-CoAs were isolated and quantitated with a procedure involving solid phase extraction with an oligonucleotide purification cartridge, followed by separation and quantitation by HPLC with special emphasis on resolution of the polyunsaturate acyl-CoAs. This procedure is uniquely suited to the rapid analysis of all molecular species of brain acyl-CoA including the polyunsaturate molecular species which are affected by ischemia. A selective 3-4 fold increase in arachidonoyl-CoA was found in rat brain after 3 min of ischemia when compared with microwaved brain. In contrast, the concentration of all other molecular species of acyl-CoA did not change over the time course of the ischemia.

Key Words: Acyl-CoA, Phospholipids, Arachidonic acid, HPLC, Brain ischemia.

INTRODUCTION

Studies on fatty acids released in rat brain during the early phase of decapitation ischemia show a rapid increase in all fatty acids with a selective increase in arachidonate and stearate (1,2). Several reports suggest that arachidonic acid is predominantly liberated from inositol-containing phospholipids by combining action of phospholipase C and diglyceride lipase or from the activity of phosphatidil-choline specific phospholipase and lysophospholipase (1,2,3,4). Changes in the fatty acids levels can affect the long chain acyl-CoAs which are essential metabolic intermediates for the incorporation of fatty acids into lysophospholipids through the action of acyltransferase (5) and for their β-oxidation in mitochondria and peroxisomes (6). Previously we have reported a fast method for quantitation of the long-chain acyl-CoAs from rat brain using isopropanol:acetonitrile extraction followed by purification with an oligonucleotide purification cartridge prior to HPLC separation (7). However, due to difficulties in the HPLC separation and quantification of the polyunsaturated long chain acyl-CoAs, levels of docosahexaenoyl- and arachidonoyl-CoA could not be directly ascertained. We now have a HPLC protocol whereby the acyl-CoAs of these two essential fatty acids can be resolved and quantified. This procedure can be readily applied to the determination of the effect of ischemia on the level of acyl-CoAs. This

is a first step in the analysis of the effect of ischemia on fatty acid flux into brain membrane phospholipids.

MATERIALS AND METHODS

Materials, brain tissue extraction, solid-phase extraction and the HPLC system were as previously described (7). The HPLC separation was performed with a Symmetry C-18, 5 micron column 250 x 4.6 mm; Waters Millipore Corp., (Milford, MA) provided with a stainless steel filter. Chromatography was performed using a combined gradient system including two mobile phases: (A) 75mM potassium dihydrogen phosphate and (B) 100% acetonitrile with a flow rate of 1.0 ml/min. The starting conditions were 56% buffer A and 44% B. B was increased to 49% over 25 min and then increased to 70% during the next 5 min, kept a 70% for 7 min and decreased to 44% over 4 min, and held at 44% for an additional 4 min before returning to the starting conditions.

Animal Preparation: Male Sprague-Dawley laboratory rats (180-210 g) purchased from Charles River Laboratories (Wilmington, MA) were maintained with free access to food and water. Animals were anesthetized with sodium pentobarbital (40 mg/kg, i.p.) and killed by focused-beam microwave irradiation (5.5 kW, 3.0 s; Cober Electronics, Stanford, CT). Ischemia was achieved by decapitation of pentobarbital-anesthetized rats. Brains were removed within three minutes. The isolated brains were either frozen in dry ice pellets at three minutes or maintained in a plastic bag at 37°C in a controled-temperature oven for 15 min and then frozen in dry ice.

RESULTS AND DISCUSSION

In this work we report the refinement of previous methodology which allowed us to rapidly analyze the individual molecular species of rat brain acyl-CoA (7). Using a more protracted gradient elution scheme with a suitable system we are able for the

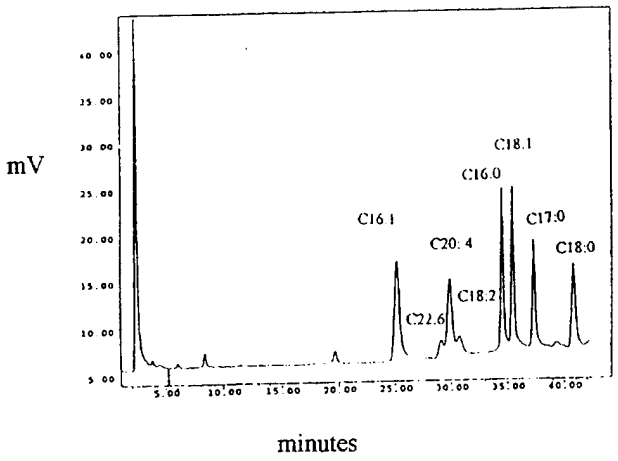


FIGURE 1 HPLC pattern of acyl-CoA standards.

first time to resolve the individual polyunsaturate molecular species namely

docosahexaenoyl-, arachidonoyl- and linoleoyl-CoA (Fig. 1). A standard mixture of acyl-CoAs was separated by combining a 25 min shallow gradient elution with acetonitrile in 75 mM potassium dihydrogen phosphate followed by a 5 min step gradient. The extraction efficiency using hexadecaenoyl-CoA as internal standard was 100% for arachidonoyl-, linoleoyl-, and docosahexaenoyl-CoAs and 95-100% for palmitoyl-, oleoyl- and 75% for stearoyl- CoAs. In order to increase the accuracy of the quantitation of the late eluting acyl-CoAs, an additional internal standard (heptadecanoyl-CoA), was added. The elution profile of acyl-CoA's isolated from

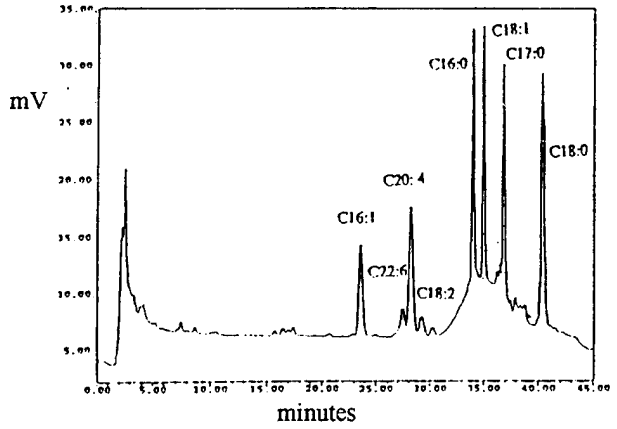


FIGURE 2 HPLC pattern of rat brain spiked with acyl-CoA standards.

microwaved rat brain spiked with the polyunsaturated acyl-CoAs together with the palmitoyl-, oleoyl- and stearoyl-CoAs (Fig 2) was achieved by combining the high performance of the oligonucleotide purification cartridge and optimized interaction of the Symmetry reversed-phase column with the amphipathic acyl-CoAs.

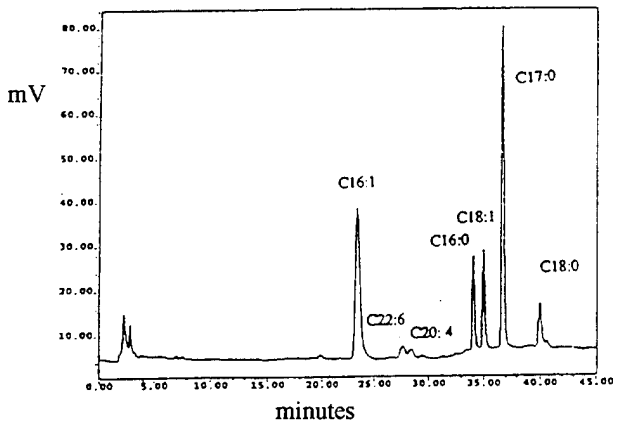


FIGURE 3 HPLC pattern of the microwaved rat brain (control).

In Fig. 3 is shown the pattern of microwaved rat brain spiked with 20 μg of

hexadecanoeoyl-CoA and heptadecanoyl-CoA, as internal standards, extracted and analyzed by HPLC. The docosahexaenoyl-CoA and arachidonoyl-CoA are indicated and linoleoyl-CoA is a smaller unmarked peak eluting at 29.3 min. The values found for the individual molecular species in microwaved brain were; 18:0, 5.1; 18:1, 10.8; 16:0, 8.4; 18:2, 0.9; 20:4, 1.6; 22:6, 1.7 nmole/g cerebral hemisphere giving a total of 28.6 nmole/g. Further, the method allowed us to monitor the selective increase in arachidonoyl-CoA during global ischemia.

Rats were decapitated after pentobarbital anesthesia and the brains excised and frozen in dry ice after 3 min and 15 min at 37°C. The HPLC elution profile of the acyl-CoA molecular species in a single rat brain analyzed after 3 min of decapitation ischemia is shown in Fig 4.

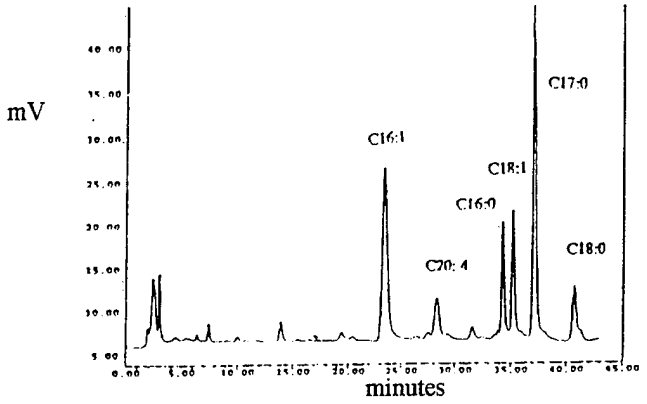


FIGURE 4 HPLC pattern of acyl-CoA obtained from rat brain after ischemia.

It is evident that there is a dramatic increase in the arachidonoyl-CoA with little apparent change in any of the other molecular species. The selective increase in arachidonoyl-CoA is of considerable interest due to the importance of this fatty acid to the stimulus-response coupling in brain and the short life for arachidonate in brain phospholipids. We believe that further measurements of acyl-CoA concentrations will bring in the future a new dimension to the knowledge of cerebral lipid metabolism.

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ENZYME ENGINEERING TOWARDS NOVEL OP-HYDROLASES BASED ON THE HUMAN ACETYLCHOLINESTERASE TEMPLATE

AVIGDOR SHAFFERMAN, ARIE ORDENTLICH, DOV BARAK, CHANOCH KRONMAN, HAIM GROSFELD, DANA STEIN, NAOMI ARIEL, YOFFI SEGALL, BARUCH VELAN.
Israel Institute for Biological Research, Ness-Ziona, Israel.

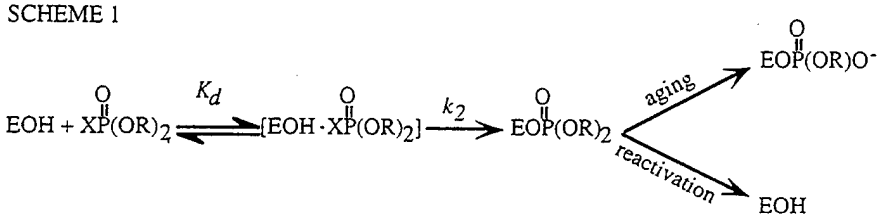
Abstract : Protein engineering technologies were used to generate various derivatives of human acetylcholinesterase (HuAChE). These enzymes were reacted with various organophosphates (OP) and reactivators in order to identify key element in the active center determining the efficiency of phosphylation, reactivation and of the aging process. Based on the results obtained we believe that novel biocatalysts with efficient OP-scavenging and possibly even OP-hydrolase activity may be generated, in the near future.

INTRODUCTION

The catalytic power of AChE and its high reactivity towards OP-inhibitors is believed to be determined by the unique architecture of the AChE active center, consisting of several subsites. Resolution of the 3D structure of *Torpedo* AChE[1], site directed mutagenesis and molecular modeling together with kinetic studies of the AChE muteins with substrates and reversible inhibitors[2-10] are beginning to unveil the functional role of the various active center subsites in the reactivity characteristics of the enzyme: a) the esteratic site containing the active site Ser-203 (human AChE aa numbering system); b) the "anionic subsite"-Trp-86 ; c) the hydrophobic site for the alkoxy leaving group of the substrate includes residues Trp-86, Tyr-337 and Phe-338; and d) the acyl pocket - Phe-295 and Phe-297. Involvement of the same binding elements in AChE reactivity towards organophosphorus inhibitors has been assumed in numerous studies during the last three decades, however a direct experimental evidence for such involvement is still scarce. Due to the high reactivity of AChEs towards OP-inhibitors they have been suggested as exogenous scavengers for sequestration of highly toxic OP-agents[11]. The AChEs react irreversibly and on a molar basis with the OP agents, however, the amounts of AChE required for treatment could be reduced provided that the OP-enzyme conjugates could be efficiently reactivated before the excess OP has reached its physiological target. This goal is difficult to attain especially in cases where the OP-AChE conjugates undergo catalytic

post-inhibitory processes termed aging (see scheme 1). In native AChEs the spontaneous reactivation, through displacement of the phosphyl moiety from the active site, is usually very slow and unable to compete with the aging process, yet efficient enzyme reactivation can be achieved by various oxime nucleophiles[12]. Our goal is therefore to generate enzymes based on the HuAChE template, the OP-adducts of which are more readily reactivated and are resistant to aging, yet still retain their high reactivity towards the OP agents. To meet this challenge, site directed mutagenesis has been utilized to induce small and controlled perturbations of the HuAChE active center functional architecture and their effects on the accommodation of organophosphate inhibitors, reactivators and the aging process were investigated.

SCHEME 1



RESULTS AND DISCUSSION

Contribution of Active Center Structural Determinants to Phosphorylation and Reactivation

Elucidation of the specific HuAChE-inhibitor interactions in the initial complex and during the subsequent nucleophilic process is essential for understanding the reactivity of AChE toward phosphate derivatives. Towards this goal, the apparent bimolecular rate constants for the irreversible inhibition of the HuAChE enzymes were determined under experimental conditions that allow the evaluation of the dissociation constants (K_d) as well as the phosphorylation rate constants k_2 (scheme 1). The organophosphate inhibitors used included: diisopropyl phosphorofluoridate (DFP), diethyl phosphorofluoridate (DEFP) and p-nitrophenyl diethyl phosphate (paraoxon) which allow to test the effects of different leaving groups and alkoxy substituents. The bimolecular rate constant values (ki) for the various enzymes tested extended over 3 orders of magnitude, irrespective of the nature of the inhibitor used. Interestingly, these values could be clustered according to the functional subsites in the HuAChE active center: mutants of the acyl pocket (Phe-295 and Phe-297) exhibiting the highest k_i values of all the enzymes tested; the alkoxy pocket (Trp-86, Tyr-337 and Phe-338) with k_i values close to that of the wild type enzyme; the H-bond network (Glu-202,Glu-450 and Tyr-133) with k_i values consistently lower as compared to the wild type enzyme. The most consistent characteristics of the HuAChE enzymes reactivity pattern toward organophosphates is that structural variations in both the enzyme and the inhibitor affect almost exclusively the stability of the initial

noncovalent complexes. While replacements of selected residues in HuAChE brought about changes in the K_d values of about 4-orders of magnitude, the corresponding phosphorylation rate constants (k_2) remained essentially unchanged. These results imply that the reaction has very stringent steric requirements within the active center and that *noncovalent complexes* which do not meet these requirements are kinetically silent.

The observed similarity of the overall effects of residue replacements at the acyl pocket, on the values of Km for substrates and K_d for phosphates indicate that the acyl pocket serves indeed an analogous purpose in both cases. However, due to the added dimensionality of the phosphates, variations in the K_d values reveal additional effects of the acyl pocket structural modifications. For the substrate, accommodation of the methyl group in this pocket together with the oxyanion hole orient the molecule in plane for the incipient nucleophilic attack. In a similar way, interaction of this subsite with organophosphates helps to orient the molecules for the in-line attack by the catalytic serine. In both cases the respective substituent is projected towards Phe-295 and therefore the corresponding complexes are more sensitive to the volume of residue at this position. Steric interactions with residue at 297 become important for branched alkoxy substituents which present larger volumes to the acyl pocket. Only marginal effects could be observed, upon replacement of the aromatic residues Trp-86, Tyr-337 or Phe-338, on the stability of complexes with DFP and DEFP underscoring the nonspecific nature of the hydrophobic interactions of the alkyl moieties with the enzyme surface. A somewhat more pronounced dependence on the structure of the alkoxy pocket is evident in the case of paraoxon which appears to originate from interactions with the p-nitrophenoxy leaving group. The potential multiplicity of the alkoxy pocket binding elements raises the possibility that both the alkoxy substituent and certain leaving groups are accommodated by this subsite.

Paraoxon inhibited enzymes were also used to gain a better understanding of the reactivation process by monoquaternary and bisquaternary oximes. It appears that the efficiency of the reactivation process depends to a large extent on the integrity of the active center H-bond network (Glu-202 and Glu-450) as well as on the anionic subsite residue Trp-86. A somewhat more surprising result was the observation that amino acids constituting the peripheral anionic site, which is located about 20Å away from the active center, can also affected the efficiency of reactivation by both bisquaternary and monoquatrnary oximes. Although some general patterns of behavior were observed, the extensive kinetic studies have not yet yielded a comprehensive picture regarding the nature of the chemical interactions between the reactivator and the OP-conjugate .

Contribution of Active Center Structural Determinants to Aging

We have recently[6] initiated a study of HuAChE derivative molecules with engineered

noncovalent complexes. While replacements of selected residues in HuAChE brought about changes in the K_d values of about 4-orders of magnitude, the corresponding phosphorylation rate constants (k_2) remained essentially unchanged. These results imply that the reaction has very stringent steric requirements within the active center and that *noncovalent complexes* which do not meet these requirements are kinetically silent.

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PHOSPHORYLATED 2-AZAALLYLIC SYSTEMS. SYNTHESIS, PROPERTIES, AND REARRANGEMENTS.

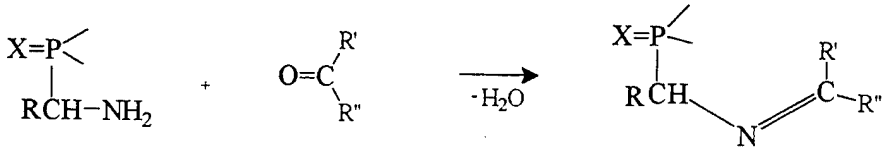
T.V. KIM, E.I. KISELEVA, P.P. ONYS'KO, A.D. SINITSA
Institute of Organic Chemistry, NAS of Ukraine
Kiev 252660, 5 Murmanskaya St., Ukraine

Abstract The methods for synthesis of mono- and bisphosphorylated 2-azaallylic compounds were developed. The relevant proto- and phosphorotropic rearrangements in the C=N-C triad were studied.

Isomerization reactions in azaallylic systems are of general importance as an integral part of heteroallylic rearrangements. Among them, the proton 1,3-transfer in azomethine-azomethine isomerizations, which is often considered as model for biochemical trans-amination reactions, has been most extensively investigated. The effects of phosphoryl groups on prototropic migrations in azaallylic compounds were hitherto not studied.

In the present work we report on developed in our Laboratory synthetic approaches to mono- and bisphosphorylated 2-azaallylic derivatives with phosphorus bonded to sp^2- or sp^3- carbon atoms in the C=N-C triad, specific effects of the phosphoryl substituents on their properties and elementotropic rearrangements within the triad.

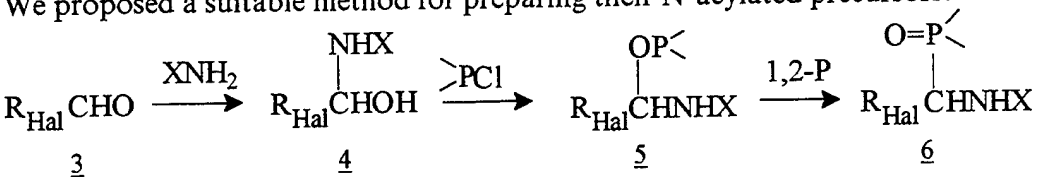
One of the general routes to sp^3-C-phosphorylated 2-azaallylic systems consists in condensation of a-aminophosphoryl and carbonyl compounds.



1 2

R: H, Alk, Ar, CF_3; R', R": H, Alk, Ar, Het; X: O, S

The limitations of the method in large measure are determined by availability of α-aminophosphonates 1. Traditional preparative pathways to compounds 1 are often unacceptable in synthesis of polyhaloalkyl derivatives. We proposed a suitable method for preparing their N-acylated precursors.

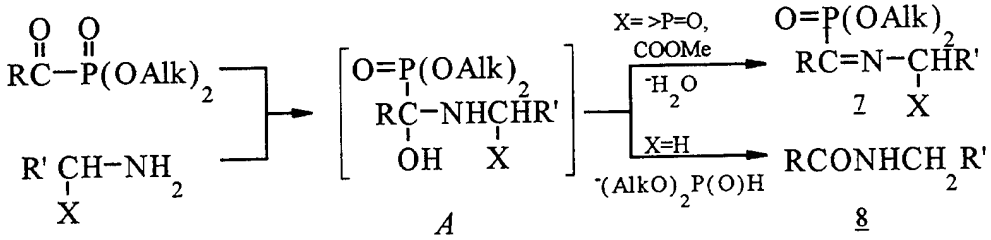


R_{Hal}: CCl_3, $H(CF_2)_4$, $H(CF_2)_6$ X: PhCO, $P(O)(OEt)_2$, $P(O)Ph_2$;

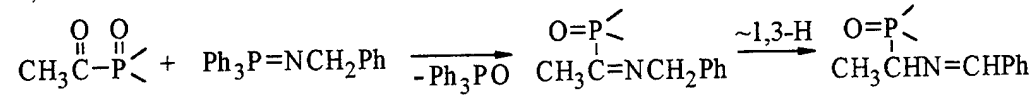
$>PCl$: $(AlkO)_2PCl$, $(R_2N)_2PCl$, Ar_2PCl

A key step in the scheme is formation of a P-C bond via phosphorotropic rearrangement 5 → 6 proceeding even at an ambient temperature. It should be noted that the reported method [1,2] based on the reaction of carbonyl compounds with carboxamides and phosphorus (III) chlorides is inapplicable to 2-haloalkylaldehydes [1].

Desired sp^2-C-phosphorylated azaallylic products 7 we obtained by treating α-oxophosphonates with amines containing an electron-accepting substituent in α-position. In the case of alkyl- and arylamines the reaction results in corresponding amides 8.

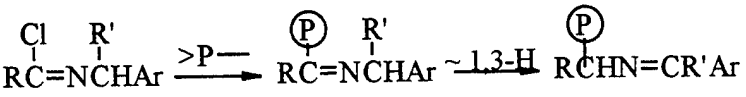


N-Benzyltriphenylphosphinimine reacts with α-oxophosphonates by the aza-Wittig scheme to give imidoylphosphonates undergoing phosphinimine-catalyzed 1,3-shift.



This method, however, is not of general application.

The reaction of N-alkyl substituted imidoyl chlorides with nucleophilic phosphorus (III) derivatives was found to be a versatile synthetic tool for preparing phosphorylated azaallylic compounds with a P-C bond either at sp^2- or sp^3- carbon atom of the C=N-C triad.



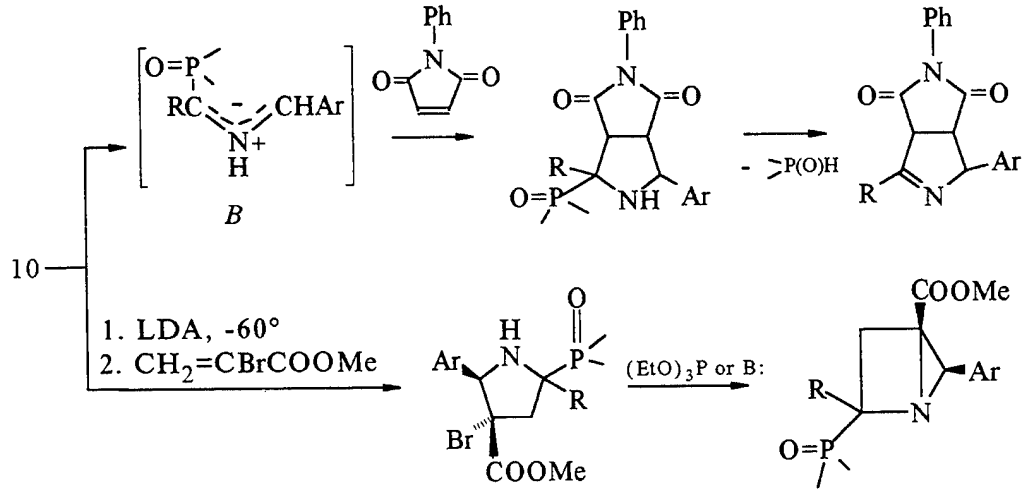
9 10

Ⓟ: $(AlkO)_2P(O)$, $(Me_3SiO)_2P(O)$, $Ar_2P(O)$, $(AlkO)_2P(=NAr)$, $Ph_3P^+Cl^-$, Ph_2P

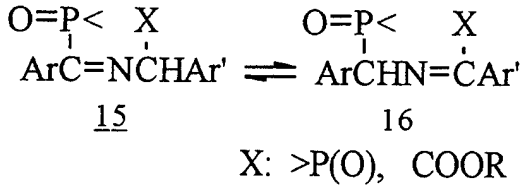
R: Alk, CF_3, Ar, Het; R' = H, Me

A phosphoryl group in products 9 considerably enhances mobility of the NCH proton thus facilitating their prototropic rearrangement to imines 10 obtained in preparative yields. At R'=H, isomerization 9 → 10 proceeds even in the absence of bases. With all R and Ar studied, the prototropic shift is virtually irreversible. The isomer with a phosphorus group at the sp^3-C-atom is thermodynamically more stable. The conjugation of the Ar substituent with the C=N bond essentially contributes to the stabilization of isomer 10. Under certain conditions compounds 9 are kinetically stable and can be isolated in the individual form. The study of the rearrangement involving optically active imines 9 has intimated that the proton transfer proceeds stereoselectively.

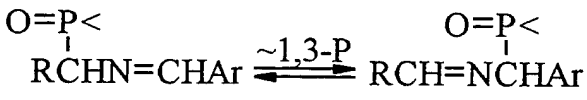
The presence of the activating phosphorus group in 10 enables, by way of 1,2-H-shift, a thermal generation of azomethine ylides *B* which can be trapped by dipolarophiles. Cycloaddition in this case is nonstereoselective. By the dipole generation in the presence of a base and subsequent reaction with an alkene containing activating (COOMe) and nucleofugic (Br) substituents, mono- and bicyclic phosphorylated heterocycles were obtained. Under these conditions the cycloaddition proceeds in a stereoselective manner.



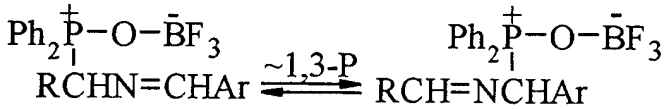
In imines 15, 16 the proton transfer is reversible that, in principle, makes it possible to perform interconversions between α-aminophosphonic and α-aminocarboxylic acid derivatives and, with regard to stereoselectivity of the H-shift, to achieve a transfer of chirality from one center to another.



Also reversible transfer of a phosphorus group in the C=N-C triad was found to be typical for 2-azaallylic systems. The isomerization is a rare in organic chemistry example of rearrangements involving cleavage-renewal of a P-C bond.



Boron trifluoride etherate is an effective catalyst of the $Ph_2P(O)$-group transfer in the azaallylic triad. The rearrangement in this case occurs in complexes formed by coordination of BF_3 to the phosphoryl oxygen atom of the imine.



In some cases such complexes were isolated and identified.

Thus phosphorylated azaallylic systems are suitable models for studying different elementotropic (E = H, P, S, Cl) isomerizations in the C=N-C triad. A possible occurrence of such rearrangements should be taken into account in preparative practice, particularly in synthesis of α-aminophosphoryl and α-aminocarbonyl derivatives.

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SYNTHETIC APPLICATIONS OF β-FUNCTIONALIZED PHOSPHORUS COMPOUNDS. AN EFFECTIVE STRATEGY FOR THE PREPARATION OF ACYCLIC AND HETEROCYCLIC COMPOUNDS DERIVED FROM AMINES AND HYDRAZONES.

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Abstract Enamines **3'A** were very easily prepared in high yield through the addition of achiral and chiral amines **1A** to propargylphosphonium salts, phosphine oxide and phosphonate allenes **2**. β-Functionalized phosphonium salts, phosphine oxides and phosphonates were used for the synthesis of β-amino phosphorus compounds **4A** and for the synthesis of homologation reagents of imines for the preparation of *E*-allylamines **8A** and β-hydroxyamino compounds **7A**. Likewise, β-enehydrazino phosphonium salts **3'cH**, β-hydrazono phosphine oxides **3aH** and phosphonates **3bH** were obtained from hydrazines **1H** and phosphorylated allenes **2**. These derivatives were used for the two-carbon elongation of hydrazones and for the synthesis of azadienes **6H** and pyrazoles **9**, **10**.

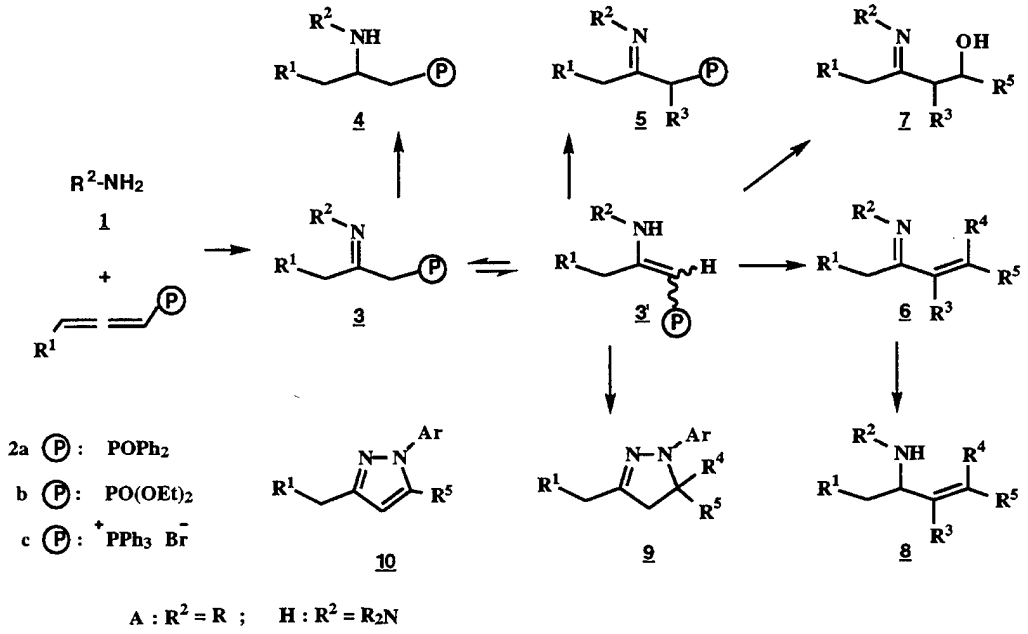
Imines[1] and hydrazones[2] are common nitrogen derivatives of ketones and aldehydes and have attracted a great deal of attention in recent years because of their range of applications.[1] They can be used not only as intermediates in heterocyclic synthesis,[3] but also in the enantioselective synthesis of natural products[4] and pharmaceuticals[5] of high enantiomeric purity. Particularly significant is the usefulness of α,β-unsaturated imines and hydrazones **1** as a result of their potential for the preparation of acyclic compounds,[6] as well as of the Diels-Alder reactivity of these substances as 1-azadienes for the construction of six membered heterocycles.[7] The lack of general methods for synthesis of these compounds has probably limited their use in organic synthesis. Simple α,β-unsaturated imines and hydrazones **6** are mostly synthesized by the condensation reaction of carbonyl compounds with hydrazines. However, the preparation of such compounds is far from simple and, specially in the case of ketones, only yields good results in very specific cases and generally leads to Michael addition.[8]

In recent years, we have used β-functionalized phosphorus derivatives as starting materials in the preparation of acyclic[9] and cyclic[10] derivatives. Continuing our interest in the reactivity of phosphorus substituted enamines and in the synthesis of azadienes[11] and in the preparation of homologation reagents of carbonyl derivatives into α,β-unsaturated imines[12] and hydrazones[13] with the introduction of two additional carbon atoms in the resulting chain, here we aim to extend this methodology to the preparation of a wide range of unsaturated compounds and to explore the synthetic use of β-functionalized phosphorus compounds in the preparation of new groups of acyclic and cyclic derivatives.

Synthesis of imino **5-7** and amino derivatives **4, 8A**.

The preparation of the phosphine oxide derivative **3aA** was very easily accomplished and in very high yields by means of simple addition of aliphatic, aromatic and functionalized amines **1A** to phosphorylated allenes **2a** in refluxing acetonitrile (see Scheme 1). Similarly, allenes derived from phosphonates **2b** and phosphonium salts **2c** also reacted with amines **1A** to give the corresponding enamines **3'bA** and **3'cA**. Functionalized phosphine oxides **3aA** and phosphonates **3'bA** were used in the preparation of β-amino compounds derived from phosphine oxides **4aA** and phosphonates **4bA** by selective reduction of the carbon-nitrogen double bond, without affecting either the phosphine oxide, or the phosphonate and/or other functional groups present in compounds **3**, when these derivative **3** were treated with $NaBH_4$ in refluxing ethanol.

Carbanions derived from imines such as metalloenamines are specially useful in organic synthesis.[1] In metalloenamines derived from compounds **3/3'A**, the presence of an anion stabilising group such as phosphine oxide or phosphonate could control the deprotonation in the internal less substituted carbon. Thus, when compounds **3/3'aA** and **3/3'bA** were treated with methyl lithium followed by addition of alkyl halides and aqueous work-up, substituted compounds **5aA** and **5bA** were obtained (see Scheme 1). Similarly, the olefination reaction of derivatives **3/3'A** were performed by treatment of these compounds **3/3'A** with methyl lithium in THF and the resulting metalloenamine was then allowed to react with aliphatic, aromatic and heteroaromatic aldehydes to give 1-azadienes **6A**. Michael addition of water to α,β-unsaturated imines **6A** led to the formation of β-hydroxi-imino derivatives **7A**. The treatment of azadienes **6A** with an excess of $NaBH_4$ in ethanol-THF gave allylamines **8A**. This procedure is highly stereoselective affording exclusively the *E* -stereoisomer.



SCHEME 1

Synthesis of α,β-unsaturated hydrazones **6H** and pyrazole derivatives **9** and **10**.

β-Hydrazono **3a-cH** and β-enehydrazino phosphorus compounds **3'a-cH** could be suitable to efficiently achieve the homologation, or two carbon elongation, of hydrazones into their vinylogous compounds **6H**. Thus, simple addition of hydrazines to allenes derived from phosphine oxides **2a** and phosponates **2b** led to the formation of hydrazones **3a,bH**, while the use of allenes derived from phosphonium salts **2c** afforded the β-enehydrazino phosphonium salts **3'cH** isolated as a mixture of the *Z* and *E*-isomers (see Scheme 1).

Carbanions derived from hydrazones are useful intermediates in organic synthesis[2] and in our case are also used for the preparation of acyclic **6H**, and cyclic compounds **9**,**10**. Thus, phosphonium salts **3'cH** were treated with a base (potassium carbonate) followed by Wittig reaction of the "in situ" generated phosphorane with aldehydes leading to α,β-unsaturated hydrazones **6H** with high *E* stereoselectivity of the carbon-carbon double bond.The reaction with ketones failed. We extended this methodology for two carbon homologation of hydrazones, by using the corresponding β-functionalized phosphine oxides **3aH** and phosphonates **3bH** instead of phosphonium salts **3cH**. In these cases, the metallation of β-hydrazono derivatives **3aH** and **3bH** with methyl lithium or LDA followed by the addition of ketones led to the formation of 1-azadienes **6H**. This strategy can also be applied for five membered heterocycle formation when N-aryl hydrazones are used. Acyclic α,β-unsaturated compounds **6H** (R_2N = ArNH) are

formed by treatment of the starting hydrazones **3aH** (R_2N = ArNH) with two equivalents of a strong base like LDA followed by addition of aldehydes. Heating these compounds at 100°C caused intramolecular Michael addition and gave pirazoles **10**. However, when ketones reacted with dianion from phosphorylated hydrazones **3aH** (R_2N = ArNH) the pyrazolines **9** were obtained.

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NOVEL SYNTHESIS OF PHOSPHONO SUGAR DERIVATIVES

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Abstract 2- And 3-phospholenes were used as the starting materials for the syntheses of sugar derivatives having a phosphorus atom in the hemiacetal ring of the sugar derivatives (phosphono sugars). Alkylation or benzyloxymethylation of 3-phospholene 1-oxides afforded phospholene derivatives with more than 5 carbon atoms. Epoxidation followed by epoxide ring opening and *cis*-dihydroxylation of 5-benzyloxymethyl-2-phospholene derivatives afforded four pentofuranose type phosphono sugars (arabinose, lyxose, ribose, and xylose). Some nucleosides and isonucleosides of phosphono sugars were also prepared. Some of these derivatives of phosphono sugars were subjected to structure elucidation and bioassay.

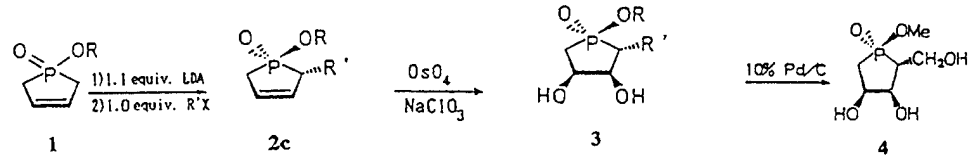
Key Words: Phosphono sugar; phospholene; LDA; Bromohydrin; Nucleoside

INTRODUCTION

Phosphono sugars, being one kind of sugar derivatives having a phosphorus atom in the hemiacetal ring of the sugar, had been expected to excert biological activities.[1] Therefore phosphono sugars were of interest in the aspects related to syntheses, structure, and biological activities. They were mainly prepared from sugar starting materials with suitable protections, functional group interconversions, cyclization, and deprotection.[1] In our previous paper, we reported the *cis*-dihydroxylation of 2-phospholenes with catalytic amount of osmium(VIII) oxide and co-oxidants.[2] The present paper deals with further conversion of 2- and 3-phospholene 1-oxide derivatives to prepare 1-deoxy pentofuranose and pentofuranose type phosphono sugars as well as their nucleosides and isonuleosides and their structural and biological analyses.

RESULTS, DISCUSSION, AND EXPERIMENTAL

1-Alkoxy-3-phospholene 1-oxides **1** were treated with 1.1 equivalents of lithium diisopropylamide (LDA) followed by alkylation with 1.0 equivalent of alkyl halides or (benzyloxy)methyl chloride in tetrahydrofuran (THF) at -78 ℃ to afford 2-alkyl or 2-(benzyloxy)methyl-3-phospholene 1-oxide, respectively. The alkylation proceeded stereoselectively to provide *syn* alkylated 2-methyl-3-phospholene 1-oxide, and only a little amount of *anti* isomer was obtained as the minor product. 2,5-(Dibenzyloxy)methyl-3-phospholene 1-oxide was also obtained as the minor product for the 2-(benzyloxy)methylation. These results are summarized in TABLE I.



1 2c 3 4

TABLE I Alkylation of 3-phospholene derivatives.

R of phospholene	Alkyl halide R'X		*C*-Alkylated product	
			Yield/%	Diastereomer excess/%
Me	MeI	**2a**	44	95
Me	BnBr	**2b**	69	100
i-Pr	MeI	**2c**	55	100
Me	$BnOCH_2Cl$	**2d**	61	100

1-Alkoxy-2-alkyl-3-phospholene 1-oxides were subjected to *cis*-dihydroxylation with catalytic amount of osmium(VIII) oxide in the presence of sodium chlorate at 40℃ to afford 3,4-dihydroxyphospholane 1-oxides **3** (racemate) stereoselectively. This stereoselectivity may be attributable to the steric hindrance and electro-repulsive effect between oxygen atoms of phosphoryl moiety and osmium(VIII) oxide. The structure of (1*S*, 2*R*, 3*R*, 4*S*)-2-benzyl-3,4-dihydroxy-1-methoxyphospholane 1-oxide (**3b**), namely, 1,4,5-trideoxy-4-[(*S*)-methoxyphosphinyl]-5-*C*-phenyl-D-ribofuranose, was established by assignment of all signals and analysis of coupling constants measured by 500 MHz ^{1}H-NMR (FIGURE I), The $J_{3,4}$ value of 9.7 Hz shows the C_3-H_3 and C_4-H_4 bonds are nearly in the *trans* relationship, whereas the small $J_{2,3}$ value of 3.0 Hz indicates the *cis*-relation (C_2-H_2 and C_3-H_3 bonds). The small $J_{3,P}$ value of 3.0 Hz and large $J_{2,P}$ value of 33.7 Hz reveals that the compound exists mainly in $^3T_2$

conformation (FIGURE I). Stereoselectively formed diol **3d** was hydrogenolyzed for 1 d at room temperature to afford 1,4-dideoxy-4-[(*S*)-methoxyphosphinyl]-D-ribofuranose (**4**) and its enatiomer. Structure of **4** was confirmed by ^{1}H-NMR spectroscopy of the peracetate ($^{3}T_{2}$). The structure of the acetonide of compound **4** was established by X-ray crystallographic analysis (FIGURE 2).

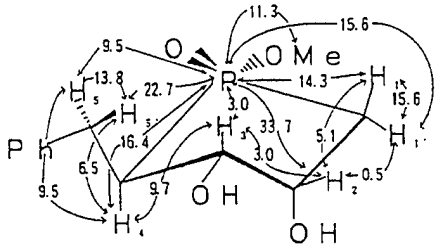


FIGURE 1 Structure of **3b**.

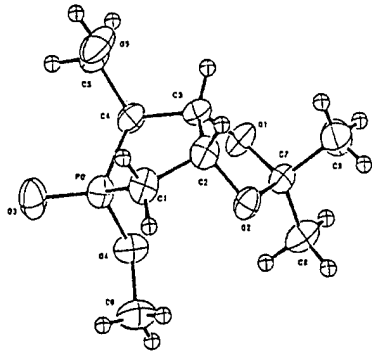
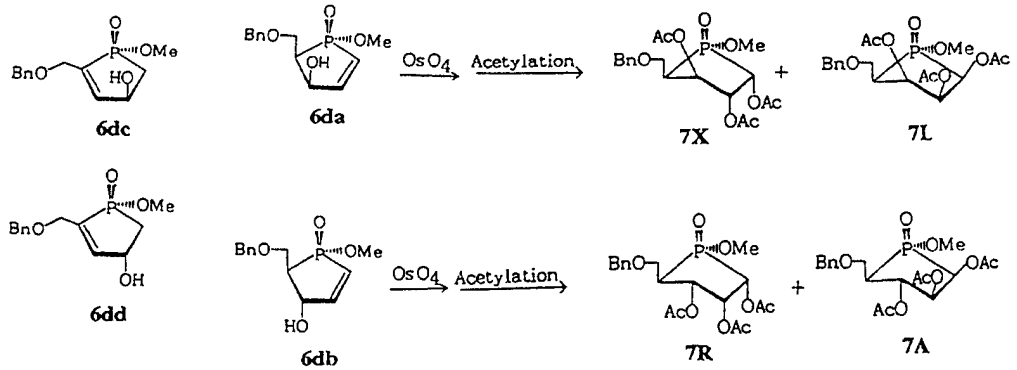


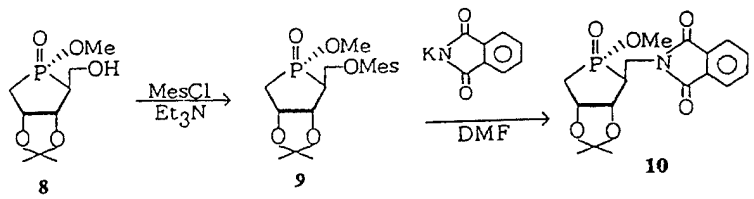
FIGURE 2 Structure of acetonide of **4**.

2-Benzyloxymethyl-1-methoxy-3-phospholene 1-oxide (**3d**) was treated with 1.7 equivalents of 3-chloroperbenzoic acid (mCPBA) in chloroform at 100°C for 2 d to afford (3*R*, 4*S*)- and (3*S*, 4*R*)-2-benzyloxymethyl-3,4-epoxyphospholane 1-oxides (**5da** and **5db**, respectively) in a quantitative yield (**5da** : **5db** = 4 : 7). Treatment of the mixture of **5da** and **5db** with triethylamine (1.0 equivalent) in ethanol at 100 °C for 2 d followed by separation by column chromatography on silica gel gave 2-phospholene derivatives **6da** (18.4%), **6db** (32.0%), **6dc**, and **6dd** (**6dc** + **6dd**, 16.8%). Osmium(VIII) oxide-catalyzed *cis*-dihydroxylation of compounds **6da** at 40 °C followed by treatment with acetic anhydride in pyridine at room temperature afforded racemic (1*R*, 2*S*, 3*R*, 4*R*, 5*R*)- and (1*R*, 2*R*, 3*S*, 4*R*, 5*R*)-2,3,4-triacetyloxy-5-benzyloxymethyl-1-methoxyphospholane 1-oxides and thier enatiomers, namely, 1,2,3-tri-*O*-acetyl-5-*O*-benzyl-4-deoxy-4-[(*R*)-methoxyphosphinyl]-α-D-xylofuranose (**7X**) and β-D-lyxofuranose (**7L**) (74 : 26; 78% total yield from **6da**). The δ values of ^{31}P-NMR in $CDCl_3$ were 51.6 and 50.3 ppm. In contrast to the result, the *cis*-dihydroxylation of acetylated compound of **6da** afforded diastereoselectively a sole product **7X** in 87% yield from **6da**. This stereoselectivity can be explained by steric and electro-repulsive effects of the oxo-substituents of the phospholene towards osmium(VIII) oxide. The same method for compound **6db** gave 1,2,3-tri-*O*-acetyl-5-*O*-benzyl-4-deoxy-4-[(*R*)-methoxyphosphinyl]-α-D-ribofuranose (**7R**, δ ^{31}P = 49.3 ppm) and -β-D-

arabinofuranose (**7A**, δ ^{31}P = 47.9 ppm) (47 : 53; 99% total yield from **6db**). The *cis*-dihydroxylation of acetylated compound of **6db** afforded products **7R** and **7A** (**7R** : **7A** = 59 : 41; **7R** + **7A** 51% yield from **6db**) upon acetylation. The four pentofuranose type phosphono sugar derivatives were first synthesized from 3-phospholenes.



Reaction of acetonide **8** with methanesulfonyl chloride in dichloromethane in the presence of triethylamine at 0 °C for 1 d afforded *O*-mesylated phosphono sugar derivative **9** (69% yield), which was further treated with potassium phthalimide in DMF at 80 °C for 8 h afforded phthalimido derivative **10** (24% yield) upon separation by thin layer chromatography on silica gel. Mitsunobu reaction of compound **8** with phthalimide (triphenylphosphine and diethyl azodicarboxylate in THF at 0°C for 2 d) gave compound **10** in 65% yield. The reaction of 1-phenyl-2-phospholene 1-oxide with bromine in protic media procceded to give bromohydrin derivative, which was further converted into triazole derivatives via 1,3-dipolar cycloaddition of azido. Some of these phosphono sugar derivatives prepared showed some biological activities.



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THIOPHOSPHATES AND SELENOPHOSPHATES IN ORGANIC SYNTHESIS. A NEW APPROACH TO EXOCYCLIC OLEFINS AND BICYCLIC ENONES.

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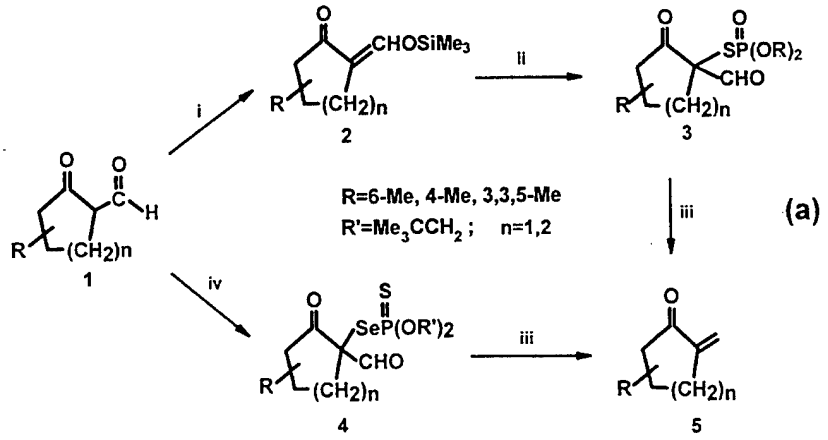
Abstract: Efficient synthesis of α-methylene-cycloalkanones, α-methylene-lactones and α-alkylidene-lactones as well as bicyclic enones were developed using thiophosphates **3**, **9**, **15** and selenophosphates **4** as key intermediates.

We have recently reported a new methodology for stereoselective conversion of carbonyl compounds into various functionalized (Z)-olefins[1] via readily available S-(2-oxoalkyl)thiophosphates,[2] S-(2-oxo-3-alkenyl)thiophosphates[3] and their seleno analogues.[4]

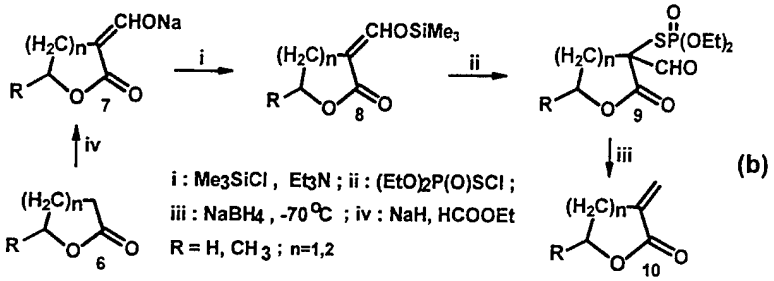
Herein we present an extention of this useful approach to the synthesis of α-methylene-cycloalkanones, α-methylene-lactones, and bicyclic enones.

α-Methylene-lactones and α-methylene-cycloalkanones are key elements of many naturally occurring sesquiterpenes or antibiotics.[5] It is not very surprising that numerous procedures have been developed for effecting α-methylenation of various carbonyl compounds.[6]

Our approaches are outlined in Scheme 1 and Scheme 2. The carbonyl compounds **1** and **7** when first O-silylated, are thiophosphorylated using $(RO)_2P(O)SCl$; this provides efficient synthesis of both new thiophosphates **3** and **9**. Selenophosphates **4** have been prepared by other protocol, the treatment of cycloalkanones **1** with $(RO)_2P(S)SeBr$ in the presence of pyridine. As expected selective reduction of the aldehyde function of phosphates **3**, **4** and **9** using $NaBH_4$ proceeded smoothly to give α-methylene-cycloalkanones **5**, α-methylene-γ-lactones and α-methylene δ-lactones **10**.

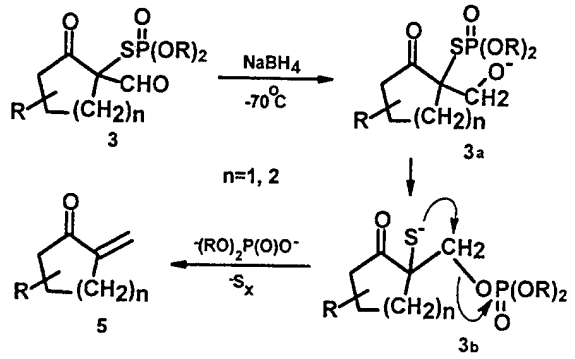


i : Me_3SiCl , Et_3N ; ii : $(EtO)_2P(O)SCl$; iii : $NaBH_4$, -70 °C ; iv: $(R'O)_2P(S)SeBr$, Py



Scheme 1

The transformation of the thiophosphates **3**, **4** and **9** into cycloalkenones **5** and lactones **10** is exemplified in Scheme 2.

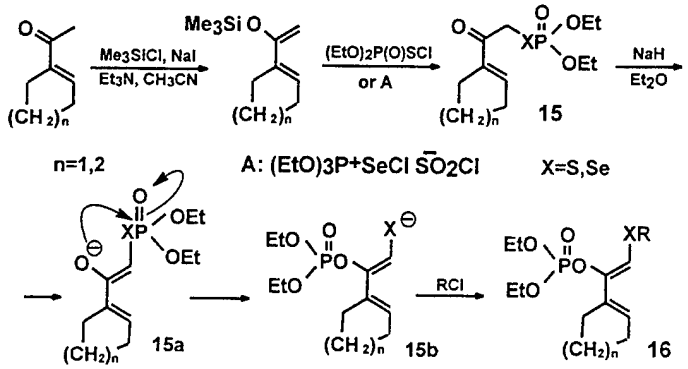


Scheme 2

The reaction of the thiophosphate **3** with sodium borohydride results in the formation of the oxyanions **3a**. The intermediates **3a** undergo rearrangement involving migration of a phosphoryl group from sulfur to oxygen affording thiolate anions **3b**. Subsequent cyclization of **3b** with the elimination of phosphate anion, and spontaneous desulfurization of resulting episulfide afford α-methylene-cycloalkanones **5**.

It is noteworthy, that all syntheses presented above can be performed as a 'one pot reaction'. The simple protocol, efficiency and mild conditions make the reactions described here attractive alternatives to known for the α-methylenation.

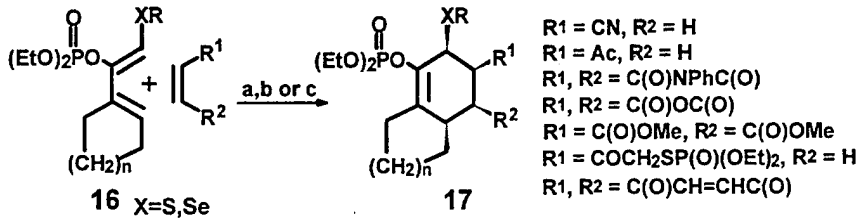
We have been also successful in the synthesis of dienes **16** containing both alkylthio (acylthio, dialkoxyphosphorylthio or diphenoxyphosphorylthio) and diethoxyphosphoryloxy substituents from readily available thiophosphates **15** (Scheme 3).



Scheme 3

Treatment of thiophosphates **15** with NaH affords enolate anions **15a** which undergo rearrangement to thiolates **15b**. The latter react with a number of electrophiles producing desired dienes **16** in good yield.

Cycloaddition of these new dienes **16** to a variety of dienophiles either in toluene solution at reflux or under Lewis acid catalysis produce the corresponding adducts in good yield. All the cycloadditions studied proceed with complete regio- and (endo)-stereoselectivity. In every case the functional group of dienophile is oriented 'orto' to the sulfide group of the diene. Here, the regiochemistry of cycloaddition is controlled by the sulfur substituent. Analogous regiocontrol by phenylthio group has been observed in the Diels-Alder reaction of several alkoxy- and acyloxy-phenylthiobutadienes.[7] The structure and configuration of the adducts **17** (see Scheme 4) were determined on the basis of ^{1}H (including COSY experiments), ^{13}C, ^{31}P, IR and high resolution MS data.



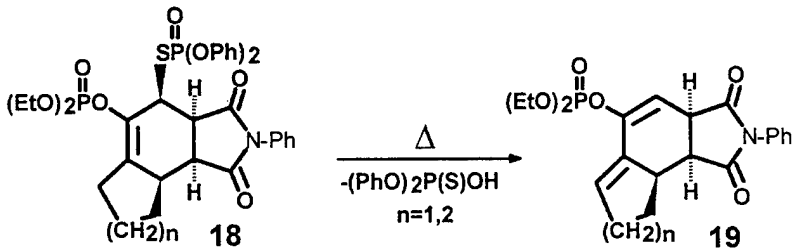
Conditions: a: 100°C, toluene b: 70°C, ZnBr2, toluene c: from -78°C to 0°C, EtAlCl2,CH2Cl2

Scheme 4

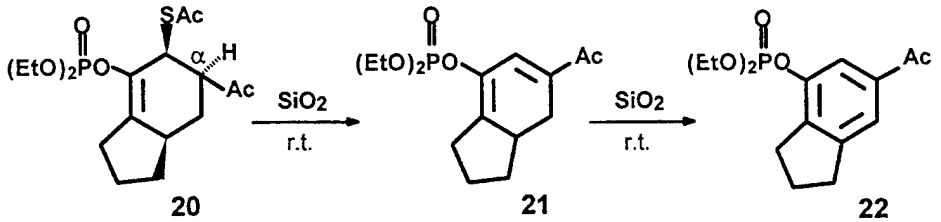
The synthetic utilities of this new annelating procedure are manifold:

1. The sulfur substituent of adducts **17** can be easily removed. We have made two interesting and useful observations:

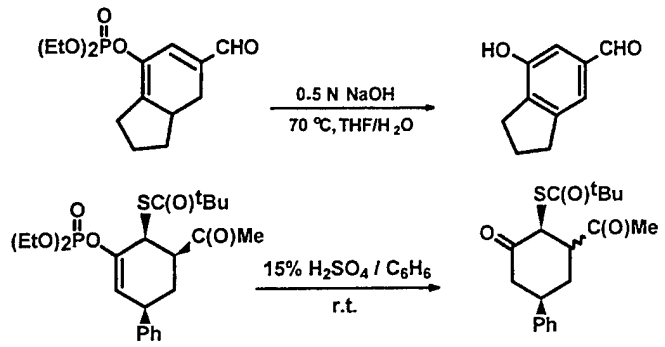
a) Adducts **18** containing an excellent leaving group like $(PhO)_2P(O)S$ undergo spontaneous elimination under conditions of cycloaddition to produce the new 1,3-dienes **19**.



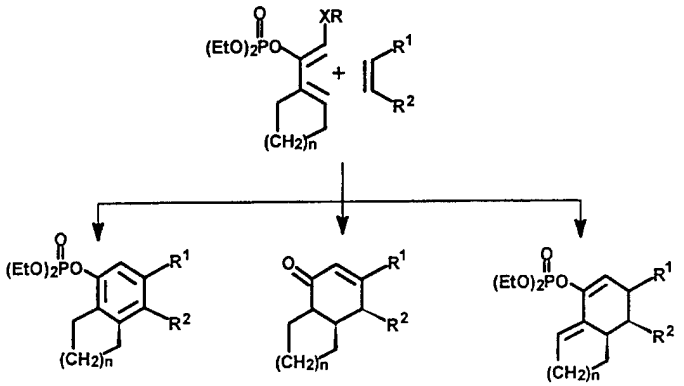
b) An efficient way to catalyzed elimination of sulfur substituent is to deposit the adducts in 5:1 CCl_4/ethyl acetate solution on silica gel at r.t. overnight, but after a further 12 h the 1,3-dienes **21** aromatize to **22**.



2. The diethoxyphosphoryloxy group can be removed by the action of NH_4F or alternatively by basic or acid catalyzed hydrolysis.[8]



3. The regiochemistry observed here complements the regiochemistry obtained with 2-alkoxyphosphoryloxy dienes.[8]
4. We have demonstrated that Diels-Alder additions of dienes **16** to dienophiles can be used as convenient route to bicyclic enones, enol phosphates and aromatic phosphates. The reaction course depends on the substituents in the diene and dienophile as well as the reaction conditions.



Acknowledgment. The financial support of this work from the Polish State Committee for Scientific Research (KBN) under Grants No 2 1325 9101 and 2 2668 9203 is gratefully acknowledged.

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REACTIVITY OF THE ACIDS OF TRIVALENT PHOSPHORUS AND THEIR DERIVATIVES. PART V. INVESTIGATION OF THE MECHANISM OF THE REACTION OF THE >P-O$^-$ NUCLEOPHILES WITH THE C-Br BOND.

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Abstract. The anions of the type >P-O$^-$ are of special interest; they are nucleophilic ambident reagents, strong bases and single electron donors. The mechanism of the reductive debromination in the course of the reaction of the P-O$^-$ ions with activated alkyl bromides has been investigated. The results of the carried out experiments suggest that the X-philic substitution is the first step in this reaction. The SET process is also being discussed.

Key Words: C-Br bond, dialkyl phosphite ions, Michaelis - Becker reaction, X-philic substitution, SET.

The Michaelis - Becker Reaction has been known for quite some time. The mechanism of this reaction, often assumed to be S_N2 involving the nucleophilic phosphorus atom, is not established with certainty. In the literature one can find some examples of an *unusual* course of this reaction. An analysis of the literature leads to several important observations. Dialkyl phosphite anions give only with primary alkyl halides a satisfactory yield of the Michaelis - Becker reaction. The reaction between bromotriphenylmethane and sodium diethyl phosphite was claimed to be a free radical process. For the synthesis of α-phosphonocarboxylates the Michaelis- Arbuzov reaction is the method of choice. We have shown recently [1] that the anions of the type >P-O$^-$ as well as >P-S$^-$ undergo reaction with α -bromocarboxylates and - phosphonates yielding debrominated products. We found also that generally for this reductive debromination the electron-withdrawing group bound to the carbon bearing the bromine atom is indispensable.



X: O; S
Y: COOR, $P(O)OR)_2$; $CONH_2$; CN

The results of our investigations show that in the case of the carbon bromine bond also the bromine atom can be a target for a nucleophilic attack by the phosphorus reagent of the type >P-O$^-$ as well as >P-S$^-$ with the release of the carbon anion as a nucleofuge, stabilised by an electron-withdrawing group (neighbouring group participation). We have to consider that the so-called *positive* bromine can also develop through SET; the radical chain mechanism or cage process. In order to provide evidence for the SET mechanism operating in reductive debromination we designed a set of experiments. We did not find any light influence on the course of the reaction in focus. In the reaction of a bromocyclopropyl system with the >P-O$^-$ ions we never observed any cyclopropyl radical - allyl radical rearrangement products, which was the case in the reaction of methyl 1-bromocyclopropylcarboxylate with tributyltin hydride.

The reaction of methyl α-bromocarboxylates with the >P-O$^-$ nucleophiles in methanol-O-d produces: methyl α-deuteriocarboxylates and methyl phosphates.
Finally we isolated the bromothiophosphate from the reaction mixture of methyl 1-bromocyclopropanecarboxylate and >P-S$^-$ nucleophile .

The absence of a significant effect of light as well as of dicyclohexylphosphine on the rates of the reaction under investigation as well as the deuterium incorporation into the product permits the exclusion of a chain mechanism of the $S_{RN}1$ type for these substrates.

Benzylphosphonates, on the other hand, with a wide range of substituents in the benzyl ring as well as phosphonomethyl pyridines are available in the Michaelis - Becker reaction. The exceptions are nitro derivatives; there is a reported failure of an attempted direct preparation of p-nitrobenzylphosphonate from p-nitrobenzyl bromide and trialkyl phosphites as well as the salts of dialkyl phosphites [2]. It was showed also that tetraphenylethane was isolated from the reaction mixture of bromodiphenyl-methane and sodium diethyl phosphite. [3]

Additionally, G. A. Russell [4] reported that dialkyl phosphite or thiophosphite anions react with p-nitrobenzyl chloride, and α,α-dimethyl-p-nitrobenzyl chloride to form p-nitrobenzylphosphonates or thiophosphonates. He claimed that this reaction proceeds at least partially by the $S_{RN}1$ scheme.

Recently we have shown [5] that the treatment of 1 equiv of p-nitrobenzyl bromide with 1 equiv of the >P-O$^-$ produces one major product; namely 1,2-di(p-nitrophenyl)ethane.

$$p\text{-}NO_2\text{-}C_6H_4\text{-}CH_2\text{-}Br \xrightarrow[\text{THF or i-PrOH}]{>P\text{-}O^-} p\text{-}NO_2\text{-}C_6H_4\text{-}CH_2\text{-}CH_2\text{-}C_6H_4\text{-}NO_2\text{-}p$$

The ion of the type >P-O$^-$ could a priori react with p-nitrobenzyl bromide either by an attack on the bromine atom, X-philic substitution (pathway A) or through SET; the radical chain mechanism or cage process with the >P-O$^-$ ion as a single electron donor (pathway B) or the p-nitrobenzyl anion as a single electron donor (pathway C).

Pathway A:

$$p\text{-}NO_2\text{-}C_6H_4\text{-}CH_2\text{-}Br + {}^-O\text{-}P< \longrightarrow p\text{-}NO_2\text{-}C_6H_4\text{-}CH_2^- + Br\text{-}\overset{O}{\overset{\|}{P}}<$$

$$p\text{-}NO_2\text{-}C_6H_4\text{-}CH_2^- + Br\text{-}CH_2\text{-}C_6H_4\text{-}NO_2\text{-}p \longrightarrow p\text{-}NO_2\text{-}C_6H_4CH_2CH_2\text{-}C_6H_4\text{-}NO_2\text{-}p$$

Pathway B:

$$p\text{-}NO_2\text{-}C_6H_4\text{-}CH_2\text{-}Br + {}^{-}O\text{-}P< \longrightarrow [\,p\text{-}NO_2\text{-}C_6H_4\text{-}CH_2\text{-}Br\,]^{\cdot -} + O{=}\dot{P}<$$

$$[\,p\text{-}NO_2\text{-}C_6H_4\text{-}CH_2\text{-}Br\,]^{\cdot -} \longrightarrow p\text{-}NO_2\text{-}C_6H_4\text{-}CH_2^{\bullet} + Br^{-}$$

$$2\ p\text{-}NO_2\text{-}C_6H_4\text{-}CH_2^{\bullet} \longrightarrow p\text{-}NO_2\text{-}C_6H_4\text{-}CH_2CH_2\text{-}C_6H_4\text{-}NO_2\text{-}p$$

Pathway C:

$$p\text{-}NO_2\text{-}C_6H_4\text{-}CH_2\text{-}Br + {}^{-}O\text{-}P< \longrightarrow p\text{-}NO_2\text{-}C_6H_4\text{-}CH_2^{-} + Br\text{-}\overset{O}{\overset{\|}{P}}<$$

$$p\text{-}NO_2\text{-}C_6H_4\text{-}CH_2^{-} + p\text{-}NO_2\text{-}C_6H_4\text{-}CH_2\text{-}Br$$

$$\downarrow \quad \text{SET}$$

$$p\text{-}NO_2\text{-}C_6H_4\text{-}CH_2^{\bullet} + [\,p\text{-}NO_2\text{-}C_6H_4\text{-}CH_2\text{-}Br\,]^{\cdot -}$$

$$[\,p\text{-}NO_2\text{-}C_6H_4\text{-}CH_2\text{-}Br\,]^{\cdot -} \longrightarrow p\text{-}NO_2\text{-}C_6H_4\text{-}CH_2^{\bullet} + Br^{-}$$

$$p\text{-}NO_2\text{-}C_6H_4\text{-}CH_2^{\bullet} + {}^{-}CH_2\text{-}C_6H_4\text{-}NO_2\text{-}p \longrightarrow [\,p\text{-}NO_2\text{-}C_6H_4CH_2CH_2\text{-}C_6H_4\text{-}NO_2\text{-}p\,]^{\cdot -}$$

$$\xrightarrow{-\,1e} p\text{-}NO_2\text{-}C_6H_4\text{-}CH_2CH_2\text{-}C_6H_4\text{-}NO_2\text{-}p$$

The major difference between these three pathways is that in pathway A and C the p-nitrobenzyl anion as an intermediate is proposed, whereas in pathway B the p-nitrobenzyl radical; and additionally in pathway B >P-O$^-$ acts as a single electron donor.

We decided to run the reaction in THF with 1 equiv of o-, m-, and p-nitrobenzyl bromides and sodium diisopropylphosphite under a variety of conditions; in darkness, day light and irradiation with 500 W bulb. From the reaction mixture in the case of o-, and p-nitrobenzyl bromide in this set of experiments we isolated mainly a dimer as a major product and the starting material. In the case of m-nitrobenzyl bromide we isolated from the reaction mixture diisopropyl m-nitrobenzylphosphonate, a dimer and a small amount of m-nitrotoluene.

We found a substantial influence of light on the yield of the isolated dimer. The yield of diisopropyl m-nitrobenzylphosphonate was not affected by the illumination of the reaction mixture by light.

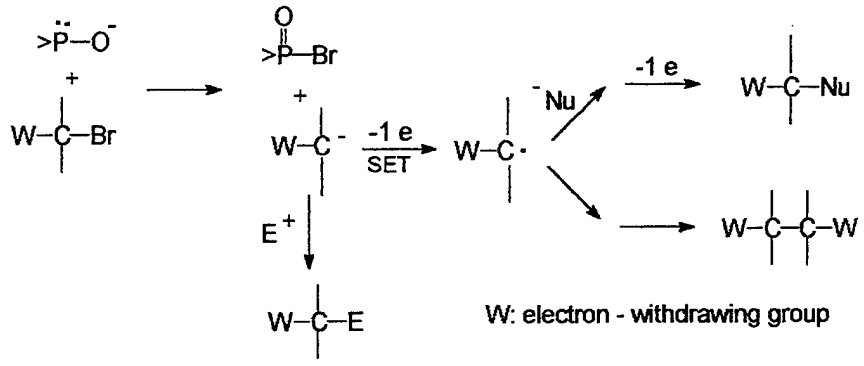
The results of these experiments strongly suggest that the SET process operates in the case of the dimer formation. On the other hand the UV investigation as well as the isolation of nitrotoluene from the reaction mixture carried out in alcohol as solvent speak for the nitrobenzyl anion as an intermediate in the investigated reaction.

Dialkyl phosphite ions are known to be radical traps [6]. We decided to run the set of experiments with the different ratio of p-nitrobenzyl bromide to sodium diisopropylphosphite. We found that increasing the amount of the dialkyl phosphite ion in the reaction mixture causes a higher yield of the benzylphosphonate production. From the reaction mixture of 10 equivs of sodium diisopropylphosphite and 1 equiv of p-nitrobenzyl bromide we isolated diisopropyl p-nitrobenzylphosphonate as a major product.

The deuterium incorporation into the methyl group of p-nitrotoluene [5] as well as the UV experiment speak strongly for the carbanion and against the free radical as an intermediate in the reaction in focus. Additionally, the isolation of methyl dibenzylphosphinate from the reaction mixture of p-nitrobenzyl bromide and dibenzylphosphine oxide in methanol [5] is in agreement with the X-philic substitution. On the other hand on the basis of the results of the crossover experiment as well as on the basis of the light influence on the dimer formation, pathway A can be excluded and the SET mechanism (pathway C) is the most plausible one.

In order to check our postulate of this mechanism as well as to check the scope and limitations of this type of reactivity of >P-O$^-$ ions, we decided to study other benzyl systems possessing electron withdrawing groups in the phenyl ring with a different redox potential. We were able to show that the dimer or reduction product formation depends on the redox potential of the bromoderivatives.

The results of our study explain a failure of an attempted direct preparation of phosphonates as well as phosphine oxides from bromoderivatives possessing electron-withdrawing groups as starting materials in the Michaelis - Becker reaction. Moreover, we are able to present a much more complete picture of the >P-O$^-$ ion reactivity towards the C-Br bond.



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P(III)-AMINES AS PHOSPHORYLATING AGENTS FOR ALCOHOLS AND AMINES. MODERN ASPECT OF THE PROBLEM.

MIKHAIL K. GRATCHEV

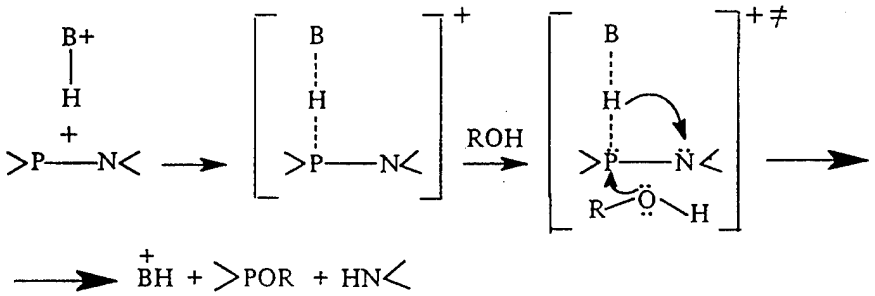
Moscow Pedagogical State University, 1 M. Pirogovskaya, Moscow 119882, Russia.

Abstract The factors governing the reactivity of P(III)-amines towards protonodonor nucleophiles are discussed. The last data on mechanism of acid catalysis, intramolecular catalysis and possibility of stereoselective phosphorylation by phosphoroamidites are represented.

Previously we have found that alcoholysis of phosphoroamidates in the presence of amines hydrochlorides occures according to **general acid catalysis**.

$$>\text{P-NEtPh} + \text{MeOH(t-BuOH)} \xrightarrow{\overset{+-}{\text{HBCl}}} >\text{P-OMe(-OBu-t)} + \text{HNEtPh}$$

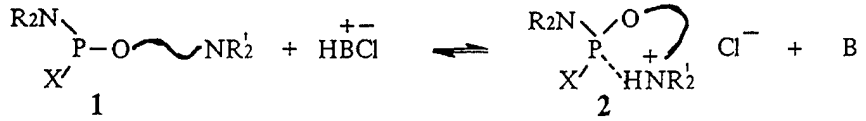
With using of Brønsted equation it was shown that catalytic process proceeds via the formation of the catalytic hydrogen-bonded complex incorporating the substrate and the catalyst as a whole:[1]



Further investigation of completely protonated phosphoroamidites allowed to discover that the presence of the bases in the reaction mixture and their tendency to the

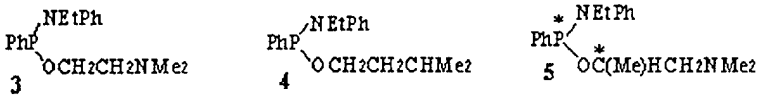
prototropic processes have decisive meaning to the reactivity of phosphoroamidites.The obtained data testify that in the catalytic H-complex proton fulfills two functions: firstly, it activates the phosphorus atom in the electrophilic reaction, for example with an alcohol, and secondly, during the reaction proton migrates from the phosphorus to the nitrogen atom, thereby assisting the breakage of the P-N bond.[2]

This observation was the basis for our investigation of possible asymmetric induction resulting from the interaction of racemic P(III)-amine with optically active alcohols in the presence of optically active amine hydrochlorides. The stereoselectivity of the reaction we studied revealed only small enrichment and did not exceed 10% d.e., apparently as a result of a weak association of phosphoproamidite and a catalyst in the catalytic H-complex.[3] Taking this fact into consideration, we undertook the task of creating phosphorylation by means of a new type of aminoalkylphosphoroamidite of form **1**. This novel molecular design was based upon the idea that compounds of this structure should be protonated by amine(B) salts and form chelates with strong intramolecular bonds **2** thus creating the high effective catalyst concentration at the reaction center.



1 **2**

It was supposed that such hydrogen bonds will conformationally stabilize the reaction center and activate it for phosphorylation. If, in our system, chiral fragments were incorporated into **2**, favorable conditions for stereoselectivity during phosphorylation might ensue. Phosphonite **3**, which under protonation may form a stable 6-membered cycle, and its analog **4** in which the dimethylamino group is substituted for the isosteric isopropyl group, were chosen for nitial studies.[4]



3 **4** **5**

The comparing methanolysis rates of racemic phosphonites **3** and **4** in the presence of amines hydrochlorides, which are essentially different in basicity, revealed that alcoholysis of phosphonite **3** *occures 300 times faster* than that of phosphonite **4**, although kinetic studies showed no dependence on acidity of catalysts in the rate of **3**. Comparison

of these rates allowed to conclude that effective **intramolecular catalysis** does occur during methanolysis of phosphonite **3** in the presence of an acid catalyst.

This novel intramolecular catalysis was used for increasing the stereoselectivity of phosphorylation. Phosphonite **5**, containing a second chiral center exactly in the "catalytic" part of the molecule, was investigated for stereoselective phosphorylation of optically active alcohols: sugar derivatives and quinine. During phosphorylation the maximum stereoselectivity equaled to 75% d.e. has been reached.[4] This result is considerably higher when only optically active phosphorylation catayst was used (as mentioned above[3]).

Acid catalysed stereospecific phosphorylation may have some practical applications in organic synthesis. The enrichment of racemic mixtures of alcohols turned out to be possible provided that the P(III)-amine contains an optically active fragment in the "catalytic" part of the molecule. The principal distinction of the proposed separation scheme from the standard ones based upon the usage of optically active reagents, consists in using of an intramolecular catalysis for ensuring of effective contact of reagents at the reaction center, containing an optically active residue. And this effect may be reinforced due to bulky chiral matrix, including effects of "guest - host" type.

For the realisation of this approach the effective methods of phosphorylation of complex natural compounds with specifically orientated in space hydroxyl groups, namely dianhydro-D-mannitol, -D-sorbitol, cyclodextrines, cellulose and chitozane have been elaborated by us. We studied factors having an influence upon the effectivity and direction of phosphorylation of indicated systems. The main difficulty, because of effective hydrogen bonds, consisted in competitive bis- and cyclophosphorylation closed in space hydroxyl groups. The phosphoro(III)azoles turned out to be the best phosphorylation means, which reduced to minimum the undesirable cyclophosphorylation.With using of phosphoro(III)azoles we obtained phosphorylated derivatives of cellulose and chitozane with high content of bonded phosphorus in their macromolecules. On the base of these phosphorylated macromolecules we have got complexes with rhodium and platinum. These complexes turned out to be very effective catalysts for hydrogenation of some unsaturated organic compounds with high stereoselectivity.[5] It is especially expected that chiral cavity of cyclodextrines will be an effective asymmetric inductor during phosphorylation. Additionally, they are of interest as chiral framework ligands for

coordination chemistry, metallocomplex catalysis and as valuable reagents for supramolecular and biomimetic chemistry.

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PHOSPHITE ADDITION TO CARBONYL GROUP AND PHOSPHORYL MIGRATION UNDER PHASE TRANSFER CATALYTIC CIRCUMSTANCES

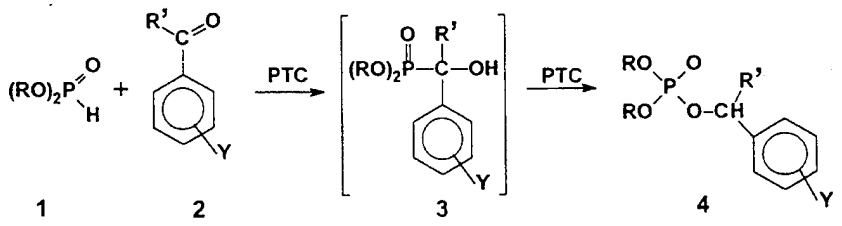
IMRE PETNEHÁZY, ZSUZSA M. JÁSZAY, LÁSZLÓ TŐKE
Dep. of Organic Chemical Technology, Technical University of Budapest,
H-1521 Budapest, Hungary

Abstract The rearrangement of α-hydroxyphosphonates to phosphates under PTC conditions usually run in a different way and gives better yield as that found in homogenous system.

The phase transfer catalysis is defined as a two phase reaction between the reagents which are in solid or aqueous phase and substrates in organic solvents in the presence of so called phase transfer catalyst. α-Hydroxyphosphonates can rearrange by a C→O phosphoryl migration resulting in the formation of phosphates.

Synthesis of phosphoric acid esters from aldehydes and ketones

According to the literature α-hydroxyphosphonates (**3**) can be prepared by the addition reaction of dialkyl phosphites (**1**) to aldehydes or ketones (**2**). In homogenous phase the reaction needs sodium alcoholate catalyst[1] and the yield are generally low because of the side reactions. These side reactions can be eliminated by performing the addition reaction on the surface of alumina[2]. This system gives good yield only in the case of aldehydes. Improving the surface by caesium fluoride[3] ketones also provide α-hydroxyphosphonates.



PTC: solid/liquid K_2CO_3 / aprotic solvent, QX or crown ether, 50-70°C
liquid/liquid aprotic solvent / 50% NaOH, QX, 20°C

R: Me, Et, iPr Y: Cl, diCl, H, NO_2 R': H, Me

Using potassium carbonate as a base in solid-liquid PTC circumstances at room temperature we succeeded in isolating α-hydroxyphosphonates which couldn't be prepared by any of the known methods, but at higher temperature the rearrangement of α-hydroxyphosphonate to mixed phosphate ester (**4**) was observed .

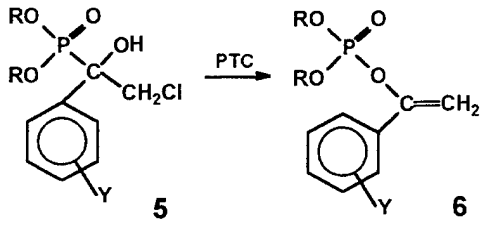
There is a relationship between the yield of the phosphate and the substituent of the aromatic ring; reaction with more electron withdrawing substituent gives higher yield in solid-liquid PTC circumstances. Though in some cases the liquid-liquid PTC reaction provides the product in excellent yield.

This procedure of ours is a new one pot method for the preparation of the mixed phosphate esters from dialkyl phosphites and oxo compounds. Numerous mixed esters have been prepared in this way. The procedure seems to be superior to those described in the literature since they acylate an alcohol by phosphorus diester chloride, and mixed ester so obtained is strongly contaminated because of the side reactions.

Synthesis of vinyl phosphates from α-chloromethyl-α-hydroxyphosphonic acid esters

The reaction is known from the literature in homogenous phase in the presence of sodium alcoholate producing two types of products[4], vinyl phosphate (**6**) and phosphonooxirane (**8**).

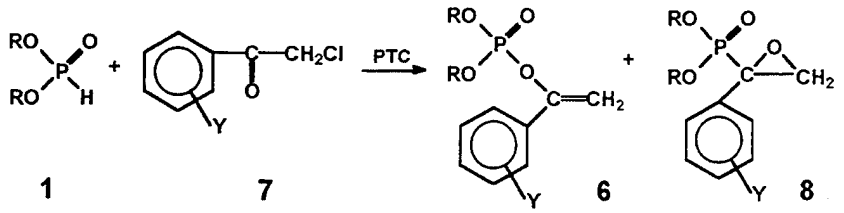
In a two phase reaction the rearrangement of the α-chloromethyl-α-hydroxyphosphonate (**5**) was formed selectively; the only product is the vinyl phosphate which can be prepared in good yield.



PTC: K_2CO_3 / benzene, QX, 70°C R: Me, Et, iPr Y: Me, H, Cl

The relative values of yields show that the increasing bulkiness of the phosphoryl group retards the rearrangement. Namely, in case of isopropyl group the yield is lower than in case of the smaller ethyl or methyl group.

Using the same one pot method which was used for the preparation of mixed esters in the reaction of the chloroacetophenone (**7**) with dialkyl phosphite both vinyl phosphate (**6**) and phosphonooxirane (**8**) were formed in comparable ratio.



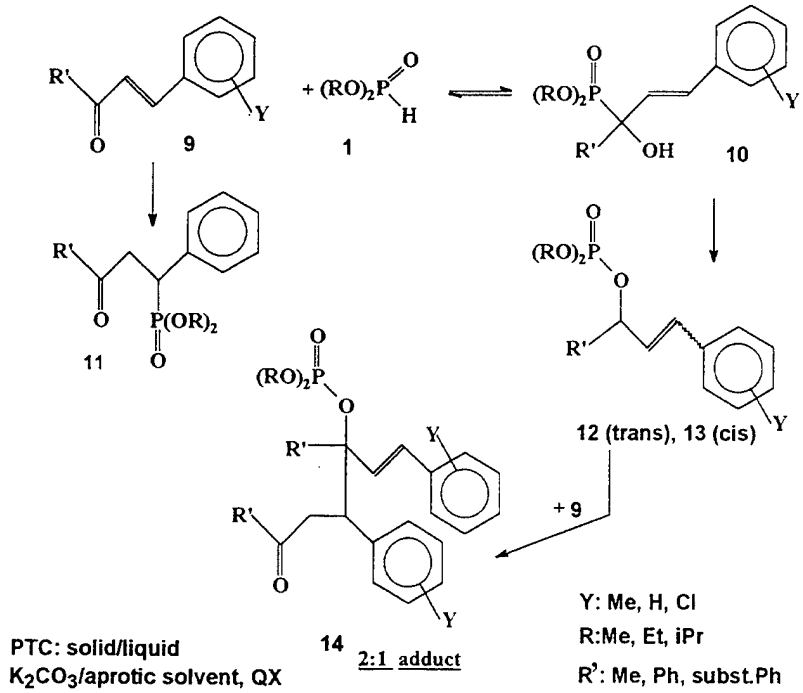
The ratio of the products shows again that the migration of the bulky phosphoryl group is hindered. In case of isopropyl group the yield of phosponooxirane (**8**) is more than three times as high as that of vinyl phosphate (**6**).

This phenomenon may be due to the difference in binding strength of the substrates **1** and **5** to the surface of the potassium carbonate.

Reactions of enones with dialkyl phosphites

In the reaction of dialkyl phosphites (**1**) with α,β-unsaturated oxo compounds (**9**) in the presence of a base in protic solvent the products are α-hydroxy-allyl-phosphonate (**10**), γ-ketophosphonate (**11**) and several diphosphonates (1:2 adduct), the letters can be formed in the reaction of γ-ketophosphonate (**11**) with an other molecule of dialkyl phosphite[5,6].

We have investigated the reaction of a series of dialkyl phosphites with α,β-unsaturated oxo compounds under solid-liquid PTC conditions.



Here, beside the three types of products, namely α-hydroxy-allyl-phosphonate (**10**), γ-ketophosphonate (**11**) and phosphoric acid allylic esters (**12** and **13**) a further product (**14**) was also isolated in crystalline form from the reaction mixture, and identified as **14**.

The ratio of the phosphates (**12**+**13**+**14**) to γ-ketophosphonate (**11**) was unchanged during the reaction, which may be explained by supposing the paralell formation of the γ-ketophosphonate and the phosphates as shown in the Scheme.

The ratio of the products depends on the substituent on the phenyl ring and on the alkyl moiety of the phosphite. In the case of electron withdrawing substituent the ratio of phosphates to γ-ketophosphonate is higher while in case of electron donating substituent it is lower than that of the unsubstituted compound. With increase of the bulkiness of phosphite moiety the ratio of the phosphate becomes lower, namely the rearrangement is restricted similarly to the rearrangement mentioned in the previous chapter. Temperature also influences the ratio of the products, high temperature favours the formation of γ-ketophosphonate.

We assume that the allylic esters (**12** and **13**) are formed on the surface of the potassium carbonate by a phosphoryl migration from the deprotonated form of α-hydroxy-allyl-phosphonate (**10**). For the formation of **14** we assumed an addition of the anion from **12** to the β-position of enone and subsequent protonation of the adduct so formed.

The differences observed in the structure of the final products in homogenous phase and in PTC conditions may be due to the solid surface of the potassium carbonate, which serves not only as a base but decreases the probability of the attack of a second phosphite to the anion of α-hydroxyphosphonate formed and kept on the surface.

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DIRECTED SYNTHESIS OF PHOSPHORUS-CARBON CAGE COMPOUNDS — A CHALLENGE IN ORGANOPHOSPHORUS CHEMISTRY [1]

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Fachbereich Chemie der Universität Kaiserslautern, Erwin-Schrödinger-Strasse, D-67663 Kaiserslautern, Germany

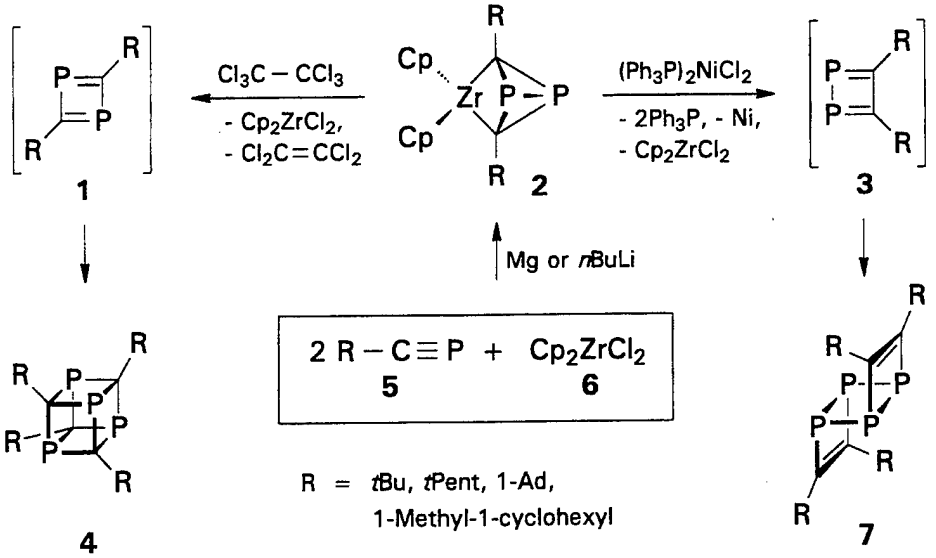
Abstract Reactions of the zirconium complexes **2** with hexachloroethane lead to the tetraphosphacubanes **4** whereas extrusion of the Cp_2Zr units by means of $(Ph_3P)_2NiCl_2$ gives rise to the tetraphosphacyclooctadienes **7**. Polycyclic phosphorus-carbon systems such as **11** or **14** and **13** are accessible from multi-step reactions of the phosphaalkyne **5** (R = *t*-Bu) with dienes **9** or tropone (**10**), respectively. The complex **16** obtained from the spirocyclotrimerization of the phosphaalkyne **5** (R = *t*-Bu) with aluminum trichloride provides the starting point for the construction of the bis(homo)prismane **19** and the hexaphosphapentaprismane **20**. Furthermore, the phosphorus-carbon-aluminum cage compounds **12**, **23**, and **24** have been prepared from the phosphaalkynes **5** and the triorganoaluminum reagents **22**.

INTRODUCTION

In contrast to their all-carbon or all-phosphorus analogs, phosphorus-carbon cage compounds have only become accessible in the past few years and the phosphaalkynes **5** have proved to be indispensable starting materials. Both purely thermal cyclooligomerization reactions of the latter to furnish tetraphosphacubanes and -cuneanes as well as the corresponding reactions in the presence of organometallic auxiliaries and the coupling reactions of di- and triphosphacyclopentadienides with platinum(II) species are unselective and provide merely modest yields [2]. In this communication, we present reaction strategies for the specific syntheses of phosphorus-carbon polycyclic systems in good to excellent yields.

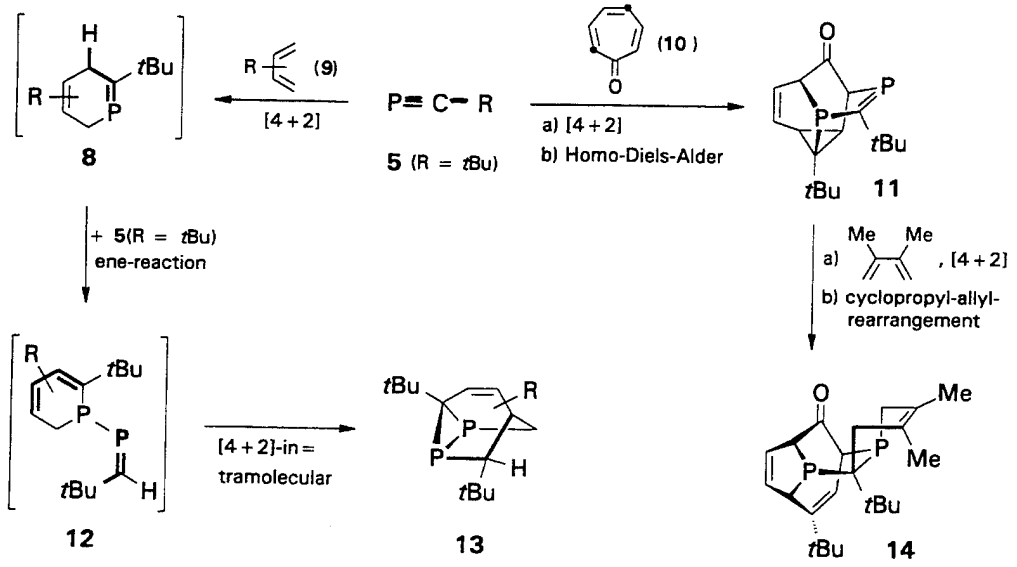
RESULTS

The specific synthesis of tetraphosphacubanes **4** starts from the zirconocene-phosphaalkyne dimer complexes **2** which, in turn, are accessible from zirconocene dichloride (**6**) and two equivalents of the phosphaalkyne **5** in the presence of magnesium or *n*-butyllithium [3].



Treatment of the complexes **2** with hexachloroethane effects removal of the zirconocene fragment to afford, after a further dimerization, the pentacyclic product **4** [3]. On the other hand, when the complexes **2** are treated with $(Ph_3P)_2NiCl_2$ instead of hexachloroethane, the tetraphosphatricyclooctadienes **7** containing a central P_4 unit are obtained. The 1,3- and 1,2-diphosphetes **1** and **3** are putative intermediates on the way to the polycyclic products [4].

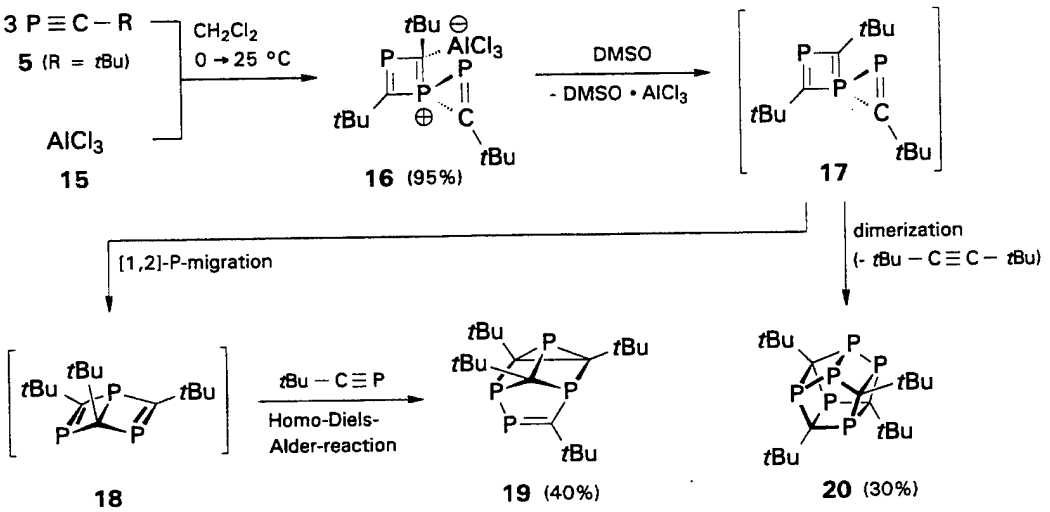
Reaction sequences initiated by Diels-Alder reactions of phosphaalkynes have opened up previously unimagined possibilities for the synthesis of phosphorus-carbon cage compounds.



Thus, reactions of the dienophile **5** (R = *t*-Bu) with variously substituted 1,3-butadienes **9** in a molar ratio of 2:1 furnish the diphosphatricyclooctenes **13** in optimum yields. The reaction mechanism involves an initial [4 + 2]-cycloaddition, an ene reaction with the second equivalent of **5** to give the cyclohexadienylphosphaalkene **12**, and spontaneous isomerization of the latter through an intramolecular Diels-Alder reaction to yield the polycyclic product [5].

With the same stoichiometry, the initial reaction of **5** (R = *t*-Bu) with tropone (**10**) affords the Diels-Alder adduct which then reacts with the second equivalent of **5** in a homo-Diels-Alder reaction to provide the diphosphatetracycloundecadienone **11** [6]. The dienophilic properties of such compounds can be exploited for the construction of further polycyclic species (e.g. **11** → **14**); in this process the cycloaddition of the 1,3-diene is followed by a sterically initiated cyclopropyl-allyl rearrangement [6].

In the presence of Lewis acids such as aluminum trichloride in a molar ratio of 1:3, the phosphaalkyne **5** (R = *t*-Bu) undergoes spirocyclotrimerization to furnish the 1-$\lambda^3\sigma^2$,3-$\lambda^4\sigma^4$-diphosphete-$AlCl_3$ adduct **16** [7].

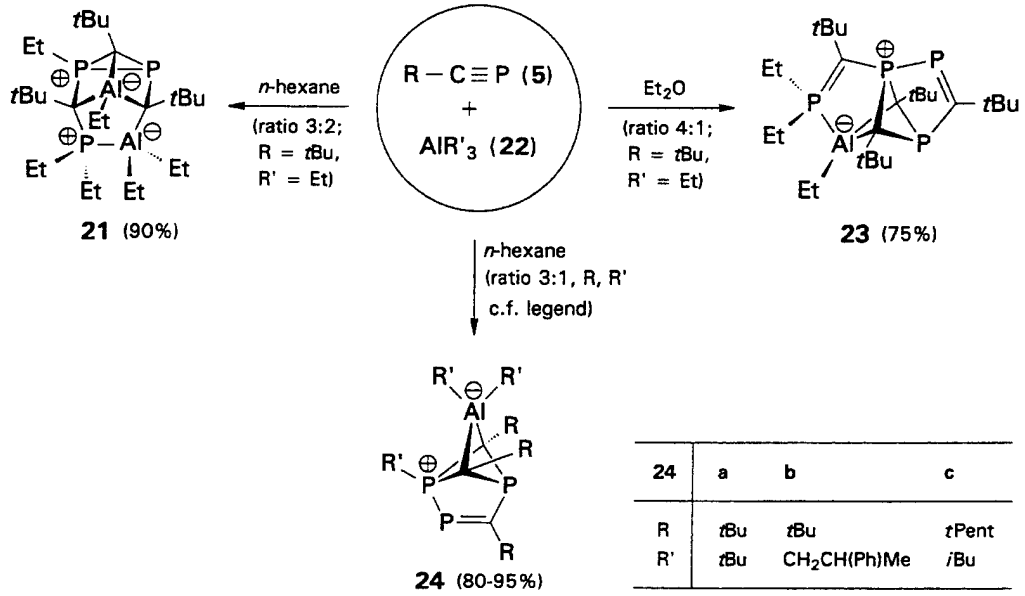


When the more energy-rich spirocyclotrimer **17** is liberated from **16** by treatment with DMSO as a Lewis base, it can only be detected by indirect methods: in dichloromethane at –45 °C rearrangement by [1,2]-P/P migration takes place to furnish the Dewar 1,3,5-triphosphabenzene **18** which, under the prevailing conditions, can only be trapped as **19** after a homo-Diels-Alder reaction with further **5** [7]. In the absence of a trapping reagent, **17** dimerizes with loss of di-*t*-butylacetylene to the hexaphosphapentaprismane **20** [8].

When phosphaalkynes are allowed to react with triorganoaluminum reagents, the latter are incorporated into the reaction products; solvent effects and the size of the substituents in the Lewis acid determine the product palette.

In the non-polar solvent *n*-hexane (molar ratio **5**:**22** = 3:2) with moderately large AlR'_3 substituents (R′ = Me, Et), the bis(homo)prismanes **21** with two-fold phosphonium-aluminate character are formed. In the more polar solvent diethyl ether (molar ratio 4:1), the tetracyclic products **23** are produced, again in high selectivity (yields in all cases ≥

75%!) [9]. Voluminous substituents at aluminum (molar ratio 3:1) result in the formation of the triphosphahomobenzvalenes **24** [10].



24	a	b	c
R	*t*Bu	*t*Bu	*t*Pent
R'	*t*Bu	$CH_2CH(Ph)Me$	*i*Bu

Acknowledgements

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4-π-ELECTRON 4-MEMBERED PHOSPHORUS HETEROCYCLES

REGIS REAU, ANTOINE BACEIREDO and GUY BERTRAND*
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Abstract The synthesis and reactivity of 4-π-electron 4-membered heterocycles possessing a phosphazene moiety is described.

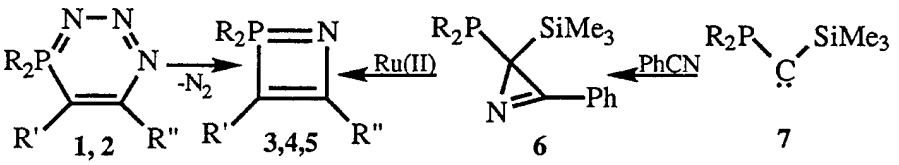
Key Words *Heterocycles, phosphazene rings, Aza-Wittig reactions, diazirines.*

INTRODUCTION

We have recently shown that the presence of only one phosphorus atom possessing no available p-orbital is sufficient to stabilize a 4-π-electron 4-membered ring[1]. Here, we report on the synthesis, structure and reactivity of such heterocycles possessing a phosphazene moiety.

SYNTHESIS

The target phosphazene rings have been obtained via ring contraction or ring expansion reactions. Extrusion of dinitrogen from 1,2,3,4λ^5-triazaphosphinine **1** and **2** occured in refluxing toluene giving 1,2λ^5-azaphosphetes **3** and **4** in 80 and 90% yield, respectively (Scheme 1)[1]. Phosphinocarbene **7**[2] reacts with benzonitrile in toluene, at room temperature, affording 3-phenyl-2,2-[bis(dicyclohexylamino)phosphino](trimethylsilyl)-2H-azirine **6** in 85% isolated yield. Interestingly, addition at room temperature of a catalytic amount of (p-cymene)ruthenium(II)chloride to a dichloromethane solution of **6**, leads to the 1,2λ^5-azaphosphete **5** in 95% yield (Scheme 1)[3a].

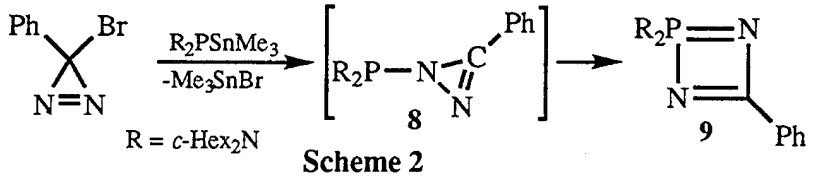


1, 3: R = *i*-Pr_2N, R' = R"= CO_2Me 5: R = *i*-Pr_2N, R' = $SiMe_3$, R"= Ph

2, 4: R = *c*-Hex_2N, R' = R" = CO_2Me 6, 7: R = *c*-Hex_2N

Scheme 1

The key step of the synthetic route used for the preparation of the 1,3,2λ^5-diazaphosphete **9** is also a ring expansion from a transient N-phosphinoisodiazirine **8**. This anti-aromatic three-membered ring **8** is transiently formed in the reaction of bromophenyldiazirine with bis(dicyclohexylamino)trimethylstannylphosphine, and spontaneously rearranges to **9** in 26 % isolated yield (Scheme 2)[4a].



R = *c*-Hex_2N

Scheme 2

CHARACTERIZATION AND STRUCTURE

Derivatives **3**, **4**, **5** and **9** exhibit some common spectroscopic data. Their ^{31}P NMR chemical shifts are around + 52 ppm (± 2 ppm) and the β carbon with respect to the phosphorus atom gives a signal at very low field in ^{13}C NMR spectra [$\underline{\delta}^{13}C$ β: +182.4 (**3**), +181.7 (**4**), +192.4 (**5**), +194.7 (**9**)]. Derivatives **3**[1a] and **9**[4b] have been characterized by X-ray diffraction studies. Both four-membered rings are nearly planar and, of particular interest, the exocyclic P-N bonds are shorter than the endocyclic ones. On the other hand, the values of the endocyclic bond lengths are halfway between those of single and double bonds. These data as a whole indicate that there is a positive charge located at the phosphorus atom and that the NCX part of the molecule can be regarded as an allylic anion. Thus, in agreement with ab initio calculations [4b], 4-π-electron 4-membered heterocycles possessing a phosphazene moiety are best described as cyclic ylides (Figure 1).

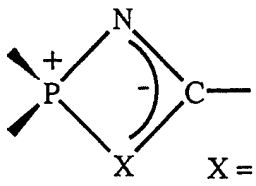
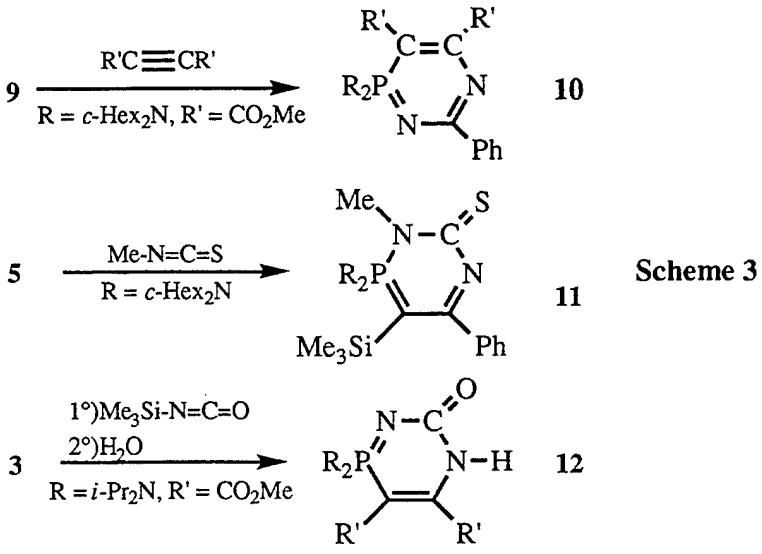


Figure 1

X = N or C-R

REACTIVITY

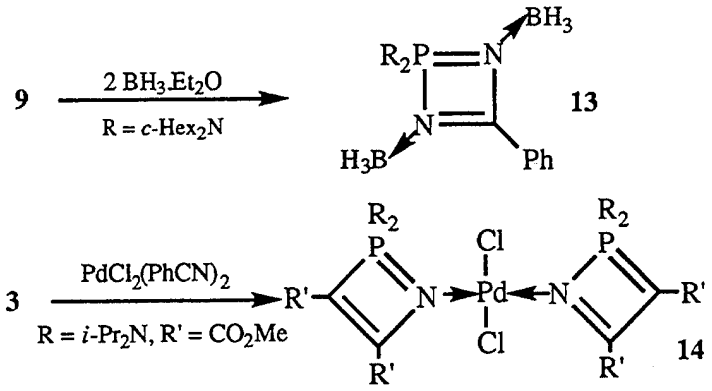
Derivatives **3**, **4**, **5** and **9** behave as aza-Wittig reagents as illustrated by the reaction involving diazaphosphete **9** and dimethyl acetylenedicarboxylate which gives rise to diazaphosphinine **10** in 70% yield[4b]. However, some unusual reactions are also observed. Phosphazenes react with isothiocyanates and isocyanates to give carbodiimides and the corresponding phosphine sulfide and oxyde, respectively[5]. In marked contrast, methyl isothiocyanate inserts into the phosphazene bond of **5** affording six-membered heterocycle **11**. In the same veine, trimethylsilyl isocyanate reacts with **3** leading, after hydrolysis, to heterocycle **12** (scheme 3)[1b]. Compound **12** exists as a hydrogen-bonded dimer in the solid state and of particular interest has a structure comparable to that of cytosine, the $C(NH_2)_2$ being replaced by a $P(NiPr_2)_2$ group.



Scheme 3

Complexation of the nitrogen atom of the phosphazene moiety occured on adding Lewis acids or transition metal fragments. Two equivalents of BH_3 react with diazaphosphete **9** leading to double adduct **13**[4b], while azaphosphete **3** reacts at room temperature with half an equivalent of $PdCl_2(PhCN)_2$ giving the bis(η^1-azaphosphete)palladium(II) complex **14** in 65% yield[1c]. From the spectroscopic data

and X-ray analyses, it appears that the 4-π-electron 4-membered ring structures are only slightly perturbated by the complexation of the ring nitrogens (scheme 4).



Scheme 4

CONCLUSION

These results demonstrate that 4-π-electron 4-membered rings featuring a phosphazene moiety are thermodynamically stable but highly reactive; they are valuable building blocks in heterocyclic chemistry and ligands for transition metal complexes.

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EFFECTS OF A STERICALLY DEMANDING P–ARYL SUBSTITUENT IN PHOSPHOLE AND 7–PHOSPHANORBORNENE CHEMISTRY

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Abstract The 2,4–di–*tert*–butyl–6–methylphenyl substituent was placed on phosphorus of a phosphole, causing restricted rotation about the P–C bond and flattening of the phosphorus pyramid. Electron delocalization was greater in this phosphole as a result of the flattening. The 7–phosphanorbornene with this substituent had the most deshielded ^{31}P nucleus ever recorded in this series, and thermally decomposed with formation of a diphosphene, suggesting a phosphinidene intermediate.

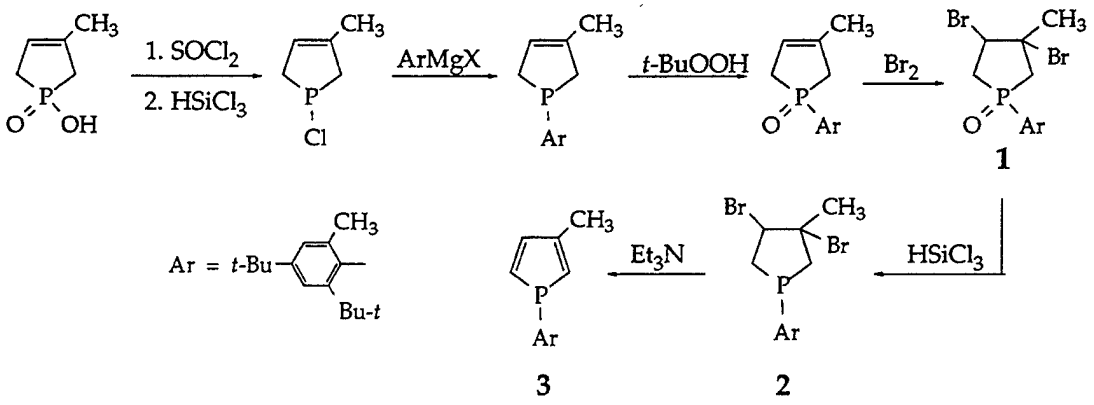
Recognizing the profound stabilization influence of sterically demanding substituents in the field of low-coordination phosphorus (and other) species, we are led to inquire about the effect of such substituents on properties of certain phosphorus heterocyclic systems where crowding can cause measurable changes in geometry and properties.

THE PHOSPHOLE SYSTEM

It is generally accepted that the phosphole ring lacks the extensive electron delocalization well-known in the S, N, O heterocyclic counterparts, largely because the P atom retains its pyramidal structure and the lone pair is prevented from efficient overlap with the π–system. From X-ray diffraction analysis,[1] it has been shown that for a simple phosphole (1–benzyl) the P–substituent is out of the phosphole ring plane by 66.9°. Theoretical studies suggest[2] that delocalization should increase as the pyramid is flattened and phosphorus shifts to sp^2 hybridization. We report here on attempts to perform the flattening experimentally, and to explore consequences of flattening on the delocalization and other properties. Molecular modeling studies have confirmed that placing a large substituent on phosphorus can indeed bring about the desired flattening effect. Thus, the angle formed between the ring plane and the P–substituent for phenyl (68.5°) decreased to 65.2° for mesityl, 63.2° and 58.0° (two conformations) for 2–*tert*–butyl–6–methylphenyl, and 55° for 2,4,6–tri–*tert*–butylphenyl. We attempted to synthesize a phosphole with the latter substituent, but the crowding

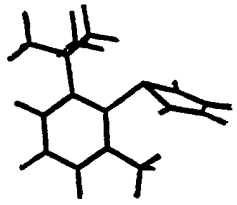
prevented the necessary reactions. Better results were obtained with the 2,4–di–*tert*–butyl–6–methylphenyl substituent (Scheme 1).

SCHEME 1

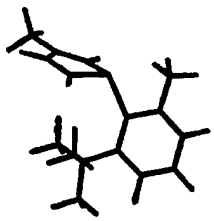


Phosphole **3** is a crystalline solid, stable in the atmosphere. Unfortunately, at this writing, the crystals have not proved entirely satisfactory for the all-important determination of molecular parameters by X-ray diffraction analysis, and this work is not complete. The ^{31}P NMR shift, recently confirmed by theoretical studies to be rather unreflective of delocalization,[2] was δ +1.8 (*cf.* to δ +7.5 for the 1–phenyl derivative).[3] The proton NMR and mass spectra were typical of phospholes and lacked any special features. More informative of increased orbital interactions was the photoelectron spectrum of the phosphole. The ionization energy of the non-bonding electrons was 0.35 eV higher than that for the corresponding tetrahydrophosphole, indicative of interaction with the π* orbital. This ionization in other phospholes is virtually the same as that of the tetrahydro counterparts.[4]

The ^{13}C NMR spectra of phospholes also reveal little about delocalization effects, but the spectrum of **3** proved to be of great interest for another reason: a marked preference for a conformation (**4**) where the two rings are orthogonal was detected, with the 2–*tert*–butyl substituent above the phosphorus pyramid and thus close to the lone pair. This places the 6–methyl on the opposite side of the lone pair. This conformation was suggested by the lack of 3-bond coupling between P and the 6-methyl carbon, as well as ring carbon 5; this coupling is controlled by the orientation of the lone pair to carbon, and can be zero if the lone pair is *anti* to the carbon. Another feature was the surprisingly large 4-bond coupling of P to the methyls of the 2–*tert*–butyl group (11.6 Hz). Molecular modeling studies have confirmed that conformation **4** is 0.8 kcal/mol lower in energy than conformation **5**, and that the ratio of the conformers **4** to **5** is about 3:1 at 25°C.



4



5

Another rotational effect arising from the large P-aryl substituent was noticed for the dibromophospholane oxide **1**. This oxide, when synthesized in the usual way by adding bromine to the 3-phospholene oxide, had a ^{31}P NMR shift that was almost unreproducible over the range δ 54 to 76, and was controlled by concentration as well as by age of the solution. The same dibromophospholane oxide when prepared by peroxide oxidation of the phosphine **2** then gave a shift of δ 49.4. Mixing the two forms having separate shifts of δ 65.6 and 49.2 gave a solution with a *single* peak, at δ 54.2. Dreiding models suggest that there are preferences for the two conformations with the rings orthogonal to minimize steric interactions. Apparently the barrier for rotation about the P–C bond is sufficient to allow observation of the two conformers, which can undergo equilibration.

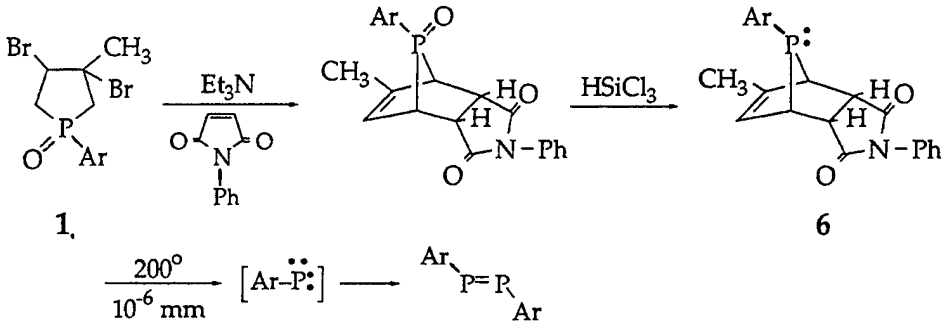
THE 7–PHOSPHANORBORNENE RING SYSTEM

This ring system is well known to abound in unusual reactivity and spectral features[5] as a result of the forced proximity of the bridging phosphorus functional group to the carbon–carbon double bond. For trivalent phosphorus, this results in extraordinary downfield shifting of the ^{31}P NMR signal. Values below δ +100 are common. A recent theoretical study[6] has shown that the deshielding is derived from a reduction in the HOMO–LUMO energy gap in the bridged system associated with the small "flap" angle relating the P group to the ring double bond. No experimental study has been made of the effect of P–substituent size on the ^{31}P shift. The availability of the dibromophospholane oxide **1** allows a synthesis of the very crowded *syn*–substituted 7–phosphanorbornene system **6** as seen in Scheme 2. This compound has the most downfield signal ever recorded for a phosphine in the 7–phosphanorbornene system, δ +153.3. Apparently, the orbital interactions controlling the size of the HOMO–LUMO gap are increased by the steric crowding of atoms in this molecule. The *anti* isomer from inversion of the configuration by treatment with methanol[7] had the most *upfield* signal (δ 0.6) ever recorded for this structural type.

Attempts in the past to produce phosphinidenes by thermolysis of 7–phosphanorbornenes have not been successful; fragmentation of the ring with loss of the P–bridge does occur, but through bimolecular reactions of the phosphines.[8] We have obtained an indication that the sterically crowded phosphine **6** may fragment by extrusion of the

phosphorus bridge as the phosphinidene. Thus, at 200°C and 10^{-6} mm, about 55% of a sample was fragmented to give as the main product the diphosphene **7**, as indicated by its ^{31}P NMR shift of δ +517.6 and its characteristic red color. The bimolecular interaction seems unlikely in this crowded molecule, and the diphosphene may be derived from the phosphinidene. Some formation of the C–H insertion product might have been expected, but none was detected.

SCHEME 2



1 **6**

7

CONCLUSIONS

It is very clear that placing very large substituents on phosphorus in both the phosphole ring and in the 7–phosphanorbornene ring system can produce important structural effects that modify the properties of these molecules. In the future, we plan to study other types of large P–substituents, with the continued goal of flattening phosphorus in the phosphole ring to an even greater extent, hopefully to the point where convincing evidence can be obtained that indeed the system can become "aromatic."

ACKNOWLEDGEMENTS

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NMR AND ESR STUDY OF PHOSPHORYLATED OXIMES AND IMINOXY RADICALS

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Abstract E,Z-isomeric forms of phosphorylated oximes were established by NMR ^{1}H, ^{13}C, ^{31}P spectroscopy. Stereospecifity of phosphorus-carbon coupling is shown to be suitable criteria for distinction of spatial isomers. The new type of phosphoniminoxy radicals was generated from these oximes and spin distribution dependencies upon phosphorus environment and spatial structure of the molecules were established.

Key words: *Phosphorylated oximes, iminoxy, structure, magnetic resonance*

INTRODUCTION

Phosphorus containing oximes and iminoxy free radicals are of great interest because of their important specific properties and biological activities. It became obvious to clarify the peculiarities of their electronic structure, the character of inter- and intra-molecular interactions in this type of organophosphorus compounds. New type of iminoxy radicals with one and two phosphorus atom to unpaired electron localization center P-C=N-O were firstly described in papers.[1,2]

RESULTS AND DISCUSSION

NMR ^{1}H, ^{31}P, ^{13}C and IR-spectroscopy studies showed that phosphorylated oximes exist in solution in the form of Z- and E-isomers, and particular isomeric forms are stabilized by intramolecular interaction.[3] The chemical shifts, spin couplings ^{1}H - ^{31}P, ^{13}C - ^{31}P as well as nuclear relaxation times of ^{1}H, ^{13}C, ^{31}P strongly depend upon geometrical factors of the molecules and phosphorus atom surrounding. Typical features of NMR ^{13}C spectrum of phosphonoxime and it parameters are shown on Figure 1. Stereospecifity of phosphorus-carbon coupling in NMR spectra is clear to be a suitable criteria for distinction of spatial isomers of phosphorylated oximes.

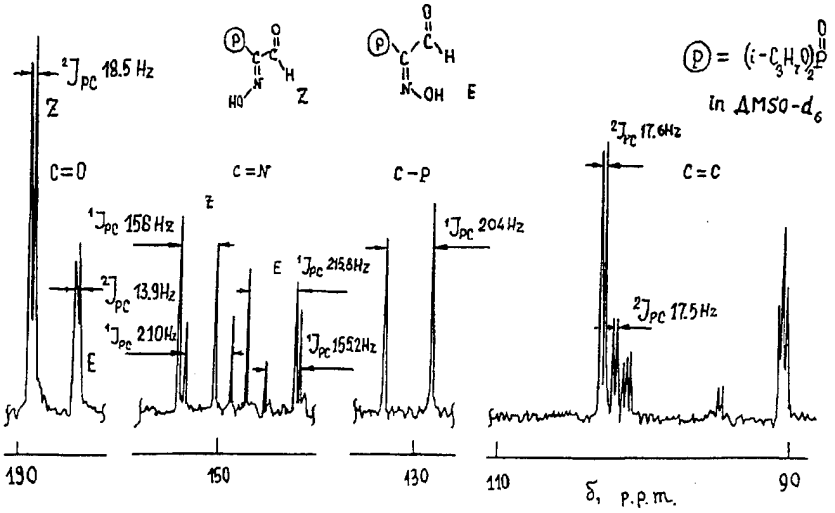


FIGURE 1. ^{13}C NMR spectra of diisopropoxyphosphoryl-α-oximinoacetaldehyde in DMSO-d^6

Iminoxyls are σ-type of free radicals with a paramagnetic fragment C=N-O·. It is known[2,3] that like the original oximes iminoxy radicals exist in two isomeric forms *Z* and *E* , marking the transition from one to the other form practically impossible. Phosphorus-containing iminoxy radicals of the $XP(O)(OR)_2C=NO\cdot$ and $[P(O)(OR)_2]_2C=NO\cdot$ types, described for the first time in [1], were produced as secondary products in the photolysis of a solution of 2-methyl-2-nitrosopropane in the presence of alkyl esters of phosphinoyliodo(bromo) acetic acid.

ESR studies showed that, like other iminoxy radicals, phosphorus-containing iminoxyls exist in two stable isomeric *syn* and *anti* forms with markedly differing values of the hyperfine coupling constants of the phosphorus atom. Iminoxy radicals with a phosphorus atom bound directly to a CNO· group have typical spectra due to hyperfine coupling of with ^{14}N and ^{31}P nuclei in two isomeric *syn* and *anti* forms of radicals (Figure 2). Parameters of ESR spectra of iminoxyl are given on Figure 3. It follows from the data obtained that the hyperfine coupling constants of the atom of the substituent at the imino carbon atom are stereospecific.

For fluorinated derivatives bearing strong electronegative substituents in aryl group spin density distributes to the fluorine atom as well. In this case it were found the small differences of fluorine hyperfine couplings in *E* and *Z* isomers. It was observed that the population of *syn* isomer exceeded the *anti* isomer one only for phosphoniminoxy with ortho-fluorine atom in aryl group. It is probably due to certain conformation position of aryl group to the unpaired electron location. In the case of bis-oximes separated by 3-6 methylene groups the usual free radical forming was established no exchange interactions being observed between radical centers.

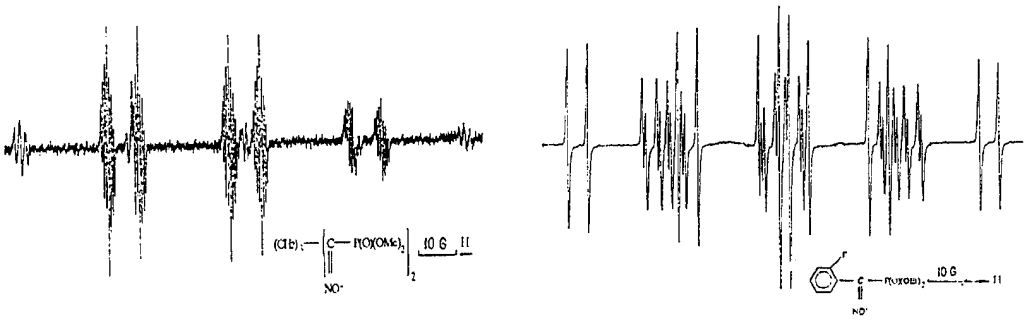


FIGURE 2. EPR spectra of the radicals in toluene, T=298K

The ratio of intensities of the ESR lines of *syn* and *anti* isomers of phosphon-iminoxyl depends on the temperature, the intensities of the ESR lines of *anti* isomers decreasing with temperature, while *syn* isomers are more stable. The studies in the

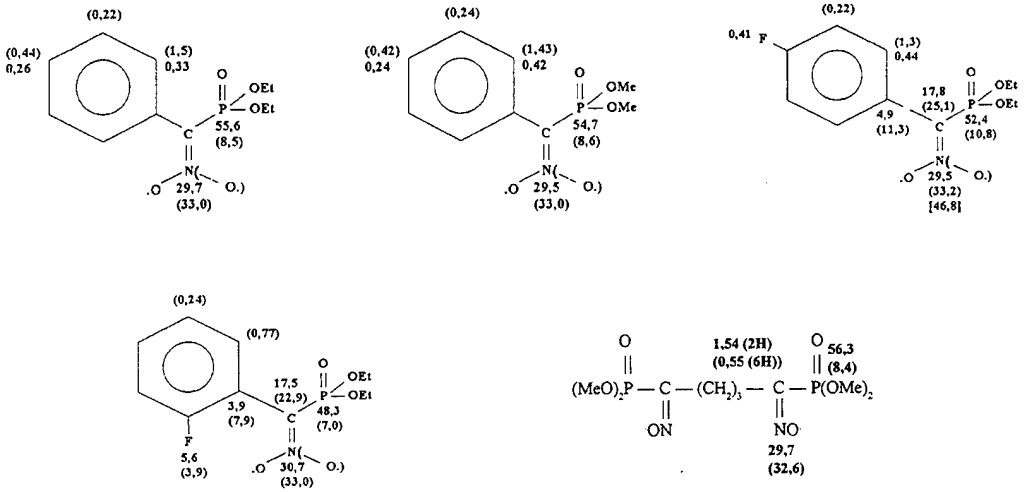


FIGURE 3. Hyperfine constants of radicals (in G). Numbers in parenthesis represent hyperfine constant for *syn*- isomer of each radical.

temperature range from -60 to +45°C showed that the hyperfine coupling constants and g-factors belonging to each iminoxyl isomers do not change.

A specific feature of phosphoniminoxyls is the different relaxation characteristics that depend on the molecular geometry. For *anti* isomers of phosphoniminoxyls narrower absorption lines and longer spin-lattice relaxation times are observed compared to those of *syn* isomers. The differences in magnetic characteristics of geometric isomers of phosphoniminoxyls indicate that molecular geometry and intermolecular interactions influence significantly the ESR spectra of such systems.

In studies of spin density distribution in the series of phosphoniminoxyls[4] $R^1R^2P(O)\,CR^3$ =NO· on successive substitution of groups $R^1 = R^2 = n$-BuO by n-Bu it was observed that in the Z isomer a^P significantly decreased (> 2 times). It should be noted that on replacement of R^1 by a less electronegativity group the stability of iminoxyls markedly decreases. A change in a^{31P} upon change in the nature of the substituent, was found also for the radicals $(R,OR)_2P(S)$-S-C -Ph_2.[5]

These new type of phosphoniminoxy radicals under investigation are certain to present the sensitive spin probes of solution parameters and conformation of surrounding molecules especially for the detection of order in biologocal tissues.

EXPERIMENTAL

The NMR ^1H, ^{13}C, ^{31}P were recorded on Bruker spectrometers WM-250 and MSL-400. Phosphoniminoxy free radicals were generated during chemical or electrochemical reactions in the special electrochemical cell.[2,6] ESR measurements of vacuumed solution of free radicals were carried out on Bruker ER 200 D spectrometer.

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REACTIONS OF DIAZOMETHYLPHOSPHONATE: THE FIRST SYNTHESIS OF A FORMYLPHOSPHONATE HYDRATE

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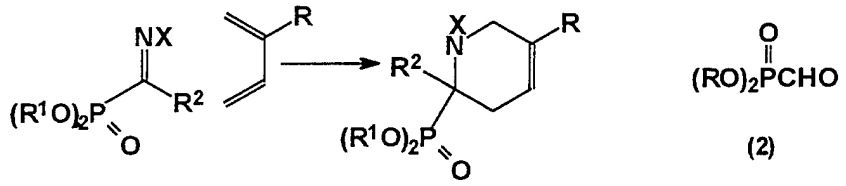
Abstract: Formylphosphonate hydrate has been synthesised by the oxidation of diazomethylphosphonate with dimethyldioxirane (DMD) and its reactions, including the formation of imines, oximes, and Wittig olefination products, have been investigated. Formylphosphonate also acts as an efficient, selective formylating agent of secondary amines. β-Ketophosphonic acids derived from a range of amino acids have been prepared by the tin (II) chloride-catalysed reaction of diazomethylphosphonate with amino aldehydes and in certain cases shown to be potent inhibitors of leucine aminopeptidase.

Key Words: Diazomethylphosphonate, formylphosphonate, amino acid-derived β-ketophosphonic acids, leucine aminopeptidase inhibitors.

The range of biological activity observed for functionalised phosphonate derivatives, especially analogues of amino acids, has highlighted the need for new, flexible routes to such compounds.[1] Due to their predictable stereochemistry and wide range of established chemistry, cycloaddition reactions, e.g. the Diels-Alder reaction, offer many attractions. For example, such reactions of 1-iminoalkylphosphonates (**1**) should provide the basis for potentially enantioselective routes to a wide range of phosphonic amino acid derivatives. However, our attempts to carry out Diels-Alder reactions with the readily available imines (**1**, R^2=alkyl or aryl) derived from acylphosphonates were unsuccessful in spite of the fact that M.O. calculations indicated favourable LUMO/HOMO energy differences in many of the examples attempted. This suggested that steric effects are of overriding importance. In view of this we turned our attention to the synthesis of formylphosphonate esters (**2**) as a source of the corresponding aldimines (**1**, R^2=H).

The only reported[2] method of the synthesis of these compounds involves the formylation of dialkyl phosphites with formic acetic anhydride. Our attempts to obtain (**2**) by this procedure have been unsuccessful (dialkyl methylphosphonates being the only

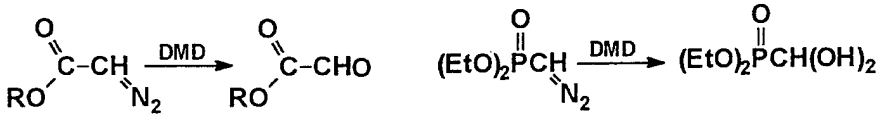
identified products) and the n.m.r. data given in the original publication[2b] do not support the proposed structure (**2**).



(**1**) (**2**)

In view of this we investigated a range of alternative approaches to (**2**), including the hydrolysis under a variety of conditions of the available[3] diethyl acetal derivative of (**2**), reduction of alkoxycarbonylphosphonates, oxidation of hydroxymethylphosphonates, ozonolysis of vinylphosphonates under reducing conditions, and a variety of alternative formylation procedures, without success.

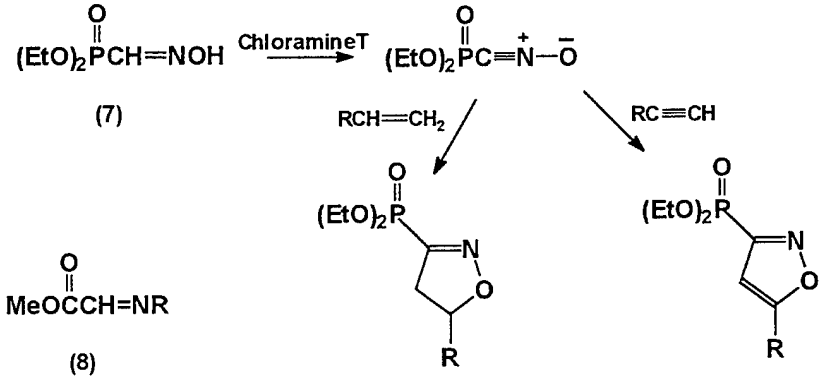
Glyoxals (**4**) have been conveniently prepared by the oxidation of α-diazoacetates (**3**) with dimethyldioxirane (DMD) in acetone solution.[4] Similar treatment of diethyl diazomethylphosphonate (**5**) gave diethyl formylphosphonate hydrate (**6**) as a yellow oil in quantitative yield as identified by its ^{13}C [δ_C ($CDCl_3$) 88.17 (d, $^1J_{PC}$=210Hz)] and ^1H [δ_H($CDCl_3$) 5.13 (1H, d, $^2J_{PH}$=9.1Hz)] n.m.r. and mass [M^+ =166.0392] spectra.[5] Further confirmation of the structure of (**6**), and the fact that it is synthetically equivalent to the corresponding aldehyde, is available from its Wittig reaction with *t*-butoxycarbonylmethylenephosphonium ylide to give the corresponding vinylphosphonate as an isomer mixture and the formation of a cyanohydrin derivative on reaction with trimethylsilyl cyanide.



(**3**) (**4**) (**5**) (**6**)

The condensation of (**6**) with primary amines ($PhNH_2$, *t*-$BuNH_2$, *c*-$HexNH_2$, and $PhCH(Me)NH_2$) leads to the formation of aldimines (**1**, R^2=H), as identified by their (for X=Ph) ^{13}C [δ_C ($CDCl_3$) 157.79 (d, $^1J_{PC}$=222.5Hz)] and ^1H [δ_H($CDCl_3$) 8.22 (1H, d, $^2J_{PH}$=61.2Hz)] n.m.r. and mass [M^+ =241.0856] spectra, generally in excellent yield. These $^1J_{PC}$ and $^2J_{PH}$ values are the largest so far reported and are diagnostic for the

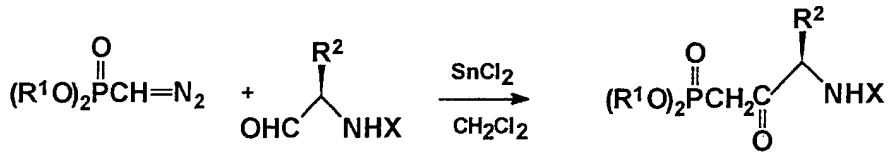
aldiminylphosphonate structure. Further confirmation of the structure of (**1**, R^2=H, X=Ph) is available from its synthesis by the Wadsworth-Emmons reaction of tetraethyl methylenediphosphonate with nitrosobenzene. The only previous report[6] of compounds (**1**, R^2=H) relies on their generation and trapping in situ and no spectroscopic or other data is available. The oxime (7) derived from (**6**) is readily formed in excellent yield [δ_C ($CDCl_3$) 142.19 (d, $^1J_{PC}$=236Hz), δ_H($CDCl_3$) 7.56 (1H, d, $^2J_{PH}$=37.9Hz); M^+ =241.0856] and, when treated with chloramine-T in the presence of alkene or alkyne, (7) provides a convenient route to the corresponding isoxazolines or isoxazoles, respectively (Scheme **1**). However, in no case did the oxime or the imines (**1**, R^2=H) prepared in this study undergo Diels-Alder reactions under the wide range of conditions tried, in spite of the fact that the direct ester analogues (e.g. **8**, X=Ph) readily undergo such reactions. In view of the in situ Diels-Alder trapping, albeit in low yield, of presumed aldimines (**1**, R=H) carrying an aryl sulfonyl or keto substituent on nitrogen[6] it seems likely that, unlike the corresponding ester analogues (**8**), an electron-withdrawing group attached to nitrogen is necessary for successful reaction. We are currently preparing such compounds.



Scheme 1

The hydrate (**6**) acts as a formylating agent towards secondary amines. Reaction with morpholine, piperidine, pyrrolidine, or dibenzylamine at room temperature leads to formation of diethyl phosphite and the corresponding *N*-formylamine in virtually quantitative yield, and a similar reaction of one mole equivalent of (**6**) with *N*-methylethylenediamine gave an excellent yield of *N*-formyl-*N*-methylethylene diamine with no evidence of competing imine formation.

In view of the postulated mechanism of action of leucine aminopeptidases and the successful design[7] of transition state inhibitors of such enzymes, it has been suggested[8] that β-ketophosphonic acids (**9**, R^1=H) derived from amino acids should also act as inhibitors. Diethyl diazomethylphosphonate reacts with N-protected amino aldehydes in the presence of tin dichloride to provide the corresponding β-ketophosphonates (**9**, R^1=Et, R^2=Me, ^{i}Pr, ^{i}Bu, Benzyl) in excellent yield. The structures of (**9**) were assigned on the basis of their n.m.r spectra, particularly the characteristic two doublets of doublets, due to the diastereotopic methylene protons adjacent to phosphorus, observed in the region δ_H 3 to 3.5 ppm. Although compounds (**9**) show substantial specific rotations, attempts to determine their optical purity using the chiral lanthanide shift reagent Eu(h.f.c.)$_3$ gave no peak separations. The compounds obtained were converted into the fully deprotected phosphonic acids (**9**, R^1 and X=H) and both these and the corresponding esters (**9**, R^1=Et) were tested against microsomal, cytosolic, and *E. Coli* leucine aminopeptidase. While the esters were inactive in all cases, the phosphonic acids acted as potent competitive reversible inhibitors.[8]



(**9**)

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[2,3]-WITTIG SIGMATROPIC REARRANGEMENT OF α-PHOSPHONYLATED SULFONIUM AND AMMONIUM YLIDES

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Abstract A study of the reactivity of ylides of α-allylamino and α-allylthio-methyl-phosphonates and a comparison with the reactivity of the corresponding carbanions demonstrate the complementarity of these intermediates for the preparation of α-heteroatom-substituted alkenylphosphonates via [2,3]-sigmatropic rearrangements.

INTRODUCTION

The [2,3]-sigmatropic rearrangement of α-(allyloxy), -(allylamino) or -(allylthio) carbanions and ylides (also called Wittig, thia- or aza-Wittig rearrangement) is a well known process which has been widely used for regio and stereocontrolled formation of carbon-carbon bonds.[1] This rearrangement is also observed with propargylic and benzylic derivatives. More often, these carbanions and ylides were generated by a deprotonation which was made easier by an α-electron withdrawing group. However, no-example of a phosphonate group used for these purpose has been published. Owing to the need for efficient and stereocontrolled methods for the synthesis of α-heteroatom substituted phosphonates (compounds of potential biological interest [2] which can be obtained via these Wittig rearrangements), we have initiated a systematic study of the reactivity of [(allyloxy)-, (allylamino)- or (allylthio)-methyl]phosphonates carbanions and ylides.

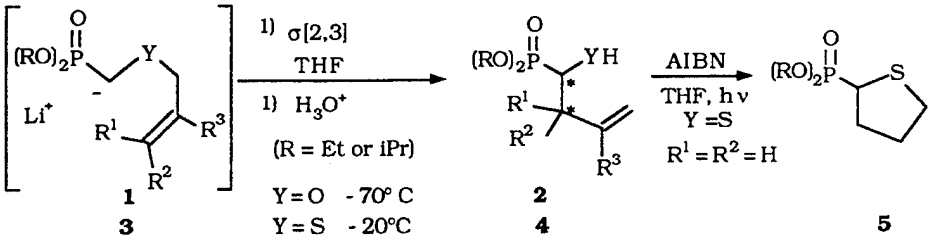
This communication summarises briefly the recent results we have obtained concerning the reactivity of the carbanions of α-allylic heterosubstituted phosphonates and then demonstrates that the use of the corresponding ylides (prepared from ammonium or sulfonium salts) complement that of the carbanions as far as the syntheses of [(dialkylamino)- or (alkylthio)-methyl]phosphonates are concerned. Moreover, although a more extensive investigation is still needed concerning the stereochemistry of these rearrangements and its rationalisation, the diastereoselectivity (very high in some

cases) can be very different according to the use of a carbanion or an ylide as intermediate. Some results related to the bis-phosphonate series are also presented.

REACTIVITY OF THE CARBANIONS OF [(ALLYLOXY)-, (ALLYLAMINO)- OR (ALLYLTHIO)-METHYL]PHOSPHONATES

The reactivity of the carbanions of [(allyloxy)- and (allylthio)-methyl]phosphonates were first studied [3]. The O-allylic carbanions **1** (with allyl, cinnamyl, crotyl and prenyl groups) resulting from a deprotonation by lithium di-isopropyl amide (LDA) undergoes at -70° C the expected [2,3]-sigmatropic rearrangement. Yields of the resulting α-hydroxyphosphonates **2** are satisfying (60 to 72%) except for the prenyl substituent (28%). A good diastereoselectivity was observed with the cinnamyl but not with the crotyl substituent.

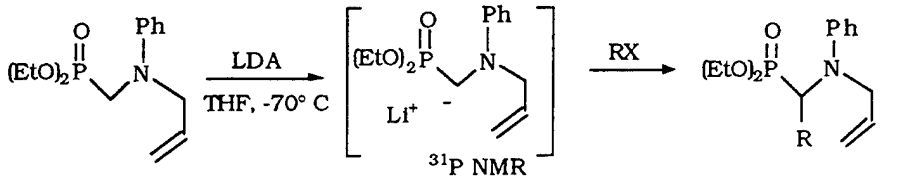
With the corresponding S-allylic carbanions **3**, obtained by allylation of the sodium salt of the mercaptomethylphosphonate,[4] a deprotonation by BuLi, led to α-mercaptobutenylphosphonate derivatives **4** in good yields (66 to 97%) via the thia-Wittig rearrangement. Low diastereoselectivity was observed with the crotyl and cinnamyl group. A synthetic application of compound **4** was the easy synthesis of the phosphorus and sulfur analogue of the proline ester **5**, not described previously, via a radical cyclisation of the (1-mercaptobut-3-enyl)phosphonate.



1 **2** **5**

3 **4**

We then examined the reactivity of the carbanion of allylamino-methylphosphonates. The deprotonation leading to carbanion **6** was observed by addition of 2 equivalents of LDA at -70° to an (N-phenyl N-allyl aminomethyl)phosphonate (deprotonation did not occur from an N-alkyl N-allyl analogue). However carbanion **6**, the formation of which being evidenced by its reaction with various electrophiles, did not undergo any sigmatropic rearrangement, even at higher temperatures.



6

^{31}P NMR
δ = 43

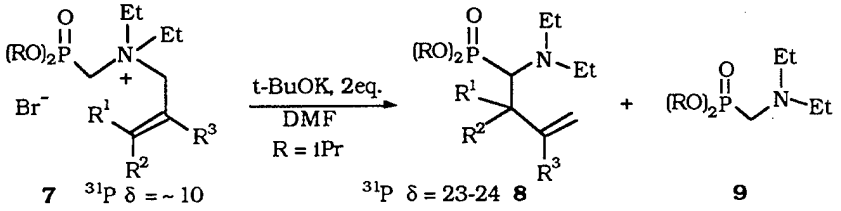
7

50 to 80 % yields

R =	$SiMe_3$	$SnBu_3$	SPh	Me
^{31}P NMR (δ)	25.1	28.2	16.2	24.5

REACTIVITY OF THE YLIDES OF [(ALLYLAMINO)- OR (ALLYLTHIO)- METHYL]PHOSPHONATES

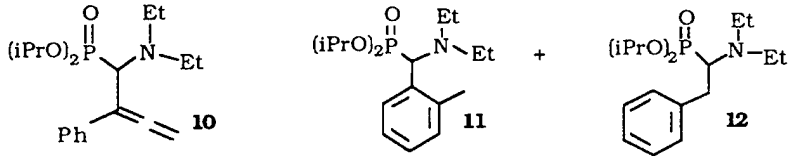
This failure to observe the sigmatropic rearrangement with carbanion **6** was an incitation to examine the reactivity of the corresponding ylide formed by deprotonation of the ammonium salt. However, we did not succeed in the quaternarisation of the N-phenyl substituted amine. Such a quaternarisation leading to salts of type **7** was obtained by addition of allyl, methallyl, crotyl, cinnamyl, or prenyl-bromides to the O,O'-diisopropyl (N,N-diethyl-aminomethyl)phosphonate (the use of isopropyl substituents appeared necessary to avoid partial phosphonate dealkylation encountered with ethyl group). The deprotonation of **7** at - 40°C by t-BuOK in DMF generated the corresponding ylides which spontaneously rearranged into α-aminobutenyl phosphonate derivatives **8** in about 75 % yields exept for the more crowded prenyl derivative (51%). The de-allylation of the ammonium salts usually < to 10% occurs more extensively (40% of **9**) in the last case .



7 ^{31}P δ = ~ 10 ^{31}P δ = 23-24 **8** **9**

Very good diastereoselectivities were observed in the formation of **8** via the N-crotyl (de = 82%) and N-cinnamyl (de = 100%) ammonium ylide rearrangements.

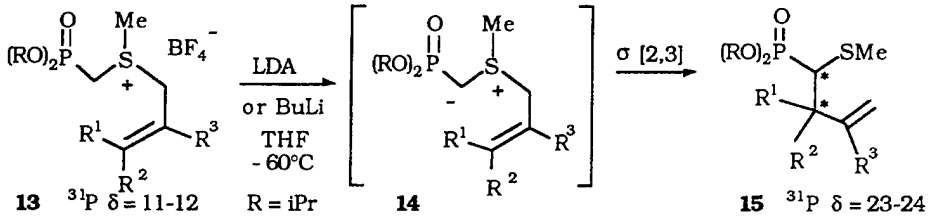
Starting from the N- propargylic ammonium salts, the expected allenic derivative **10** was obtained and, from the N-benzylic ammonium salts, both [2,3]- and [1,2] sigmatropic rearrangements occured in the ratio 2/1 to give α-amino phosphonates **11** and **12** respectively.



10 **11** **12**

Then, in order to investigate the reactivity of ylides in the sulfur series, we prepared the precursor allylic sulfonium salts **13** in nearly quantitative yields by methylation of the corresponding allylthio, crotylthio and methallylthio-methylphosphonates, in acetonitrile in the presence of $AgBF_4$. These salts, treated with one equivalent of Buli in THF at -60°C, led readily to α-alkylthio butenylphosphonate derivatives **15** in 80 to 90% yields via the non isolated ylides **14**. A good diastereoselectivity (de = 80%) was observed for the rearrangement of the S-crotyl ylide. This was not the case for the rearrangement of the corresponding carbanion (*vide supra*). We did not observed any rearrangement of the corresponding S-benzylic ylide, although

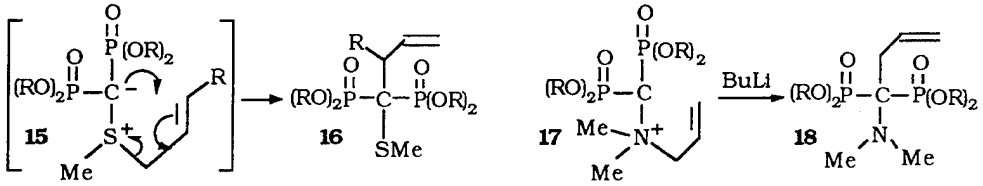
the formation of which was confirmed by trapping with PhNCO.[5]



As far as the potential uses of this rearrangements for stereocontrolled formation of α-heteroatom-substituted phosphonates are concerned, first experiments using the O,O'-dimenthyl substituent on the phosphonate function (prepared from l-menthol) as a chiral auxiliary gave the following results : an excellent asymmetric induction (de = 92%) was obtained for the rearrangement of the carbanion of the (allyloxy methyl)phosphonate **1** (R=menthyl) but a low diastereoselectivity (de=8%) was observed via the sigmatropy of the S-allyl ammonium ylide generated from **7** (R=menthyl, R^1=R^2=R^3=H). In the sulfur series, the diastereoselectivity of the rearrangement of the carbanion **3** and ylide **14** with the same optically active phosphonate group will be also examined.

REARRANGEMENT OF SULFONIUM AND AMMONIUM YLIDES IN THE BIS-PHOSPHONATES SERIES

Preceeding work has shown that a [2,3]-sigmatropic rearrangement of an intermediate S-allylic or propargylic sulfonium ylides **15** can be assumed in the reaction of allylic or propargylic bromide with a [(methylthio)-phosphoranylidene-methyl]phosphonate to give the methylene bis-phosphonate derivative **16**.[6] We have now shown that the deprotonation of the S-allylic ammonium salt **17** led to the (N,N-dimethylamino-allyl-methylene)bis-phosphonate **18**. These rearrangements are thus convenient methods for the preparation of new functionalised methylene bis-phosphonates.



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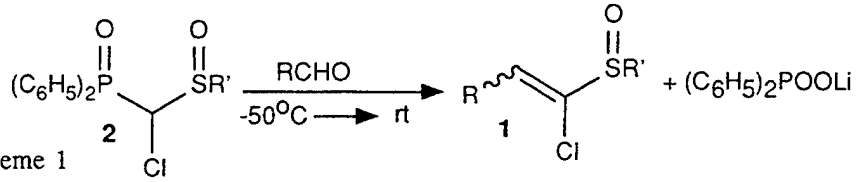
A HORNER-WITTIG SYNTHESIS OF 1-CHLOROVINYL SULFOXIDES.

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Abstract 1-Chlorovinyl sulfoxides **1** were prepared by Horner-Wittig reaction of the readily accessible [(α-chloro)sulfinylmethyl)diphenylphosphine oxides **2** with aldehydes. Excellent *Z*-selectivity was observed in most cases.

INTRODUCTION

1-Chlorovinyl sulfoxides **1** form a class of multifunctional compounds that is expected to possess a versatile chemical reactivity which is yet to be investigated (Michael-additions, Diels-Alder reactions, (2+2)- and 1,3-dipolair cycloadditions). Satoh *et al.*[1] recently described a three step procedure for the conversion of aldehydes into their corresponding one-carbon homologated 1-chlorovinyl sulfoxides **1** which were obtained as mixtures of *E*- and *Z*-isomers of unknown ratio. We now report the one-step transformation of aldehydes into their homologous 1-chlorovinyl sulfoxides by a Horner-Wittig reaction with [(α-chloro)sulfinylmethyl]diphenyl-phosphine oxides **2** (Scheme 1).

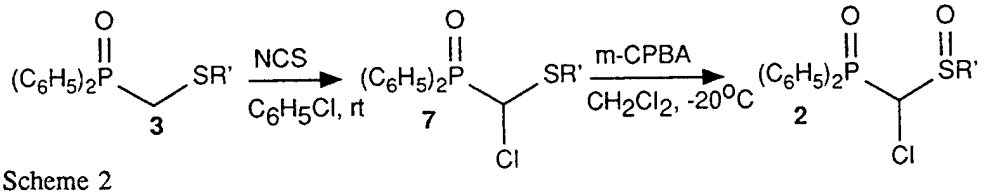


Scheme 1

RESULTS AND DISCUSSION

Diphenylphosphine Oxides

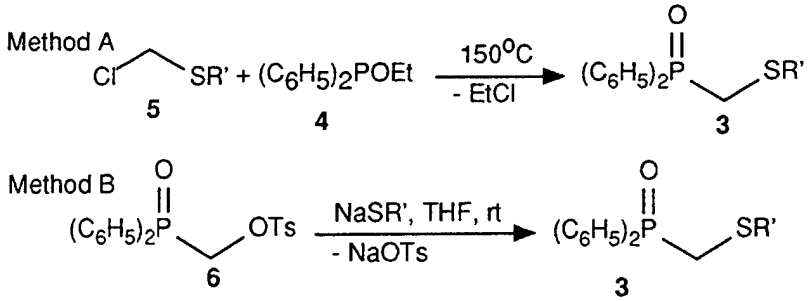
The requisite phosphine oxides **2** are readily accessible by chlorination and subsequent oxidation of (thiomethyl)diphenylphosphine oxides **3** (Scheme 2).



Scheme 2

We have elaborated two different routes for the preparation of (thiomethyl)-diphenyl phosphine oxides **3** (Scheme 3). Arbuzov reaction of *O*-ethyl diphenylphosphinite **4** with an appropriate (chloromethyl)thioether **5**, according to a literature procedure[2], gave phosphine oxides **3a** and **3c** (R'= methyl and phenyl) in good yields (method A). The Arbuzov reaction also proved suitable for the preparation of phosphine oxide **3d** (R'= *p*-tolyl) which was obtained in quantitative yield (Table I). The synthesis of **3** by this route

is somewhat restricted by the limited availability of (chloromethyl)thioethers **5**. Therefore, it was decided to develop a more general procedure for the synthesis of phosphine oxides **3**. Nucleophilic displacement on (tosyloxymethyl)diphenylphosphine oxide **6** with sulfur nucleophiles (method B) gave access to a wide range of substituents R' in **3**. Extractive work-up afforded phosphine oxides **3** which were sufficiently pure for further elaboration. Table I shows that method B proceeded with almost quantitative yields throughout.



Scheme 3

TABLE I (Thiomethyl)diphenylphosphine oxides **3**.

	R'	Method	Yield (%)
3a	methyl	A	80
3b	*c*-hexyl	B	95
3c	phenyl	A	85
3d	*p*-tolyl	A	98
		B	96
3e	*n*-butyl	B	95
3f	*t*-butyl	B	98

The α-protons of an aliphatic thioether are susceptible to chlorination with *N*-chlorosuccinimide (NCS). The more acidic protons are known to be substituted by preference[3]. In the case of phosphine oxides **3**, it was expected that the anion stabilizing capacity of the phosphinoyl substituent would direct a regioselective substitution in **3a**, **3b** and **3e**. Indeed, treatment of these phosphine oxides with one equivalent of NCS in chlorobenzene[4] resulted in formation of the desired phosphine oxides **7**. The concomitantly formed succinimide was removed by repeated extraction with water. The phosphine oxides were isolated after drying and evaporation of the solvent. In all cases, high yields of mono-chloro phosphine oxides **7** were obtained (Table II). The chemoselective mono-chlorination of **3** indicates that substitution of the methine proton of **7** by a second chlorine atom is much slower than mono-substitution. The use of an excess of NCS led to di-substitution, which was observed to occur at the same position.

Selective mono-oxidation of phosphine oxides **7a** and **7b** with one equivalent of *m*-CPBA proceeded cleanly at -20°C. Extractive work-up yielded the desired sulfoxides **2a** and **2b** in excellent yields. No further purification of these phosphine oxides was necessary for subsequent application in the Horner-Wittig reaction. Oxidation of **7f** (R'=*t*-butyl) with *m*-CPBA proceeded less satisfactory. After several hours at room temperature, only partial oxidation of the sterically shielded sulfide was observed. Treatment of **7c** and **7d** with one equivalent of *m*-CPBA led to almost complete conversion (>95%) of the starting material. Oxidation of the aryl substituted sulfur center to the sulfone had only occurred to a small extent (<5%)[5].

TABLE II [(α-chloro)thiomethyl]diphenylphosphine oxide **7**.

	R'	Yield (%)
7a	methyl	95
7b	*c*-hexyl	83[a]
7c	phenyl	89
7d	*p*-tolyl	98
7e	*n*-butyl	95
7f	*t*-butyl	80[a]

[a] After crystallization from CH_2Cl_2/petroleum ether (40/60).

TABLE III [(α-chloro)sulfinylmethyl]diphenylphosphine oxide **2**.

	R'	Yield (%)
2a	methyl	93
2b	c-hexyl	97
2c	phenyl	97[a]
2d	*p*-tolyl	98[a]

[a] 95% Conversion, 5% sulfone.

Horner-Wittig Reaction

Phosphine oxides **2** were readily deprotonated with LDA in THF between -50°C and -40°C to give a yellow colored anion solution. Deprotonation at lower temperatures was hampered by insufficient solubility of the phosphine oxides. The lithiated anions proved sufficiently stable at these temperatures to allow efficient reaction with a wide range of aldehydes. The Horner-Wittig reaction was completed by stirring a few hours at ambient temperatures. Extractive work-up afforded the 1-chlorovinyl sulfoxides **1**, which were conveniently purified by column chromatography[5]. Some representative results are compiled in Table IV. In the case of **2c** and **2d**, the yields were obtained using the crude phosphine oxides[5]. Good yields were obtained with all types of aldehydes. Attempted reaction with a ketone (cyclohexanone) and the sterically hindered pivaldehyde remained without success. The preparation of 1-chlorovinyl sulfoxides **1h** and **1l**, the simplest and hitherto unknown members of this class of compounds, by a Horner-Wittig reaction with p-formaldehyde, deserves special mention. These compounds may well turn out to be excellent reaction partners in a variety of (cyclo)addition reactions[6].

The stereoselectivity with which the new double bond was formed, was found to depend on the nature of the aldehyde as well as on the phosphine oxide used. With aromatic or α,ß-unsaturated aldehydes, almost exclusive formation of one stereoisomer was observed (entries **1a**, **1b**, **1f**, **1g**, **1i** and **1j**). A crystal structure determination of **1b** unambiguously showed the double bond to possess the *Z*-configuration. The stereoselectivity of straight chain aliphatic aldehydes in the Horner-Wittig reaction with **2** was found to depend on the substituent R' in the phosphine oxide. If R' was methyl or *c*-hexyl (**2a** and **2b**), only a modest stereoselectivity was found (entries **1c** and **1e**). On the other hand, a Horner-Wittig reaction with **2c** (R'=phenyl) showed again a strong preference for formation of only one double bond isomer (entry **1f**). In all three cases, the major isomer is expected in analogy to possess the *Z*-configuration.

A strikingly low selectivity arose from use of the sterically more hindered cyclohexanecarboxaldehyde (entries **1d** and **1k**). Not only reaction with **2a** (R'= methyl), but also with **2c** (R'= *p*-tolyl) resulted in the formation of a 3/1 ratio of the two stereoisomers. This indicates that steric effects stemming from the aldehyde substituent R may also play a dominant role in the outcome of the Horner-Wittig reaction.

TABLE IV 1-Chlorovinyl sulfoxides **1**, prepared by the Horner-Wittig reaction.

1	R	R'	Yield (%)	Z/E
1a	phenyl	methyl	75	98/2
1b	*p*-methoxyphenyl	methyl	71	98/2
1c	*n*-butyl	methyl	63	4.7/1
1d	*c*-hexyl	methyl	68	3/1
1e	*n*-butyl	*c*-hexyl	56	5.2/1
1f	*n*-butyl	phenyl	63	96/4
1g	1-propenyl	phenyl	63	97/3
1h	H	phenyl	72	-
1i	phenyl	*p*-tolyl	60	98/2
1j	*p*-methoxyphenyl	*p*-tolyl	66	98/2
1k	*c*-hexyl	*p*-tolyl	69	3/1
1l	H	*p*-tolyl	70	-

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4. In the case of **3c** and **3d**, the presence of water in the solvent led to the contamination of **7c** and **7d** with appreciable amounts of the corresponding [(arylsulfinyl)methyl]diphenylphosphine oxides. Formation of these sulfoxides was completely suppressed by using dry chlorobenzene.
5. The small 1-chlorovinyl sulfide and 1-chlorovinyl sulfone impurities could easily be separated from the desired 1-chlorovinyl sulfoxides **1** by column chromatography. Therefore, the crude phosphine oxides **2c** and **2d** did not need further purification.
6. Recent investigations showed that 1-chlorovinyl sulfoxides **1h** and **1l** can be excellent Michael acceptors. (To be published)

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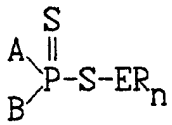
SYNTHESIS AND PROPERTIES OF MIXED ORGANIC DERIVATIVES OF ELEMENTS OF III, IV and V GROUPS AND PHOSPHORUS (IV) THIOACIDS

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Abstract New convenient methods of synthesizing useful mixed organic derivatives of B, Si, Ge, Sn, Pb, As and phosphorus (IV) thioacids with a P(S)S-E fragment were developed. Their spectral, structural and chemical properties were studied.

INTRODUCTION

Organoelement derivatives of phosphorus (IV) thioacids with the general formula



A, B = AlkO, ArO, AlkS, Alk_2N, Alk, Ar; R = Alk, Ar;
E = B, Si, Ge, Sn, Pb, As; n = 2, 3

with a P(S)S-E fragment serve as intermediates for synthesizing numerous linear and heterocyclic organothiophosphorus compounds. In this case a series of fundamental problems of phosphorus chemistry could be solved. However there no convenient methods of their synthesis. They were obtained by the interactions of dithiophosphoric acids or their salts with organoelement halides. These techniques are multistep procedures, as the initial dithiophosphoric acids had to be synthesized by treatment of organic hydroxy compounds with P_4S_{10} with the evolution of gaseous H_2S.

RESULTS AND DISCUSSION

The reactions of P_4S_{10} with trimethylsilyldialkylamines

and bis(trimethylsilyl)sulfide were reported to yield S-trimethylsilyl N,N'-bis(dialkylamido)dithiophosphates and tris(trimethylsilyl) tetrathiophosphates.[1] We have tried to extend these degradation reactions of P_4S_{10} to other organosilicon compounds. We used the trimethylsilyl protecting group in protonodonating reagents such as saturated and unsaturated alcohols, enols, thiols and diols and have developed facile methods of synthesizing S-trimethylsilyl dithio- and tetrathiophosphates directly from P_4S_{10} and thus avoided the formation of H_2S. Similar results were obtained in the reactions of P_4S_{10} with alkoxy- and alkylthiogermanes, stannanes and plumbanes at 20-40°C.

$$P_4S_{10} + 8\ RXER'_3 \longrightarrow 4\ (RX)_2P(S)SER'_3 + 2\ (R'_3E)_2S$$

R = Alk, $H_2C{=}CHCH_2$-, $HC{\equiv}C{-}CH_2$-; R' = Alk, Ar; X = O, S;

E = Si, Ge, Sn, Pb

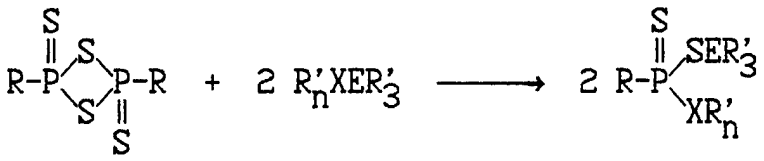
$$P_4S_{10} + 4\ R(OSiMe_3)_2 \rightarrow 4\ R\langle O_O\rangle P(S)SSiMe_3 + 2\ (Me_3Si)_2S$$

R = alkylene

These preparative methods are characterized by minimum steps, simple operations, mild conditions, high yields of products and no by-products. Alkoxysilanes have proven to be less reactive toward P_4S_{10} than alkylthiosilanes. The reactivity of alkoxides of main IV group elements increases in the following series: Si < Ge < Sn < Pb.

The mechanism of the reaction of P_4S_{10} with silylamines has been discussed by Roesky and Remmers[1] when the nucleophilic nitrogen atom attacks the phosphorus atom of P_4S_{10}. We assumed that during the destruction process of P_4S_{10} some intermediates can be formed in which a structural fragment may be similar to that of 2,4-bis(alkylthio)-2,4-dithioxo-1,3,2λ^5,4λ^5-dithiadiphosphetanes (homologues of Davy's reagent) in their trimer form. Consequently the

interaction of 1,3,2,4-dithiadiphosphetane-2,4-disulfides with organoelement derivatives can be used as a model reaction of some intermediate processes of degragation of P_4S_{10}. We varied the 1,3,2,4-dithiadiphosphetane-2,4-disulfides on the one hand and the silicon, germanium, tin and lead derivatives on the other hand.

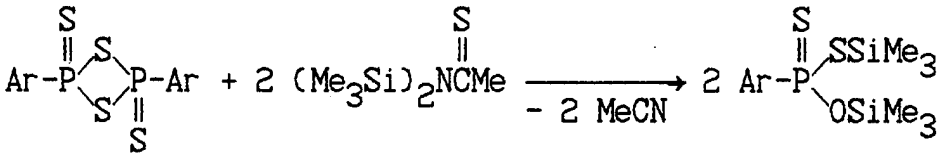


R = SAlk, $NAlk_2$, $4\text{-}MeOC_6H_4$; R' = Alk; R'' = Alk, Ph;

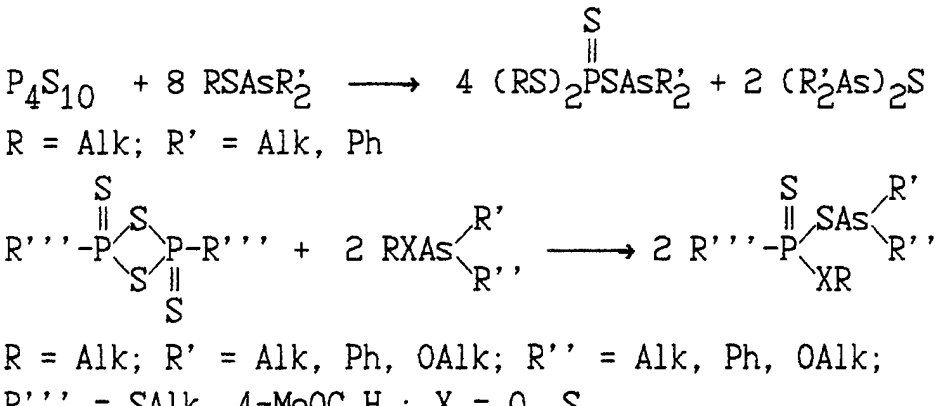
X = O, S, N; E = Si, Ge, Sn, Pb; n = 1, 2

The reactivity of alkoxides of main IV group elements towards 1,3,2,4-dithiadiphosphetane-2,4-disulfides increases in the series: Si < Ge < Sn < Pb. Ultrasonic irradiation leads to the increased reaction rate and the reduction in reaction temperature and time in the reactions of P_4S_{10} and Lawesson's reagent with bis(trialkylstannyl)sulfide and alkylthiostannanes and to the increased yields of stannyl tetrathiophosphates and aryltrithiophosphonates.

Bis(trimethylsilyl)acetamide reacts with 2,4-bis-(aryl)-1,3,2,4-dithiadiphosphetane-2,4-disulfides to form O,S-bis(trimethylsilyl)aryl dithiophosphonates.



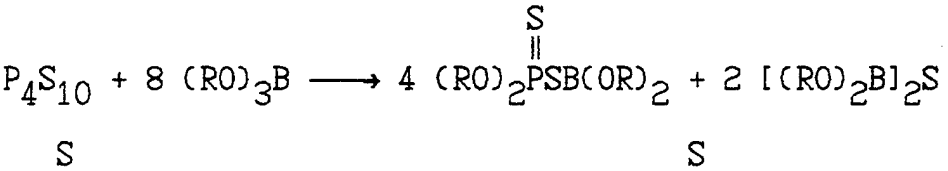
We extended this approach to the organic derivatives of main III and IV group elements. New preparative methods of synthesizing S-organoarsenic derivatives of tetrathiophosphoric and aryldithio- and trithiophosphonic acids were developed on the basis of the reactions of P_4S_{10}, Davy's and Lawesson's reagents with alkoxides and alkylmercaptides of arsenic (III) at 20°C.

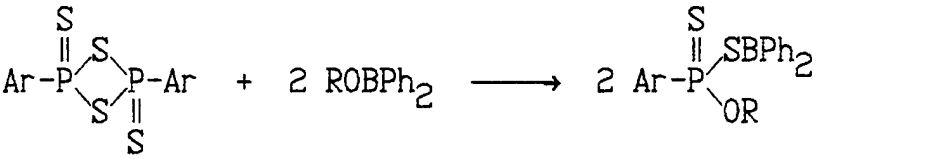


R = Alk; R' = Alk, Ph

R = Alk; R' = Alk, Ph, OAlk; R'' = Alk, Ph, OAlk;
R''' = SAlk, 4-MeOC$_6$H$_4$; X = O, S

However reactions of P_4S_{10} and Lawesson's reagent with alkoxides of boron take place under severe conditions (130-150°C, 2-3 h) with the formation of boron derivatives of dithiophosphoric and aryldithiophosphonic acids. These reactions were also facilitated when ultrasound was employed (60-90°C, 20-50 min).





R = Alk; Ar = 4-MeOC$_6$H$_4$

The products obtained serve as intermediates for synthesizing linear and heterocyclic organothiophosphorus compounds. Reactions of trimethylsilyl tetrathiophosphates with aldehydes, acetals, ortho ethers, aminals, thioacetals, bis(thiocyanato)methane, disulfides and alkyl halides resulted in the products of tetrathiophosphate structure. Heterocyclic compounds were obtained in the reactions of O,S-bis(trimethylsilyl)aryl dithiophosphonates with α-halogen carboxylic esters.

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SYNTHESIS OF FUNCTIONALIZED P-HETEROCYCLES INCLUDING PHOSPHINE-BORANE COMPLEXES

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[1]Department of Organic Chemical Technology, Technical University of Budapest, 1521 Budapest, HUNGARY

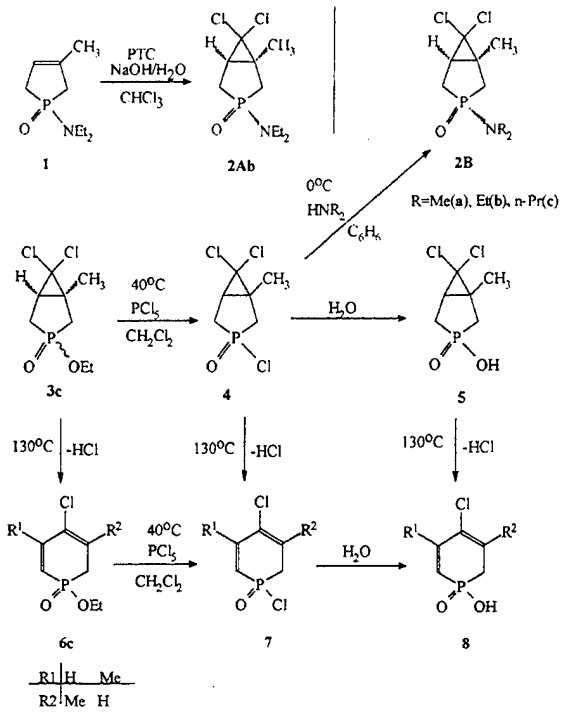
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Abstract Preparation of phosphinic chlorides, amides, and sulfide derivatives, as well as phosphine-borane complexes of P-heterocycles is described.

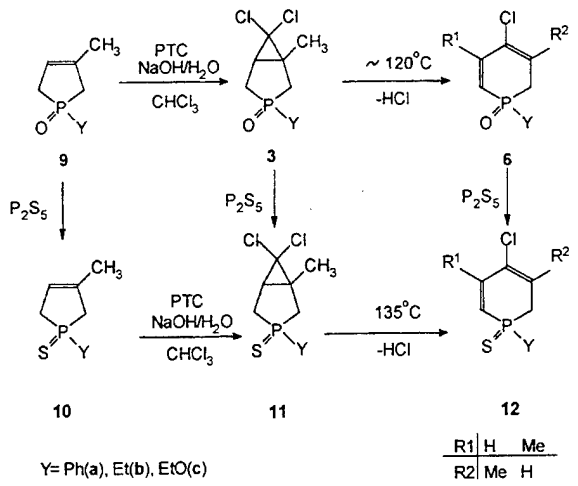
Synthesis of 3-phosphabicyclo[3.1.0]hexanes and 1,2-dihydrophosphinines having tertiary phosphine oxide or phosphinic ester functions has been described earlier.[1-3] In this paper, we show methods for the preparation of phosphinic chlorides, amides, acids, sulfide derivatives and phosphine-borane complexes.

P-amino phosphabicyclo[3.1.0]hexane oxides (2) were prepared by the addition of dichlorocarbene to the double bond of phospholene oxide 1, or by substitution at the phosphorus atom of phosphabicyclohexane 3c. The two approaches resulted in different diastereomers, isomer 2A or isomer 2B, respectively (Scheme I).[4] Phosphinic chloride 4, intermediate of the second method was also converted to phosphinic acid 5. Isomers of the P-hydroxy dihydrophosphinine oxide (8) were synthesised by the thermolysis of dichlorocyclopropane 5, or by substitution at the phosphorus atom of dihydrophosphinine 6c (Scheme I).[4]



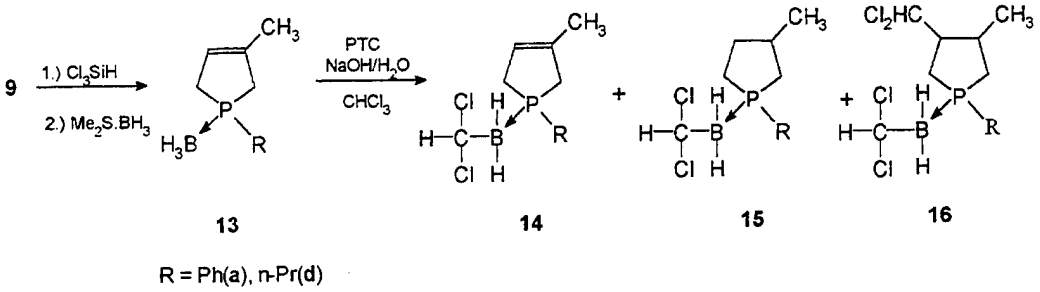
Scheme I

The P-sulfide derivatives of phosphabicyclohexanes (11) were prepared by the addition of dichlorocarbene to the double bond of phospholene sulfides (10), or by change in the functionality of the corresponding oxides (3) (Scheme II).[5] Isomers of the dihydrophosphinine sulfides (12) were obtained by the thermolysis of phosphabicyclohexane 11, or by thionation of oxide 6 by phosphorus pentasulfide (Scheme II).[5]



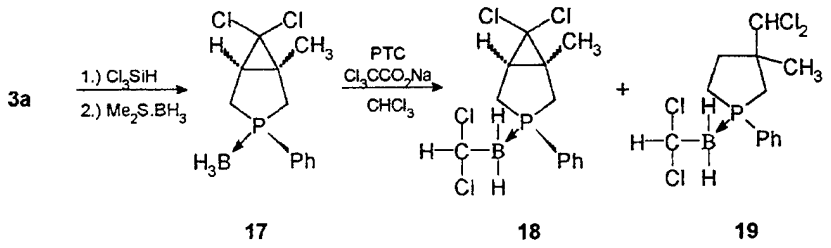
Scheme II

The 3-phospholene oxides (9) were deoxygenated by trichlorosilane and the phosphine intermediates so obtained reacted with dimethylsulfide-borane to afford phosphine-borane complexes (13). Reaction of 13 with dichlorocarbene did not give the expected phosphabicyclohexane (18), but resulted in a mixture containing phospholene 14, phospholane 15 and 3-dichloromethylphospholane 16 (Scheme III).



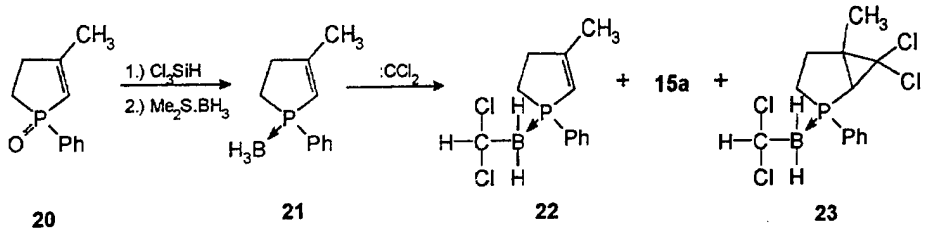
Scheme III

The phoshabicyclohexane-borane complex (17) could be prepared by change in the functionality of phosphine oxide 3a (Scheme IV). To prepare a more stable product, the dichloromethylborane derivative (18) was also synthesised (Scheme IV). Interestingly, a 3-dichloromethylphospholane (19) formed by the reductive type opening of the dichlorocyclopropane ring in 18 could also be isolated from the mixture (Scheme IV). This experience suggests that cyclopropane intermediates might be involved in the reaction resulting in the formation of 3-dichloromethylphospholanes 16. Reductions taking place during the work with phosphine-borane complexes are not unusual at all.[6]



Scheme IV

Due to the presence of the electron-withdrawing phosphoryl group, the double bond of 2-phospholene oxides failed to react with the electrophilic dichlorocarbene. To increase the reactivity of the double bond, phosphine oxide 20 was transformed to phosphine-borane complex 21. Reaction of 21 with dichlorocarbene gave the expected phosphabicyclohexane (23), but only in poor yields, as the main products were phospholene 22 and phospholene 15a (Scheme V). Forcing reaction conditions led to decomposition of the starting material (21) and the products (22, 15a and 23).



20 21 22 23

Scheme V

ACKNOWLEDGEMENT This work was supported by OTKA (grant no.: T 014917).

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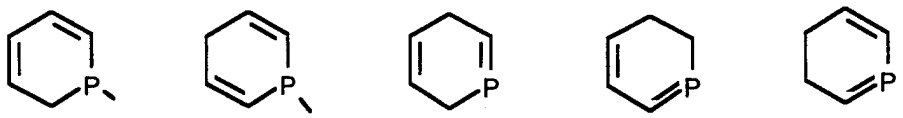
SUBSTITUTED DIHYDROPHOSPHININES, SYNTHESIS AND BASE-INDUCED ISOMERISATION

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Abstract The synthesis of α-chloro-tetrahydrophosphinines by inter- or intramolecular [4+2] cycloaddition reactions involving unstabilized phosphaalkenes is presented. Conditions for a selective base-induced isomerisation of substituted dihydrophosphinines are precised. A tautomeric phosphaalkene/vinylphosphine equilibrium was for the first time evidenced.

INTRODUCTION

While a number of substituted dihydrophosphinines of structure **1** or **2** have been reported in the literature[1], any representant of the other three expected isomers **3-5** have been to our knowledge described.



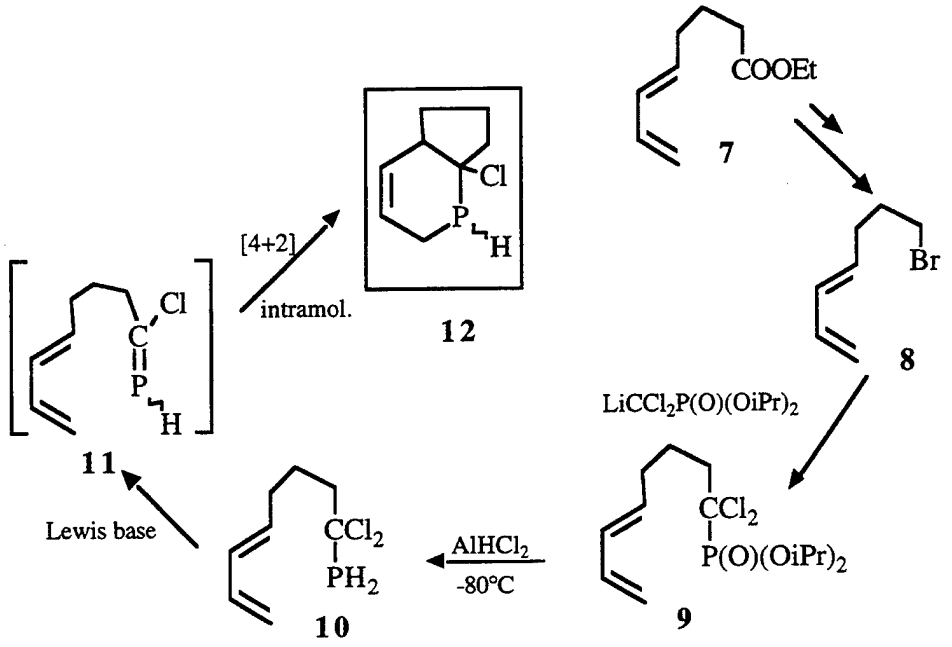
1 **2** **3** **4** **5**

Since phosphaalkene/vinylphosphine transformations and reverse reactions are well known processes[2], isomerisation of the dihydrophosphinines **1-5** can be consequently expected. We present in this work the formation of the two differently substituted transient 2,5-dihydrophosphinines **7** and **19** (derivatives of structure **3**) by dehydrohalogenation of the corresponding α-chlorophosphine precursors **6** and **12** and we precise the conditions for their base-induced isomerisation (formation of derivatives of structure **1** or **4**).

RESULTS

The first α-chlorophosphine precursor **6** has been synthesized according to the literature procedure by a [4+2] cycloaddition of dimethylbutadiene with the transient

phosphaalkene (Cl)CH=P-H, easily formed by a selective monodehydrochlorination of α,α'-dichlorophosphine in the presence of an excess of pyridine (yield 70%)[3]. The second α-chlorophosphine precursor **12** is formed according to the sequence outlined in Scheme 1. The bromoheptadiene **8** was first obtained by reduction of **7**[4] followed by a mesyl/bromine exchange. The dichlorophosphonate **9** is then formed by condensation of the dichloroalkyllithium derivative on **8**. The dichlorophosphine **10** obtained by chemoselective reduction of **9** cannot be distillated. After hydrolysis and filtration, the crude mixture is treated by an excess of pyridine. A selective monodehydrochlorination slowly occurs at room temperature and the phosphaalkene intermediate **11** was trapped by a stereoselective intramolecular [4+2] cycloaddition. The α–chlorophosphine **12** was obtained in 80% overall yield.



Scheme 1

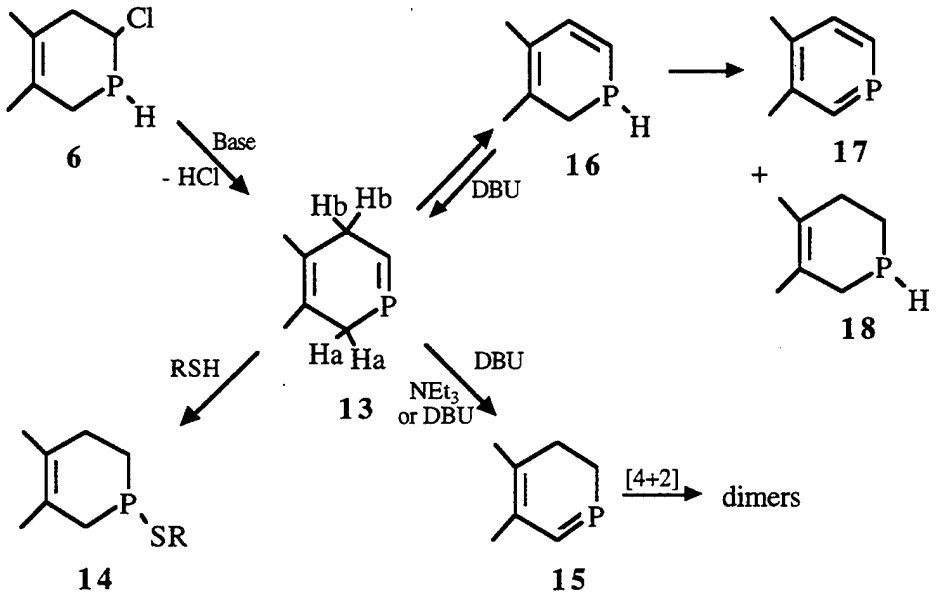
Obtention of the adducts **14** and **20** by dehydrochlorination of **6** and **12** respectively with Et_3N in the presence of a large excess of iPrSH indicates that the 2,5-dihydrophosphinines **13** and **19** are the primary products. Consequently, the following reactions realized by treatment of **6** or **12** with various Lewis bases in absence of thiol have formally **13** and **19** as starting material (Schemes 2 and 3).

In the presence of Et_3N, the rearrangement of the dihydrophosphinine **13** into the dihydrophosphinine **15** is observed. The characteristic ^{31}P NMR signal of this intermediate[5] (δ = 226 ppm) slowly decreases. Finally, a clean dimerization [4+2]

cycloaddition) is observed (presence of two isomers in 85:15 molar ratio). These results are in good agreement with the generally observed behaviour of the 1-phosphabutadiene structures. [5]

In the presence of DBU, the dihydrophosphinine intermediate **13** rearranges into a new isomer, the 1,2-dihydrophosphine **16** (δ = -114 ppm; $^1J_{PH}$ 197 Hz). This product is stable during few hours (NMR at room temperature) . However, a disproportionation was observed[6] during the purification leading to a mixture of phosphinine **17** and tetrahydrophosphinine **18.** These compounds were characterized by comparison of the NMR data with those of authentic samples. [7,8] The selectivity of the rearrangement of **13** is consequently depending on the strenght of the Lewis base.

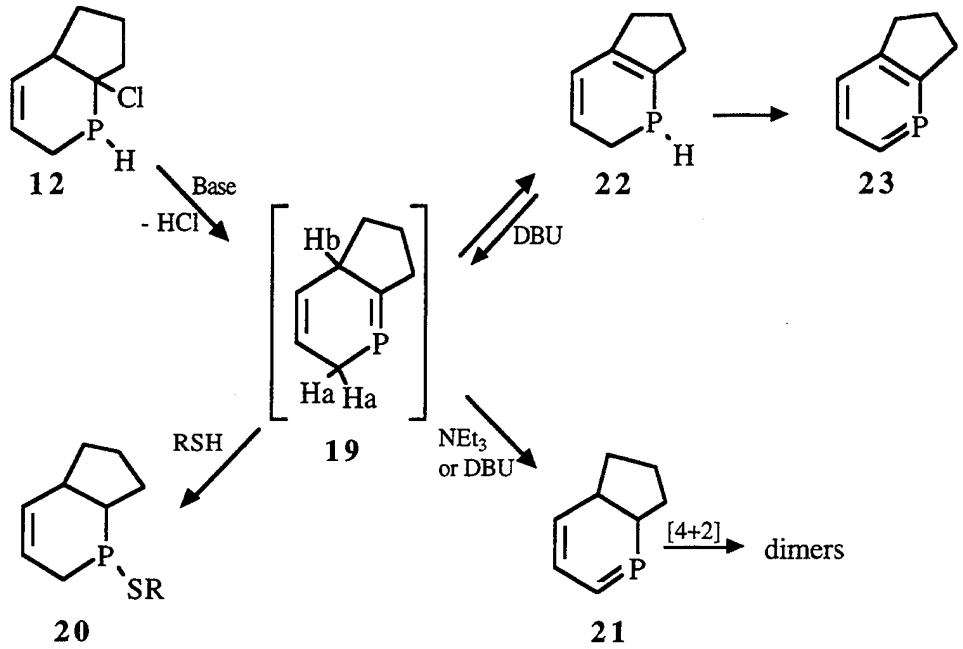
We have elsewere observed the formation of the thiophosphine **14** by addition of iPrSH onto the phosphinine **16** in the presence of a catalytic amount of DBU. This result indicates that **16** rearranges into the isomeric structure **13**. A tautomeric equilibrium vinylphosphine/phosphaalkene is thus for the first time evidenced.



Scheme 2

Similar rearrangements were observed by treatment of the bicyclic phosphaalkene **19** with various Lewis bases. The structures of the observed isomers were depending on the strenght of the base (Scheme 3). The transient phosphabutadiene isomer **21** (δ_P = 187) observed after addition of Et_3N rapidly dimerized (presence of 5 isomers which are not fully characterized). The other dihydrophosphinine isomer **22** was observed by addition of DBU. This phosphine (δ_P = -114, $^1J_{PH}$ 190 Hz) can be analyzed at room temperature by NMR but is too unstable to be isolated in pure form ; a partial oxidation to

the bicyclic phosphinine **23** (δ_P =193) is observed. A tautomeric vinylphosphine/phosphaalkene equilibrium was also observed (formation of **20** by addition of thiol on **22**).



Scheme 3

In conclusion, unknown dihydrophosphinines were characterized and the conditions for their base-induced isomerization precised. Intramolecular [4+2] cycloadditions should allowed to introduce unstabilized phosphaalkenes as powerful tools in the synthesis of complexe structures.

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INTERACTION BETWEEN PHOSPHORIC ANHYDRIDE AND ORGANIC COMPOUNDS WITH PROTOTROPIC PROPERTIES

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Abstract: Phosphoric anhydride has been shown to interact with organic compounds with prototropic properties, i.e. unsubstituted and monosubstituted amides, pyrimidinetriones, azoles and esters. Some products of phosphorylation have a tendency to exhibit phosphorotropy (1-3 and 1-4 shifts).

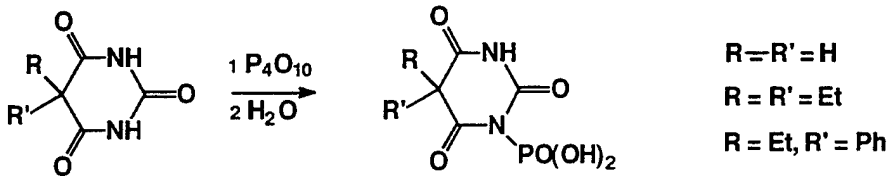
Key words: Phosphoric anhydride, phosphorylation, phosphorotropy.

The synthesis of various acidic phosphates is of high importance for medicinal and pharmaceutical chemistry as well as for industrial fire retardants, pesticides and photographic materials, etc. A variety of complicated and hazardous technological approaches are often used for the production of such compounds. Our study of the reactionof phosphoric anhydride with different types of organic compound has a potential for the development of a useful reagent for the preparation of acidic phosphates.[1-6]

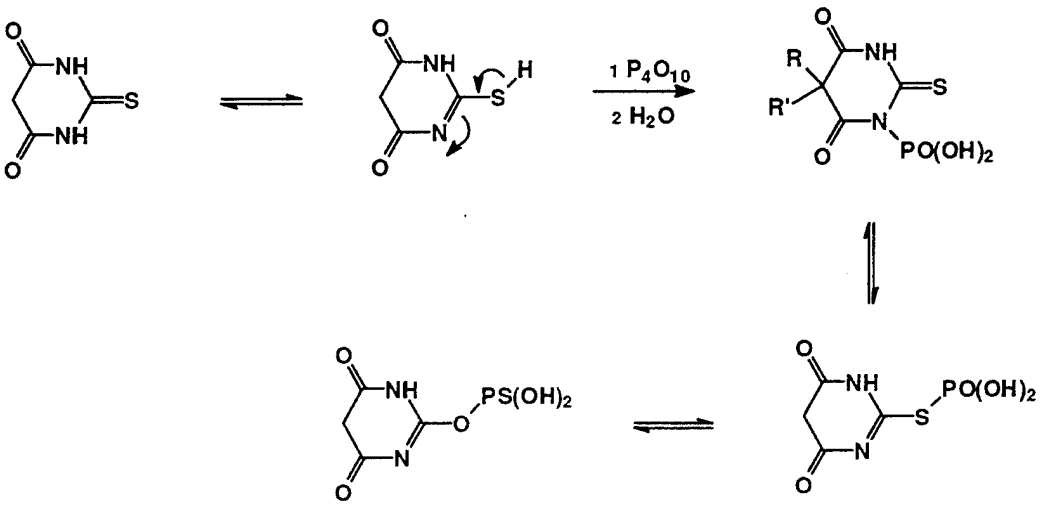
Phosphoric anhydride reacts with many compounds which are able to tautomerise. The initial products are pyrophosphates but with careful hydrolysis of the residual phosphoric anhydride bonds it is possible to isolate phosphorylated products.

Cyclic compounds such as cyclohexane-1,3-diones are converted to the corresponding enol phosphates in satisfactory yields,[7] whereas pyrimidinetriones react with P_4O_{10} more readily forming N-phosphorylated amides.[8]

*On subbatical leave from St Petersburg Institute of Cinema and Television, St Petersburg, Russia

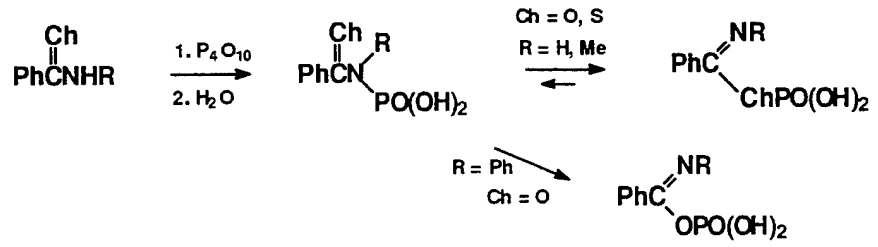


Thiobarbituric acid undergoes N-phosphorylation but this is not the terminal step of the reaction and the initial products rearrange reversibly to thiophosphate. ^{31}P NMR data indicated that the latter exists as an equilibrium of phosphorylthio-thiophosphoryl forms:

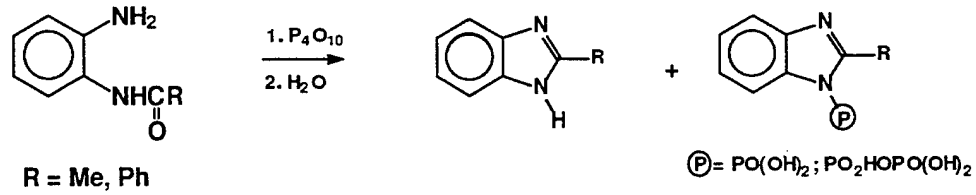


Whilst five-membered rings with the fragment NH-C(O) or NH-C(S), such as pyrrolidones and hydantoins are inert towards P_4O_{10}, thiohydantoin reacts with the formation of 3-N-(dihydroxophosphoryl)thiohydantoin for which no phosphorotropy was observed.

1-3 Shifts of the dihydroxyphosphoryl group is typical of phosphorylated non substituted amides.[1] The process of phosphorylation followed by migration of the phosphorus group was monitored by means of ^{31}P NMR spectroscopy. Initial attack by P_4O_{10} was directed towards the more nucleophilic nitrogen atom. The primary products tend to be unstable and under the action of protic solvents or moisture rearrange to the corresponding O-phosphorylated amides. For benzamides and acetanilides N→O migration is reversible,[5] whereas phosphorylated benzanilides rearrange irreversibly:



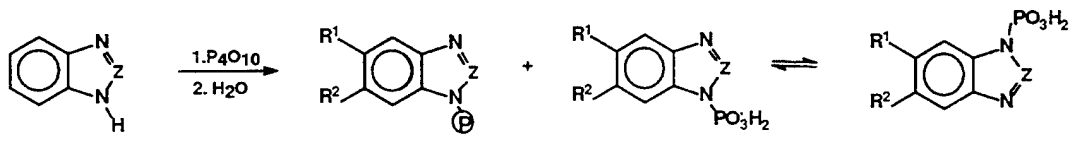
Acetanilides are reactive towards P_4O_{10} to give N-phosphorylated products. However, no intramolecular dehydration occurs[9] as observed in the reaction of N-acyl and N-benzoyl-o-phenylenediamines:[4]



Benzoylhydrazine reacts with P_4O_{10} with phosphorylation of the terminal nitrogen. This is followed by a reversible rearrangement (1-4 shift) to give a mixture of O- and N-phosphorylated compounds:

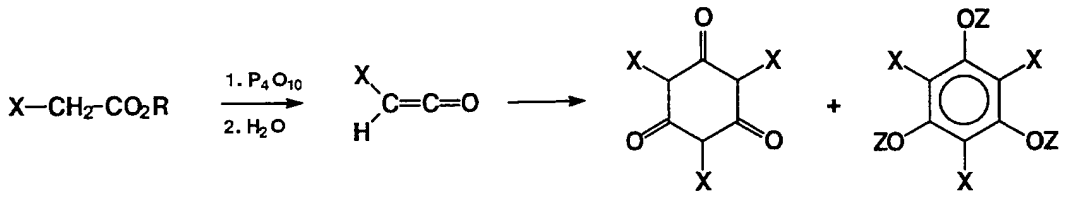


Phosphorylated azoles[2] are produced readily from the corresponding parent compounds and P_4O_{10} :



Z = CH; N P = $PO_2HOPO_2H_2$

The NMR data of phosphorylated 5,6-dimethylbenzotriazole supported the existence of facile phosphorotropy.[2] The reaction of P_4O_{10} and esters of monosubstituted acetic acid leads to the elimination of alcohol and gives monosubstituted ketenes that trimerise spontaneousely to give polysubstituted benzenes - 2,4,6-trisubstituted phloroglucinols and their derivatives:[3]



X = Ar, CN, NO_2; Z = H, $PO(OH)_2$, $PO(OH)OPO(OH)_2$

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REACTIVITY OF N-PHOSPHORYLATED MUSTARDS

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AGNES M. MODRO
Centre for Heteroatom Chemistry, Department of Chemistry, University of Pretoria,
Pretoria 0002, South Africa

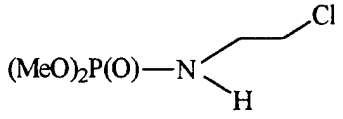
Abstract Products and mechanisms of the fragmentation of ionic phosphoramidates containing the N-(2-chloroethyl) functionality are discussed.

INTRODUCTION

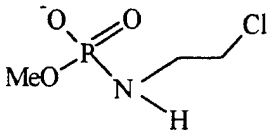
The metabolism of the anticancer prodrug cyclophosphamide is well understood, except of the exact mechanism of the alkylating reactivity of the phosphoramidate mustard, $(HO)(H_2N)P(O)N(CH_2CH_2Cl)_2$ (**1**). Although it is known that **1** is capable of bis-alkylating nucleophilic centres *via* aziridinium ion derived intermediates,[1] whether it reacts as an intact molecule, or the P-N bond cleavage is a prerequisite of the alkylation, remains controversial. In this work, we approached the problem by investigating the fragmentation behavior of some N-phosphorylated nitrogen mustard derivatives (**2**), closely related to **1**, and arrived at the general mechanistic pattern for the reactivity of that system.

RESULTS AND DISCUSSION

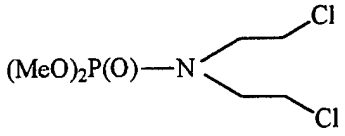
The following compounds **3** were prepared and used as precursors for the ionic substrates **2**, employed in the fragmentation studies.



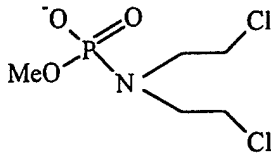
3a



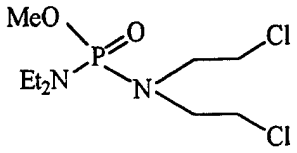
2a



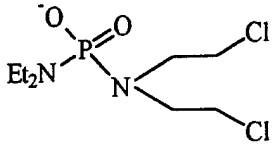
3b



2b

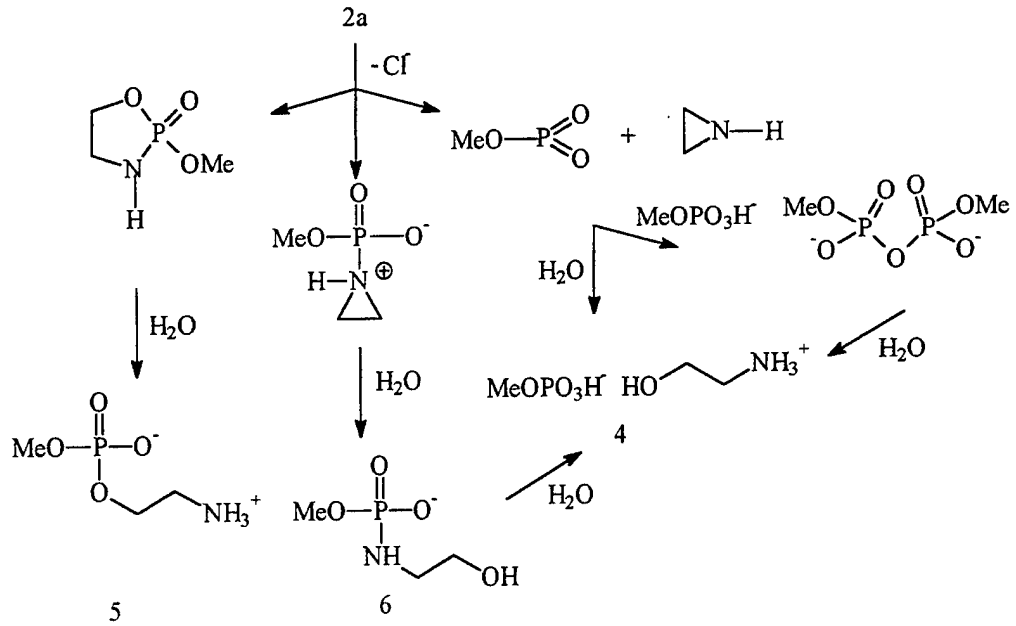


3c



2c

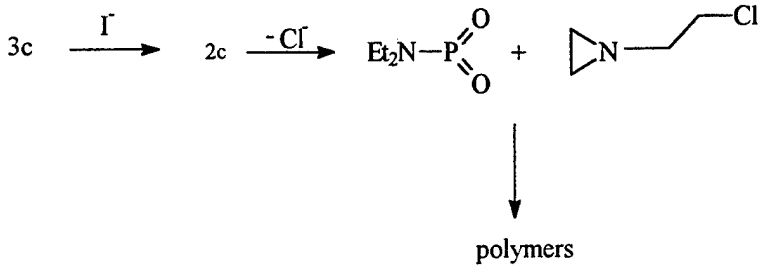
Ions **2a** and 2b could be easily prepared as lithium salts by demetyhylation of the corresponding **3** with LiI. Their fragmentation was then studied in aqueous, or in aqueous - pyridine solutions; the composition of the reaction mixtures as a function of time was determined by NMR spectroscopy, and the individual products were identified by comparison with independently prepared authentic compounds.[2] Fragmentation of **2a** follows three parallel pathways, and the full course of the reaction is presented below.



5 6 4

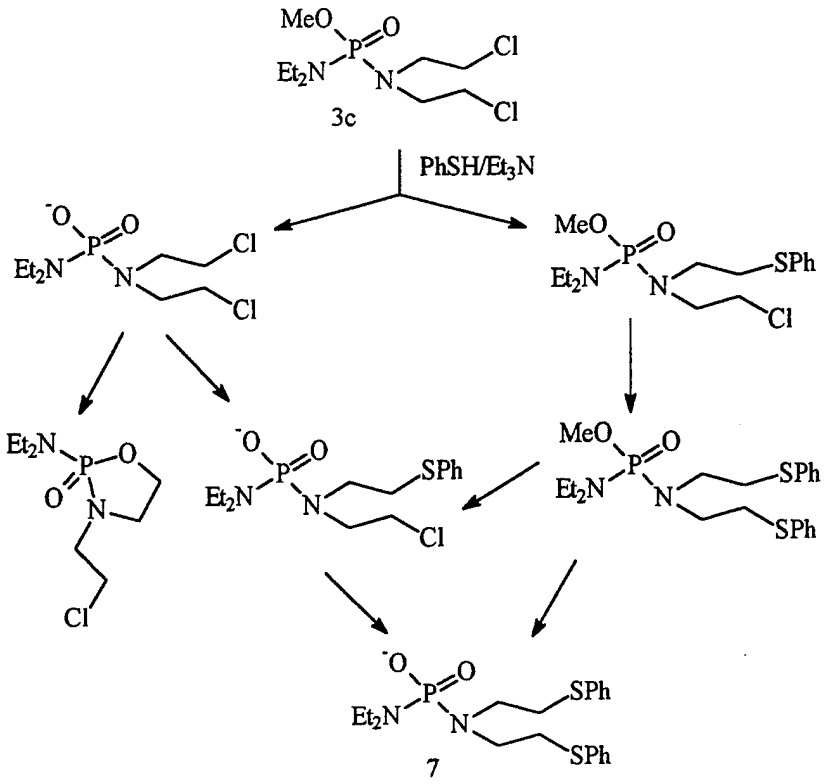
The first pathway is the 1,5-cyclization to a 1,3,2-oxazaphospholidine, which then undergoes slow hydrolysis to a stable diester **5** (*ca* 3%). Second pathway (*ca* 15%) is the 1,3-cyclization to N-phosphorylated aziridinium ion, which reacts fast with water (or any nucleophile present) to give an amidoester **6**, which breakes down slowly to the final product - the salt **4**. The major pathway involves, however, a fragmentation of **2** to methyl metaphosphate and ethylenimine, both reacting fast with water giving directly salt **4**. The metaphosphate can be also trapped by methyl phosphate, yielding transient dimethyl diphosphate, which also hydrolyzes finally to **4**. At the end of the reaction **4** represents *ca* 97% of the product, but it is formed *via* more than one pathway, each involving alkylation of water by an aziridine derivative. Minor product **5** represents the "inactive" direction in a sense that the cyclic intermediate is devoid of any alkylating properties. In the presence of pyridine, the fragmentation followed only the second pathway, with the methyl phosphate salt of N-(2-aminoethyl)pyridinium cation formed as a sole product. The behavior of **2b** paralled that of **2a**, with the "metaphosphate" mechanism representing the major, and the 1,5-cyclization the minor pathways.

The diamidate derivative **2c** demonstrated much higher reactivity than the amidoesters **2a** and **2b**. All attempts to prepare a salt of **2c** by demethylation of **3c** failed, as the demethylation product decomposed spontaneously as soon as it was formed from its precursor. When **3c** was heated with LiI, only a polymeric product was obtained, presumably derived from the monomeric intermediates formed according to the"metaphosphate" mechanism.



The alkylating behavior of **2c** was studied in the decomposition of its precursor **3c**, by incubating **3c** in CD_3CN with an excess of PhSH and Et_3N. All products (transient and stable) were identified by comparison with the standards and the course of the reaction

is shown below.



In the first step two S_N2 reactions take place: the O-demethylation, and the direct displacement of Cl by PhS^-. The demethylated intermediate can undergo 1,5-cyclization or can exchange both Cl atoms for the PhS groups; the other intermediate undergoes further S_N2 reactions. The final **7** is a product of bis-alkylation of thiophenol with **3c**, with the P-N bond retained. It decomposes slowly, yielding the product with $\delta_P \approx -20$, typical for the polyphosphate species observed in other reactions involving release of a metaphosphate intermediate.[3]

In conclusion, we found that the nitrogen mustards of the type **2c** are much more reactive than the ester analogues **2a**, **2b**, and that the alkylation by those systems can involve different mechanisms, including the release of a metaphosphate fragment.

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DEGRADATION PRODUCTS OF CYCLOPHOSPHAMIDE SYNTHESIS AND STRUCTURAL STUDIES

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Abstract The degradation of cyclophosphamide in neutral or slightly acidic aqueous solution starts with an intramolecular alkylation leading to an intermediary bicyclic compound which hydrolyses immediately and exclusively to a nine-membered heterocycle. Subsequent acid-catalyzed hydrolysis of the P-N-bond leads to a phosphoric acid monoester. In strongly acidic solutions (1 N HCl) cyclophosphamide decomposes exclusively to bis(2-chloroethyl)-amine and to the corresponding phosphoric acid monoester $H_2N(CH_2)_3OP(O)(OH)_2$. In solid samples of cyclophosphamide, heated up to its melting point, the first pathway predominates over the second one. The structures of the phosphorus compounds were established by ^1H and ^{31}P NMR spectroscopy, and synthesis. The structure of the bicyclic compound 2 is confirmed by a single crystal X-ray diffraction study which allows an explanation for the selective and immediate hydrolysis with formation of a nine-membered heterocycle and for the absence of the isomer with a six-membered ring.

Key Words: Cyclophosphamide, degradation pathways, ^{31}P NMR spectroscopy, X-ray crystal structure analysis

INTRODUCTION

Cyclophosphamide 1, clinically introduced in 1958, is a standard drug in tumor therapy. This alkylating substance is not active itself but requires in the first step an enzymatic activation in the liver to 4-hydroxycyclophosphamide. This first metabolite releases spontaneously via aldophosphamide the alkylating form, phosphoramide mustard.[1] Beside the metabolism of 1, its degradation in aqueous solution was also intensively studied.[2] These results were summarized and completed, using ^{31}P NMR spectroscopy and X-ray crystal structure analysis.

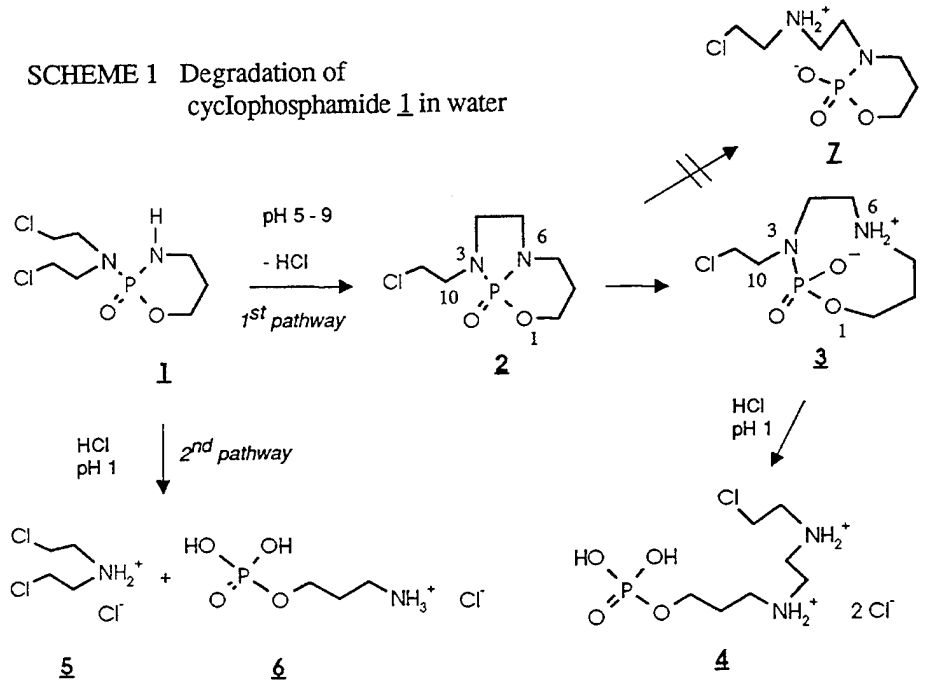
DEGRADATION PATHWAYS

Two pathways of degradation are known for 1 in aqueous solution. Scheme 1 shows the degradation products. In neutral or slightly acidic aqueous solutions (at pH values between 5.4 and 8.6) the first pathway starts with an intramolecular alkylation of 1 to the intermediate, not detectable bicyclic compound 2, which hydrolyses immediately and exclusively to form the nine-membered heterocycle 3. The possible isomer of 3, i.e. the six-membered ring compound 7, is not formed. Subsequent acid-catalyzed hydrolysis in aqueous solvents leads to the phosphoric acid monoester 4.

In strongly acidic solutions the second pathway of the decomposition of 1 leads exclusively to the hydrochloride salt of bis(2-chloroethyl)amine (nor-nitrogen mustard) 5 and of phosphoric acid monoester 6 ($t_{1/2}$ = 1.4 days at pH 1.2 and 37 °C) by the breakdown of the two P-N bonds. In the range of pH 2.2 - 3.4, both degradation pathways coexist.[2]

In solid samples of cyclophosphamide monohydrate, heated up to its melting point, the first pathway predominates over the second. All the above mentioned degradation products are found and, additionally, further compounds, which are formed by inter- or intramolecular alkylation reactions. Traces of compound 2 were detected by ^{31}P NMR spectroscopy in highly decomposed samples, dissolved in anhydrous solvents.

SCHEME 1 Degradation of cyclophosphamide 1 in water



SYNTHESIS

The pure compound 2 can be synthesized by treament of anhydrous 1 with sodium hydride in tetrahydrofuran. After addition of water compound 2 hydrolyses spontaneously and exo-thermally to compound 3. Further hydrolysis in hydrochloric acid transforms compound 3 to 4. Compound 6 is obtained from phosphoric acid phenyl ester dichloride by treatment with 3-amino-1-propanol, acid-catalyzed hydrolysis of the P-N bond, and removal of the phenylester group by hydrogenation with PtO_2/H_2.

STRUCTURAL STUDIES

^{31}P NMR spectra are a useful tool for the analysis of the hydrolysis mixtures of 1. The spectrum after 17 days at pH 3.4 at 37 °C shows the following well separated signals: *diamidoester* 1 at 15.58 ppm, *monoamidoester* 3 at 8.10 ppm, *monoesters* 4 at 1.49 and *monoesters* 6 at 1.28 ppm. In heated solid samples of 1 the ^{31}P signal ($CDCl_3$) of 2 is found at 24.80 ppm and that of 1 at 12.94 ppm. The nine-membered ring compound 3 is characterized by the lack of H-P and C-P couplings between $CH_2(7)$ and P and , especially, by the observation of couplings between $CH_2(10)$ and phosphorus in both the ^1H and ^{13}C NMR spectra which rule out the six-membered ring compound 7.

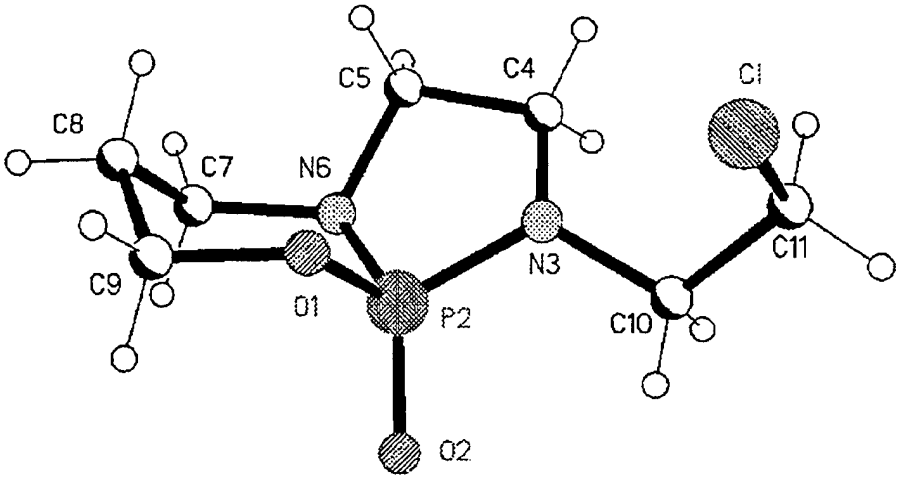


Figure 1 The crystal structure of the bicyclic compound 2

In order to rationalize the selective cleavage of the P-N6 bond of compound 2, instead of the P-N3 bond, the strain energy between these bonds was calculated by means of the force field program PIMM. The difference in strain energy is between 0.3 - 0.4 kcal/mol, which could be sufficient to explain the experimentally observed cleavage of the P-N6 bond.

The crystal structure of compound 2 shows that the six-membered ring exhibits almost a chair conformation with an axial phosphoryl oxygen (Figure 1). The phosphorus atom is displaced by 65.6 pm and the carbon atom 2 by -67.4 pm outside the plane formed by C9, C7, O1 and N6. The average deviation from this plane is 3.5 pm. The five-membered ring exists in an envelope conformation with P, N6, C4 and N3 in a plane, from which C5 is displaced by -47.7 pm (average deviation 1.4 pm). Both ring planes form an interplanar angle of 41.9°.

The phosphorus atom is oberved in a slightly distorted tetrahedral coordination geometry. The largest angles at phosphorus were found for the doubly-bonded O2, with 117.89(7)° O2-P-N3, 117.98(7)° O-2-P-N6 and 110.66(7)° O2-P-O1. The smallest angle with 97.36(7)° is found between the nitrogen atoms N3 and N6.

Significant differences are observed for the bond angle and bond length of both N-atoms. The angle sum at N6 shows with 339.11° a more pronouncedly pyramidal conformation than at N3 with 350.36°, and, moreover, the P-N3 bond length (162.99(14) pm) indicates a stronger π-bond character than the P-N6- bond length with 165.93 (14) pm.

In summary, the theoretical calculations of the strain energies of the P-N bonds of compound 2 as well as the P-N bond lengths determined in the crystal structure provide a plausible explanation for the observed selective hydrolysis of the P-N6 bond leading to compound 3.

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C-PHOSPHORYLATION OF AZOLES WITH TRIVALENT PHOSPHORUS HALIDES

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Abstract Simple method of C-phosphorylation of azoles by trivalent phosphorus halides in the pyridine solution have been developed. Hetaryldihalogen, dihetarylhalogen-, trihetarylphosphines, which were transformed into new types of P(III) and P(IV) derivatives, have been synthesized. Features of their reaction ability stipulated by the influence of hetaryl residues are found.

INTRODUCTION

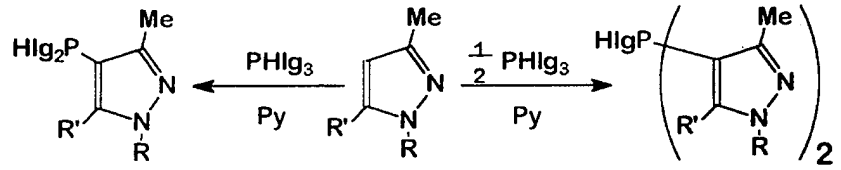
We have found C-phosphorylation's conditions of pyrrole, furan, thiphene derivatives [1] and related compounds. We have ascertained that the method of phosphorylation can be extended to phosphorylation of pyrazole and imidazole derivatives, their benzanalogs and more complicated heteroaromatic condensed systems, containing azole fragment.

RESULTS AND DISCUSSION

Pyrazoles **1** are easily phosphorylated by phosphorus (III) halides (Hlg = Cl, Br) in the pyridine solution at the fourth position. One or two pyrazole residue can be introduced at a single phosphorus atom.

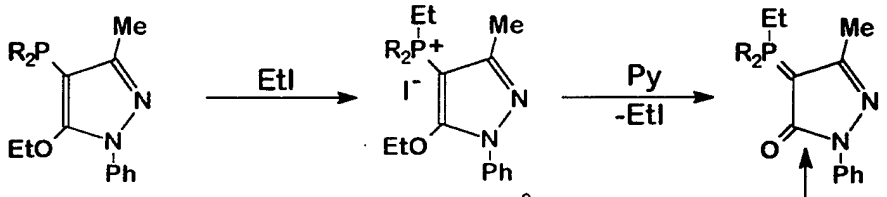
Proceeded from halogenphosphines **2** and **3** different derivatives were prepared. Among them, compounds **4** containing the alkoxy group at the fifth position

of the ring possess an especial reaction ability, namely, under heating or action of alkylhalides they are rearranged into ylids **5** [2].



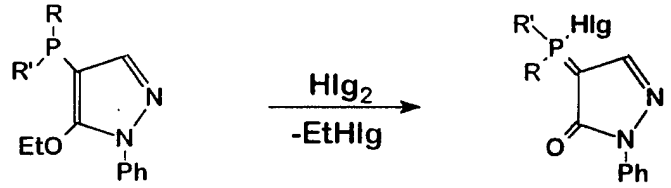
Hlg = Cl, Br ; R= Me, Ph ; R' = AlkO, Alk, Cl

3 **1** **2**



4 **5**

The rearrangement discovered was used for synthesis of P-halides **6a,b** [3].

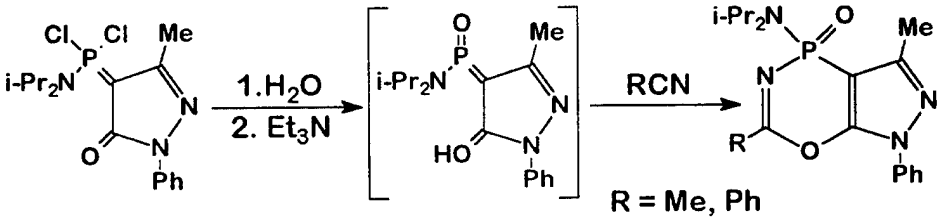


a: R = R' = Ph, R_2N ; Hlg = Cl, Br ;
b: R = i-Pr_2NH, R' = Cl ; Hlg = Cl ;

6 a,b

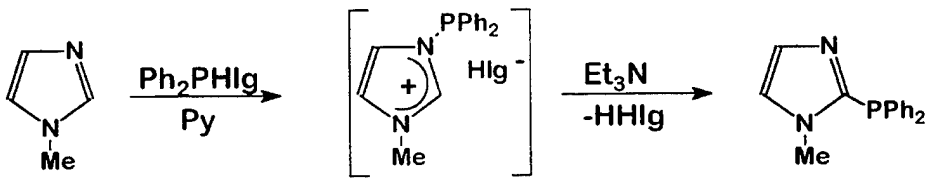
Chlorine atoms in the P-chlorides **6a,b** are sufficiently mobile and easily substituted under action of O,N,S-nucleophiles. In the case of dichloroylids, the derivatives containing double P=E bond (E = N, O, S) are formed. Reactions of dichloroylide **6b**, when P=E bond is formed under action of one mole of a nucleophile, present particular interest. For example, the reaction of **6b** with one mole of water directs to the formation of the derivative of a methylene(oxo)phosphorane (**7**), which have been transformed into novel types of phosphopruscontaining heterocycles

(**8**) under action of nitriles.



6b **7** **8**

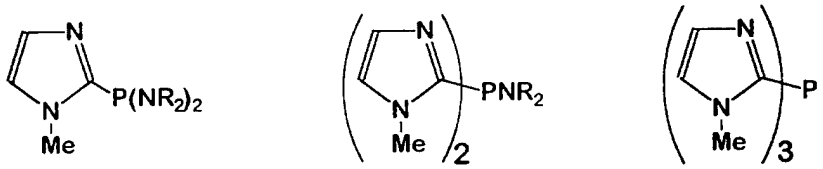
Phosphorylation of N-substituted imidazoles by trivalent phosphorus halides proceeds into the stage of formation of N-phosphinoimidazolium salts **10**, which are transformed into resulted phosphines, such as, for example, **11**.



Hlg = Cl, Br, I ;

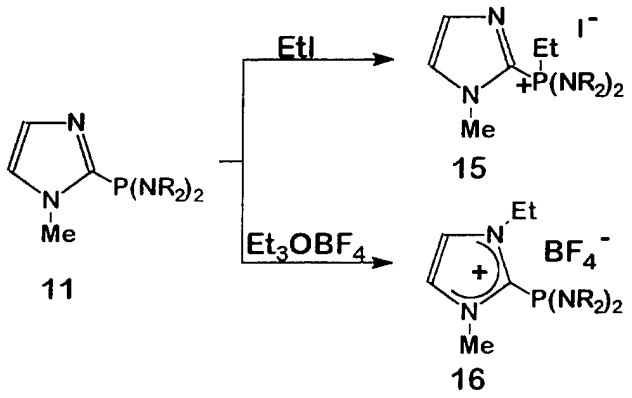
9 **10** **11**

Phosphines **12-14** are formed depending from the ratio of N-methylimidazole and phosphorus (III) halides in the reaction [4].

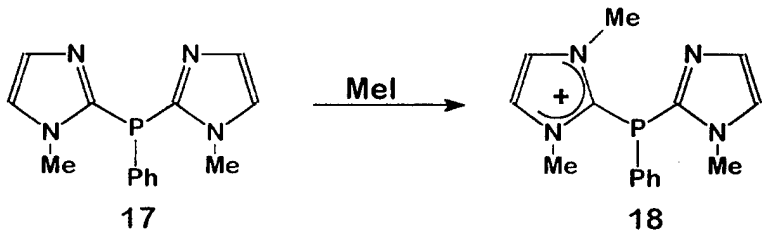


12 **13** **14**

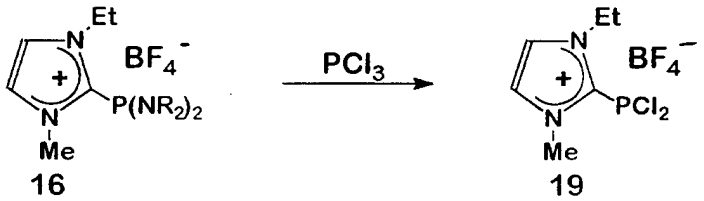
Phosphines **12-14** display unusual properties in the reactions of alkylation [5]. Either phosphonium salts (**15**) or imidazolium ones (**16**) are formed depending from hardness and softness of an alkylation reagent used.



Alkylation proceeds at the nitrogen atom even under action of methyliodide in the case of phosphine **17**.



Reaction of imidazolium salt **16** and phosphorus trichloride directs to the novel type of dichlorophosphines **19** which can be used for the synthesis of different derivatives.



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AN EFFICIENT AND REGIOSELECTIVE SYNTHESIS OF 1-ARYL(ALKYL)-4-DIETHOXYPHOSPHORYL-5-TRIFLUOROMETHYLIMIDAZOLES

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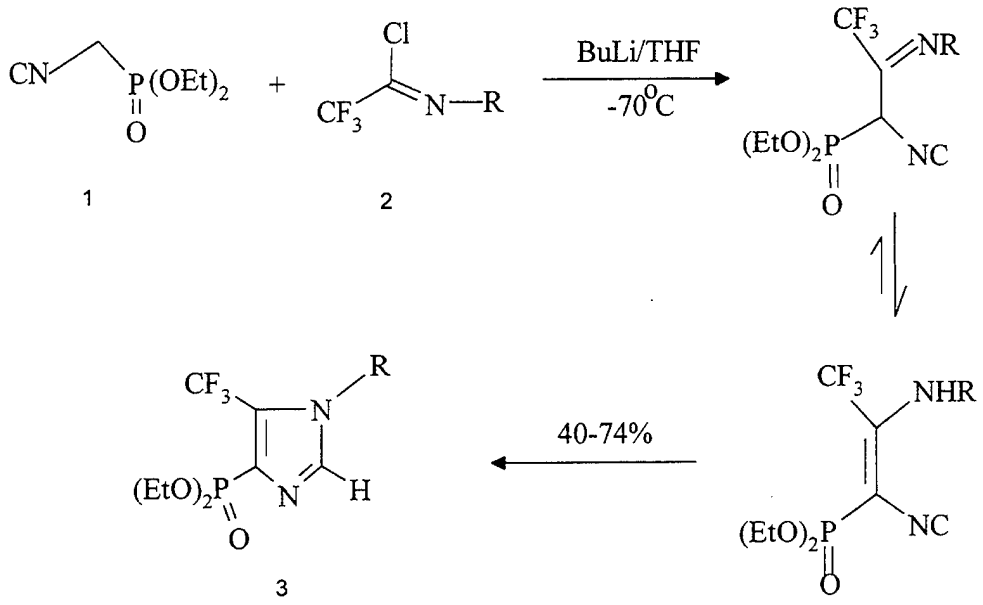
Abstract 1-Substituted-4-diethoxyphosphoryl-5-trifluoromethylimidazoles are prepared regioselectively from diethyl isocyanomethylphosphonate and N-substituted trifluoroacetimidoyl chlorides. The reaction mechanism was discussed.

Key words: trifluoromethylimidazole, phosphorylimidazole, regioselective synthesis.

Organophosphorus compounds received a renewed interest in the past decades with the discovery of more and more naturally occurring C-P compounds, which exibit significant biological activity. On the other hand, heterocyclic compounds have been attracting attention of chemists because of their pharmaceutical importance and extensive application in organic synthesis. Heterocycles in which the phosphoryl group is directly linked to the nucleus are difficult to prepare by the conventional reactions for C-P bond formation. However, the building block strategy can be exploited to undo this knot. Schollkopf and his co-workers synthesised phosphoryl oxazole and thiazole by the reaction of isocyanomethylphosphonate with acyl chlorides or carbon disulfide.[1] We also demonstrated that diethyl isocyanomethylphosphonate was useful synthetic block for 2-phosphorylpyrrole in its reaction with conjugated nitroolefins.[2] Herein we wish to report a base-induced cycloaddition of diethyl isocyanomethylphosphonate **1** to N-substituted trifluoroacetimidoyl chloride **2** , providing 1-substituted-4-diethoxyphosphoryl-5-trifluoromethylimidazole **3** . To the

best of our knowledge, neither synthesis of phosphoryl imidazole nor reaction of isocyanomethylphosphonate with C=N bond has been reported.

As shown in Scheme 1, the carbanion derived from **1** with BuLi at -70°C displaced smoothly the chlorine of **2** to form an imine intermediate, which upon rearrangement followed by cyclization, gave **3** in moderate to good yields. Signals at 7.60-7.79ppm(N=CHN) in ^{1}H NMR spectra definitely revealed the formation of imidazole. The yields of compound **3a** and **3b** were somewhat lower than that of 1-aryl derivatives, presumably due to the base-induced isomerization of corresponding imidoyl chlorides.[3] Usually, the addition of amine to isocyano-carbon requires the participation of the catalyst.[4] The driving force of such cyclization seems to be the tendency towards aromatization. Attempt to isolate the imine or the enamine intermediate was not successful.



R = n-C_8H_{17}(a), $PhCH_2CH_2$(b), C_6H_5(c), p-MeC_6H_4(d), m,p-$Me_2C_6H_3$(e), p-MeC_6H_4(f), p-ClC_6H_4(g), p-$NO_2C_6H_4$(h).

SCHEME 1

TABLE 1 Data of compounds **3**

Entry	Yield (%)	mp (°C)	IR(film) P=O	(cm^{-1}) C-F	^{19}F NMR	^{31}P NMR	MS (M+1)
3a	48	oil	1240	1180	21.7(s)	8.18(s)	385
3b	40	oil	1240	1180	21.2(s)	8.15(s)	377
3c	64	46-48	1250	1170	23.6(s)	7.99(s)	349
3d	62	56-58	1255	1160	23.3(s)	8.12(s)	363
3e	74	44-46	1250	1160	23.6(s)	8.14(s)	377
3f	60	40	1250	1180	23.2(s)	8.13(s)	379
3g	72	58-60	1240	1170	23.6(s)	7.64(s)	383
3h	70	116	1255	1185	24.0(s)	7.11(s)	393(M)

Replacement of BuLi by NaH in this reaction failed to give imidazole compounds. Quenching of the reaction mixture produced a complex which was difficult to separate by column chromatography.

The regiochemistry of this reaction deserved more attention. The single chemical shift in ^{31}P NMR and ^{19}F NMR spectra demonstrated the only structure of the products. The regioisomers of 1-substituted 2-phosphoryl-5-trifluoromethylimidazole, which may be resulted from 1,3-dipolar cycloaddition, were not detected. The ^{13}C NMR spectra confirmed the regiochemistry. The doublets of C-2 and C-4 and the dq signals of C-5 indicated that the phosphoryl group was linked to C-4.

Meanwhile, another pathway where the cyclization precedes the elimination of chlorine is possible.[5] This addition-cyclization-prototropic-elimination process, however, was precluded since the reaction of diethyl 1-isocyanoethylphosphonate with N-phenyltrifluoroacetimidoyl chloride gave 1-isocyano-2-imino phosphonate rather than imidazoline derivative. This result means that the elimination of chlorine from the N-anion is more rapid than the cyclization.

Consequently, the suggested effective and regioselective synthesis of 1-aryl(alkyl)-4-diethoxyphosphoryl-5-trifluoromethylimidazole from **1** and **2** undergoes an addition-elimination-isomerization-cyclization mechanism.

As shown by us, the logarithm values of ^{31}P NMR chemical shifts for resulted **3** correlated linearly with the σ parameters of the nuclear substituents in benzene ring, located on N-1 position.

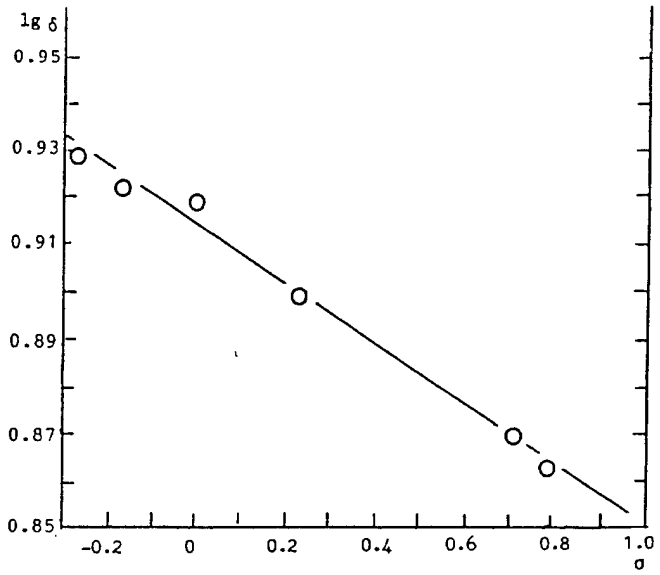


FIGURE 1 ^{31}P NMR chemical shift as the function of Hammett constant of phosphoryl imidazoles

$\log \delta = -0.0584\,\sigma + 0.898$ (n=6, r=99.33%)

The present method is convenient since both trifluoroacetimidoyl chlorides[6] and diethyl isocyanomethylphosphonate [7] are easily obtainable.

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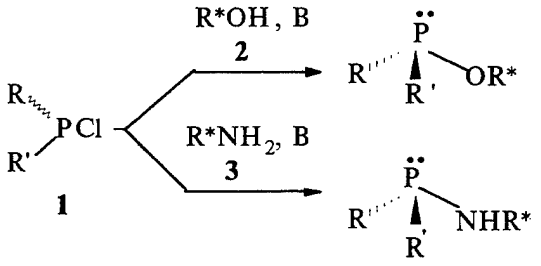
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DIASTEREOSELECTIVE REARRANGEMENTS AND EPIMERIZATION OF ORGANOPHOSPHORUS COMPOUNDS

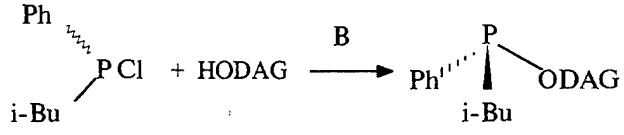
OLEG I. KOLODIAZHNYI, EVGEN GRISHKUN, OLEG GOLOVATYI, SERGEI USTENKO
Institute of Bioorganic Chemistry, National Academy of Sciences of Ukraine, Murmanskaya Street, 1, KIEV, 253094, Ukraine

Abstract New examples of asymmetric syntheses of organophosphorus compounds are described.

The presented work concerns the asymmetric synthesis of organophosphorus compounds proceeding under condition of kinetic or thermodynamic control and the application of obtained compounds for the organic synthesis. [1]
We found, that the stereoselectivity of the reaction of dialkyl- and diarylchlorophosphines **1** with chiral secondary alcohols **2** or with chiral primary amines **3** depends strongly on the structure of starting reagents and on the experimental conditions. Next factors increase the stereoselectivity: *a*- starting reagents **1-3** are sterically hindered: R(R')P = t-Bu(i-Bu)P, t-Bu(Ph)P, i-Bu(Ph)P, i-Pr(Ph)P; R*=L-menthyl, 1:2;5:6-diisopropylidene-D-hlucofuranose, CH(Me)Ph, $CH(R)CO_2Me$, $CH(Me)CH_2NEt_2$; $CH(Me)CH_2CO_2Et$; *b*- base B is strong, sterically hindered tertiary amine, such as DABCO or triisopropylamine; *c*- lowering of the temperature; *d*- excess of the chlorophosphine.

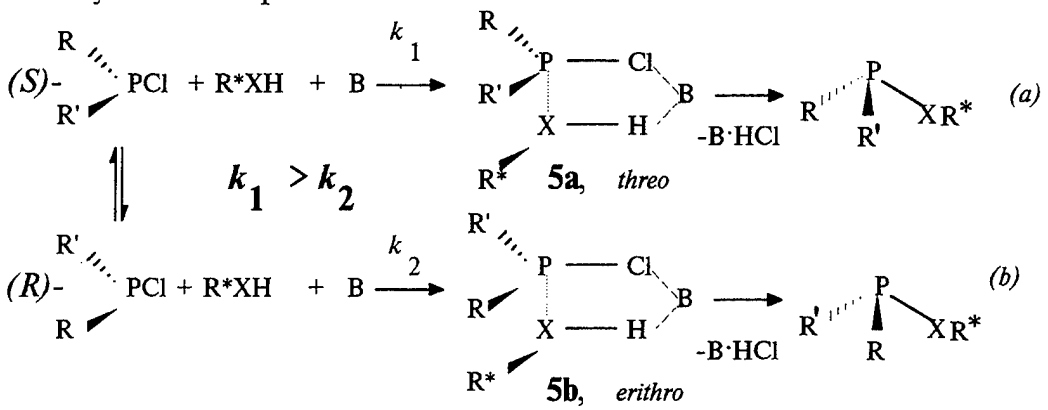


Thus, the diastereomer ratio of **4** in case of the reaction of isobutylphenylchlorophosphine with 1:2;5:6-diisopropylidene-D-hlucofuranose (HODAG) in depending on the nature of the base B is changed in the next sequence: DABCO (11:1), Et_3N (9:1), $PhNMe_2$ (1:1), Pyridine (4:6). It is remarkably that in the presence of pyridine the minor diastereomer becomes major. The asymmetric induction is absent when chlorophosphines **1** react with sodium alcoxides. The proposed method is simple, quick and convenient for the preparation of chiral phosphinic acid esters.

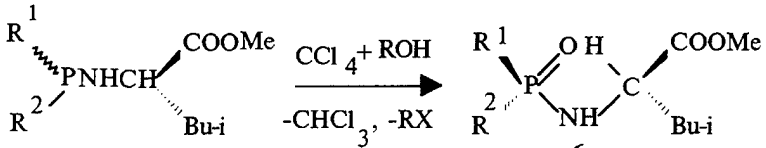


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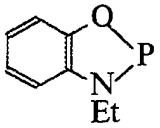
The reaction of the nucleophilic substitution at the tervalent phosphorus atom of the chlorophosphines **1** proceeds under conditions of kinetic control, via the formation of intermediate complexes **5** having the structure of *threo*- or *erithro*-diastereomers. Free activation energies of two competing directions *(a)* and *(b)* are different, that determines a difference between the rate constants k_1 and k_2 and the stereoselectivity of the reaction. The complex **5** is probably formed via frontal attack of the tervalent phosphorus atom by the nucleophile [2]



The oxidation of amines of phosphinic acids by the pair of tetrachloromethane-methanol (or water) proceeds with high stereoselectivity. In some cases the stereoselectivity achieves 100%. This reaction is especially of interest for the preparation of stereochemically pure derivatives of N-phosphorylated amino acids **6**, having important practical significance, because existing methods for their synthesis are not stereoselective. [3,4]

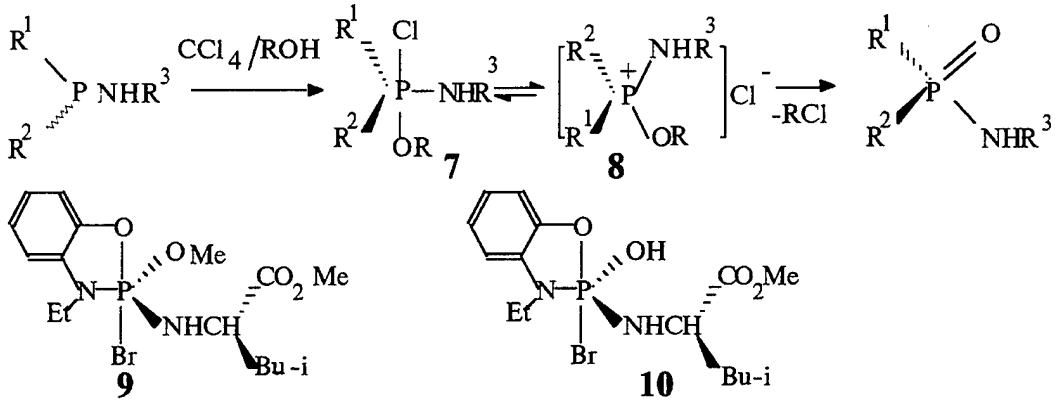


6

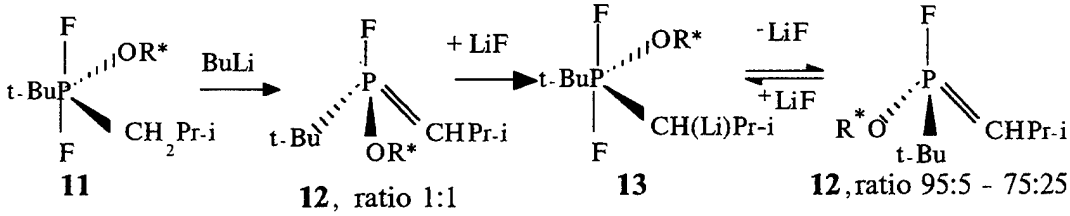
N of Comp.	$R^1(R^2)P$	Yield, %	diastereoisomeric ratio
6a	t-Bu(i-Bu)P	85	~100:0
6b	t-Bu(Ph)P	80	88:12
6c		80	75:25

The NMR spectroscopic studies showed that the reaction proceeds via the formation of alcoxyhalogenophosphorane **7**, which result in the pseudorotation gives the most thermodynamic stable diastereomer and via the alcoxyphosphonium salt **8** converts into the amidophosphinate. Alcoxyhalogenophosphorane have been succeeded to register in case of the compounds bearing the five-membered 1,3,2-oxazophospholane cycle, stabilizing pentacoordinate state of phosphorus atom. The ratio 94:6 (δp -56 and -58 ppm) shows high thermodinamical advantage of the one of the

diastereomers. Phosphorane **9** converts gradually into the resulting amidophosphate **6c** (half-life time ~5h). Analogously the hydroxybromo-phosphorane **10** have been obtained by the reaction of amidophosphinate **5** with $CBrCl_3/H_2O$. The chemical shift of the **10**, δ_P -55 ppm, responds to the pentacoordinate phosphorus atom.[4]



The dehydrofluorination of alcoxyfluorophosphoranes **11** bearing chiral ligands, resulting in the mixture of diastereomers of P-fluoroylids**12** in 1:1 ratio. However then in the presence of the lithium fluoride the epimerisation of P-fluoroylids proceeds. As a result the ratio of diastereomers changes strongly in favor of one of them, thermodynamically more advantageous. The epimerization is explained by the formation of the fluorophosphorane intermediates **13**, which adds and eliminates the lithium fluoride to convert gradually into the most thermodynamic stable diastereomer. [5]

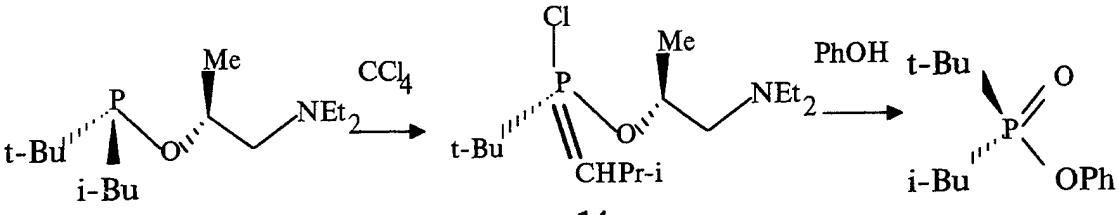


R* = DAG (a), (S)- $CH(Me)CH_2NEt_2$ (b); Menthyl (c)

The determination of heats of formation for ylid **11b** bearing the (S)-diethylamino-2-propoxyl group by means of CNDO calculation revealed, that the (R ,S) diastereomer is energetically more advantageous, than (S,S)-diastereomer. The difference 3.2 kkal/mol corresponds to the position of equilibrium, which is really observed.

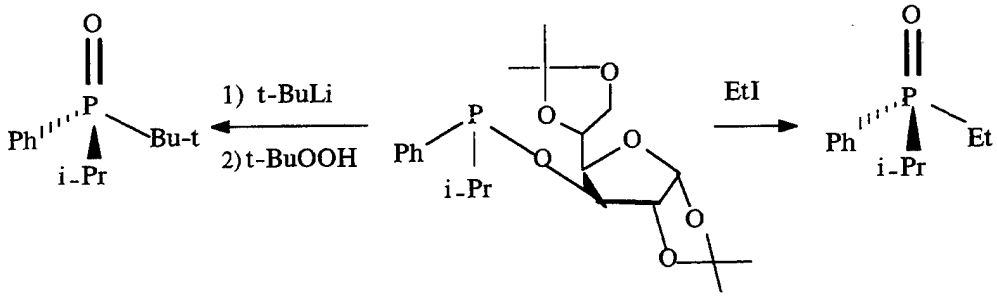
Chiral phosphinic acid esters are starting compounds for the synthesis of the enantiomers of valuable organophosphorus compounds, in particular of P-chloroylids **14**. The reaction of chiral phosphinic acid esters with tetra-chloromethane proceeds stereospecifically without the change of the sign of optical rotation. Chiral P-chloroylids **14** easily add compounds bearing mobile hydrogen atom the (phenols, ammonium) to convert into chiral derivatives of phosphinic acids, with abstraction of the chiral alcoxyl group.

The optical active P-chloroylids are perspective chirons for the organic synthesis. [6]



14

The chiral phosphinic esters react with haloid alkyls to form stereospecifically enantiomers of tertiary phosphines oxide. The comparison of the optical rotation with this one of the compounds described in the literature allows to determine the configuration of the phosphorus atom, including the configuration of starting phosphinic acid esters. The phosphinic acid esters smoothly oxidized by peroxides, add the sulfur. Reactions of phosphinic acid esters with organolithium compounds provide chiral tertiary phosphines.



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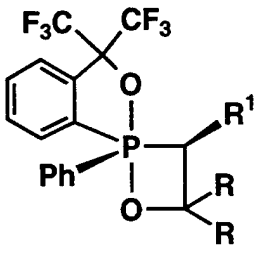
SYNTHESIS AND THERMOLYSIS OF PENTACOORDINATE 1,2-AZAPHOSPHETIDINES

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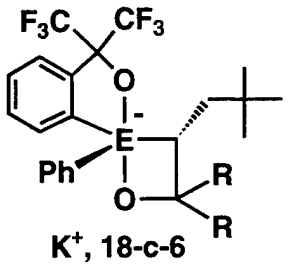
Abstract Pentacoordinate 1,2-azaphosphetidines bearing the Martin ligand were synthesized by the intramolecular dehydration of the corresponding β-amino phosphine oxides with Mitsunobu reagent (Ph_3P-$EtO_2CN{=}NCO_2Et$). The X-ray crystallographic analysis of 1,2,4,4,-tetraphenyl derivative shows that it has a distorted trigonal bipyramidal structure with oxygen and nitrogen atoms at apical positions. Their thermolyses gave the corresponding olefins along with a cyclic iminophosphorane, which was readily hydrolyzed to give the cyclic phosphinate and aniline.

INTRODUCTION

In the course of our study on oxetanes bearing a highly coordinate main group element at the neighboring position we achieved the syntheses and isolation of intermediates of pentacoordinate 1,2-oxaphosphetanes **1a,b**,[1], 1,2-oxasiletanides **2**,[2] 1,2-oxagermetanides **3**,[3] and 1,2-oxastannetanides **4**,[4] i.e., intermediates of the Wittig, Peterson, germanium-Peterson, and tin-Peterson reactions, respectively. Bestmann and Seng reported phosphorus ylides undergo the Wittig-type reaction with alkylideneamines instead of carbonyl compounds to give the corresponding olefins,[5] but there has been reported no evidence for the intermediates. We now report synthesis and thermolysis of pentacoordinate 1,2-azaphosphetidines which is formally derived from a phosphorus ylide and alkylideneamine.

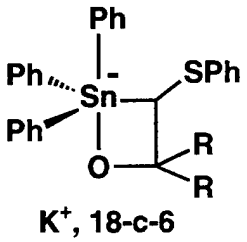


1a: R= H
1b: R= CO_2Me



K^+, 18-c-6

2: E= Si
3: E= Ge

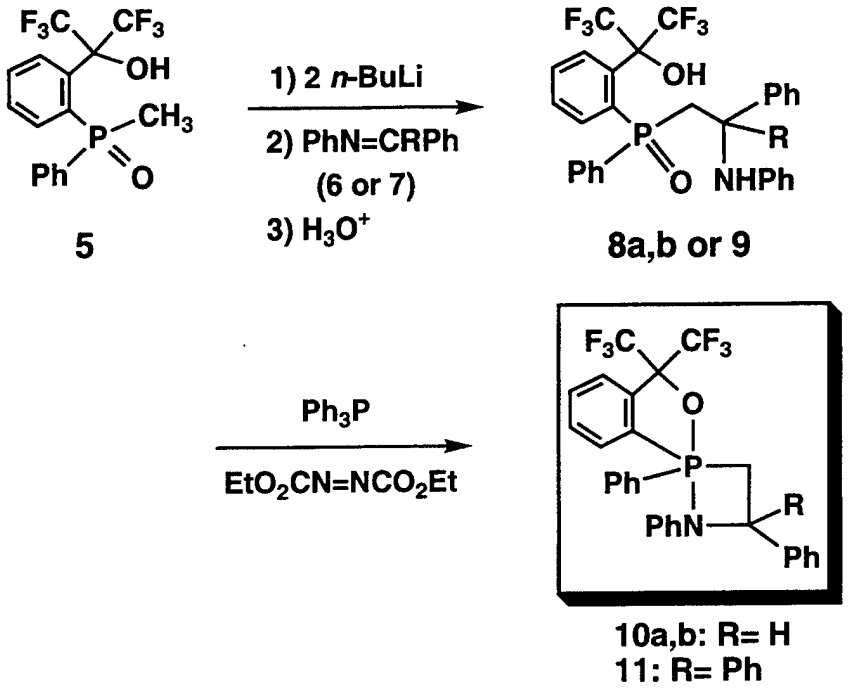


K^+, 18-c-6

4

RESULTS AND DISCUSSION

Sequential treatment of methylphenylphosphine oxide (**5**) having the Martin ligand[6] with 2.3 equiv of *n*-BuLi, with 2.4 equiv of benzylideneaniline (**6**) or diphenylmethyleneaniline (**7**) in THF at 0 °C, and then with aqueous NH_4Cl gave a diastereomeric mixture of β-amino phosphine oxides **8a,b** (52%) and **9** (44%) respectively. Intramolecular dehydration of **8a,b** and **9** with Mitsunobu reagent[7] provided target molecules **10a,b** and **11**, respectively. Their ^1H, ^{19}F, and ^{31}P NMR spectral data are partially summarized in Table 1, indicating that **10a,b** and **11** have a trigonal bipyramidal structure with nitrogen and oxygen atoms at apical positions. Compounds **10a,b** were very moisture-sensitive and readily hydrolyzed to the starting **8a,b**, but **11** could be isolated as colorless crystals (73%) by reprecipitation from CH_2Cl_2 by the addition of ethanol, indicating that 4,4-diphenyl groups can protect sterically and efficiently the lone pair of the nitrogen atom.



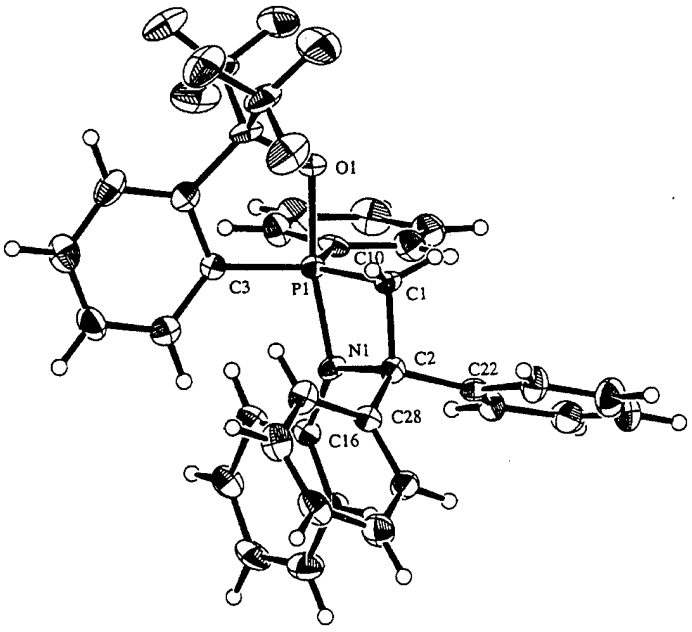
The X-ray crystallographic analysis of **11** indicates that it has a distorted trigonal bipyramidal structure with nitrogen and oxygen atoms at apical positions, very similar to those of pentacoordinate 1,2-oxaphosphetanes **1a,b**, 1,2-oxasiletanides **2**, and 1,2-oxagermetanides **3** (Figure 1). The apical bond P-N (1.789(5) Å) is close to that (1.782(3) Å) of spiro-1,3,2-diazaphosphetidine **12**,[8] but the P-O (1.796(5) Å) bond is

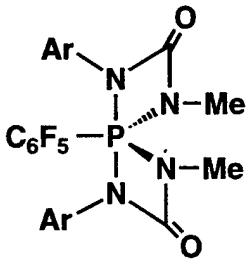
slightly longer than those of **1a,b**.[1] The bond angle between two apical bonds deviates by 13.1(3)° from 180°. The phosphorus atom is placed in the equatorial plane and the torsion angle P-C-C-N is -0.1°, indicating that the four membered ring is almost planar. Interestingly, the nitrogen is trigonal and the plane of the benzene ring on the nitrogen is placed in the same plane of the four membered ring.

Table 1. The ^{1}H, ^{19}F and ^{31}P NMR Data of **10a,b** and **11**.

	$\delta(^{1}H)$			$\delta(^{19}F)$	$\delta(^{31}P)$
Compounds	CHH'		CHN		
10a	3.49-3.55(m)	3.57-3.61(m)	4.57(m)	-73.5, -74.9[a)]	-30.6
10b	3.32(ddd)[b)]	4.10(ddd)[c)]	4.52(ddd)[d)]	-72.8, -75.2[a)]	-30.2
11	4.22(dd)[e)]	4.55(dd)[f)]	-	-73.6, -75.5[g)]	-29.4

a) A_3B_3 like, not resolved. b) ^{2}J(HP)= 21.1 Hz, ^{2}J =16.5 Hz, ^{3}J =5.0 Hz. c) ^{2}J(HP)= 19.6 Hz, ^{2}J =16.5 Hz, ^{3}J =8.7 Hz. d) ^{3}J(HP)= 12.2 Hz, ^{3}J =8.7 Hz, ^{3}J =5.0 Hz. e) ^{2}J(HP)= 19.6 Hz, ^{2}J =17.0 Hz. f) ^{2}J(HP)= 21.6 Hz, ^{2}J =17.0 Hz. g) q, ^{4}J(FF)=9.9 Hz.



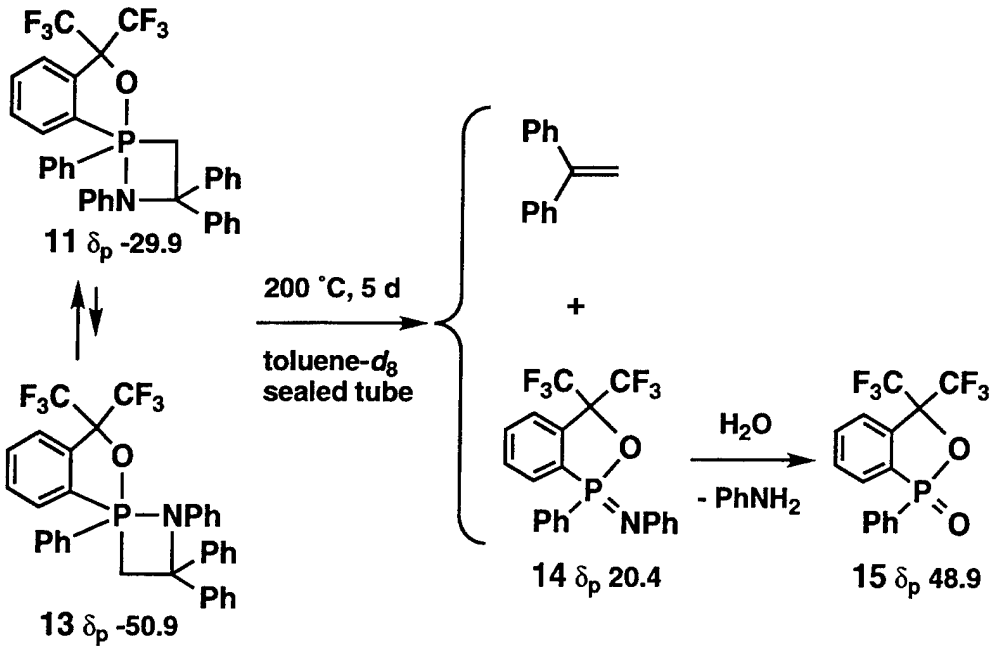


Ar= *m*-$CF_3C_6H_4$

12

Figure 1. ORTEP drawing of **11**.

Thermolysis of **10a,b** at 180 °C in a toluene-d_8 solution in the presence of $Ph_3P{=}O$ and $EtO_2CNHNHCO_2Et$ as products gave a trace of styrene. When **11** ($\delta(^{31}P)$ -29.9) was dissolved in toluene-d_8, another signal appeared at $\delta(^{31}P)$ -50.9, probably due to pseudorotamer **13** with the nitrogen being equatorial.[9] Heating of the solution at 200 °C for 5 d in a sealed tube gave quantitatively 1,1-diphenylethylene and the corresponding iminophosphorane **14**, which was hydrolyzed to the corresponding cyclic phosphinate **15** along with aniline.



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METHYLENEPHOSPHINOPHOSPHORANES. UNUSUAL ADDITION REACTION IN ORGANOPHOSPHORUS CHEMISTRY.

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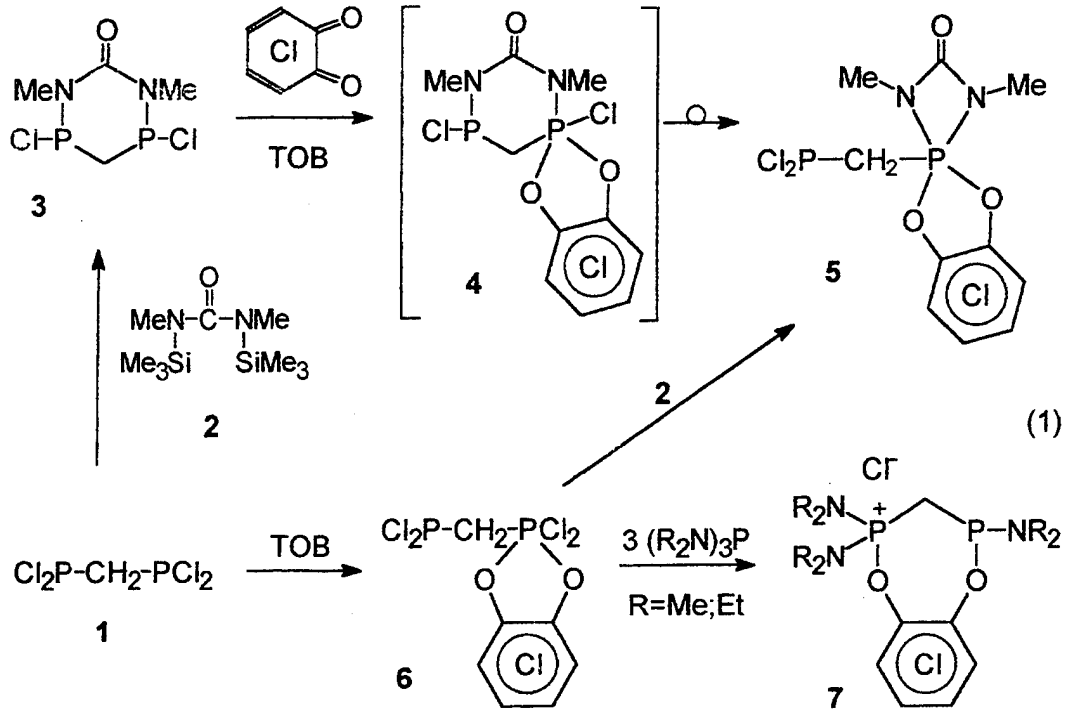
Abstract: Intermediate **4** is unstable and rearranges into **5**. Substitution of chlorine atoms in **5** by dialkylamino groups gives **8** and **9**. **8** reacts with TEA to give phosphaalkene **10**, which slowly dimerizes into **11**. Methylenephosphinophosphorane **9** shows unusual properties. It adds isocyanates to two phosphorus atoms to give zwitterionic structural isomers **12a,b**. The structure of **12a** was resolved by X-ray analysis. **9** reacts with azides unexpectedly giving the zwitterionic product **13**. Reaction of **9** with hexafluoroacetone is unusual and leads to the ylid **14a,b**. According to the X-ray data it exists in zwitterionic form **14b** and displays a new type of coordination at phosphorus atom. HFA can react in a similar way with other phosphines. For example, with **15** it gives the double ylid **16**.

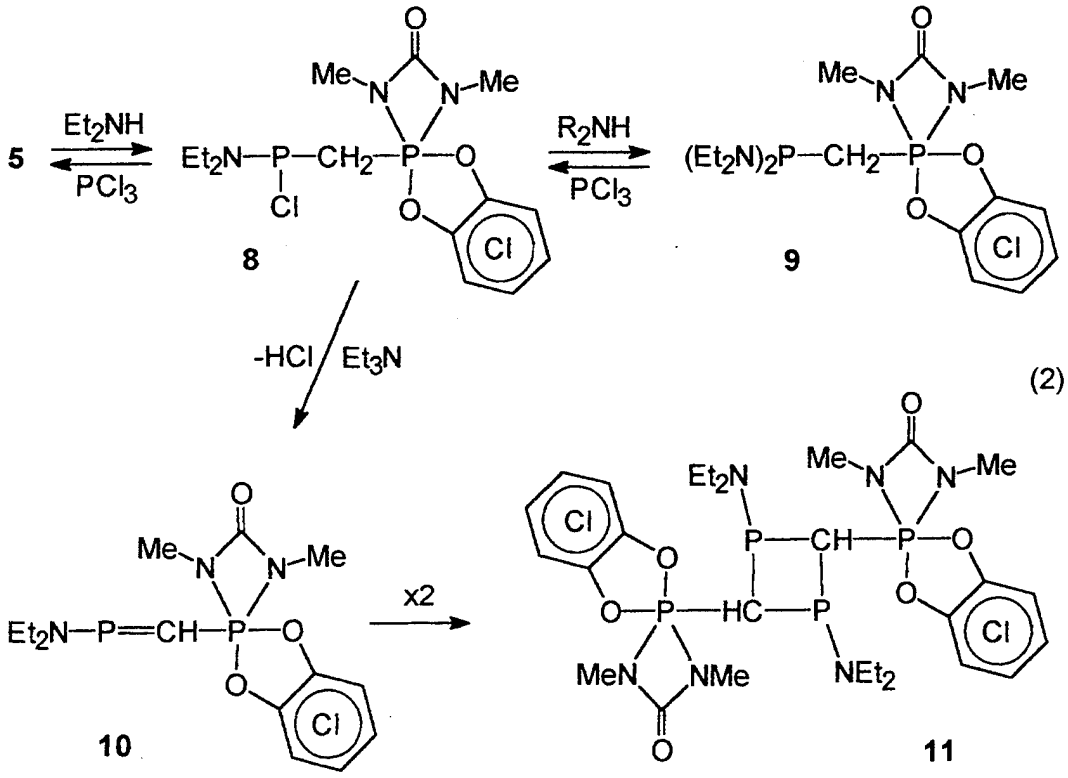
Methylenephosphinophosphorane, isocyanate, addition, hexafluoroacetone, oxydation

The reaction of methylenebis(dichlorophosphine) **1** with silylated urea **2** leads to 1,5-Diaza-2,4-diphosphorinan-6-one **3**.[1] Oxydation of one phosphorus atom of **3** by tetrachloroorthobenzoquinone (TOB) occurs easily but it does not give the expected product **4** which is unstable and undergoes an interesting rearrangement into methylenephosphinophosphorane **5**. The oxydation of **1** by TOB leads to another methylenephosphinophosphorane **6**. The reaction of **6** with silylated urea **2** also gives compound **5**. Thus methylenephosphinophosphorane **5** can be obtained in two ways, both of them include the formation of unstable intermediate product **4**. The reaction of **6** with tris(dialkylamino)phosphine proceeds with the substitution of chlorine atomes by dialkylaminogroups and causes an interesting rearrangement into seven-membered heterocyclic system **7** which includes both phosphorus atoms. (Fig. 1)

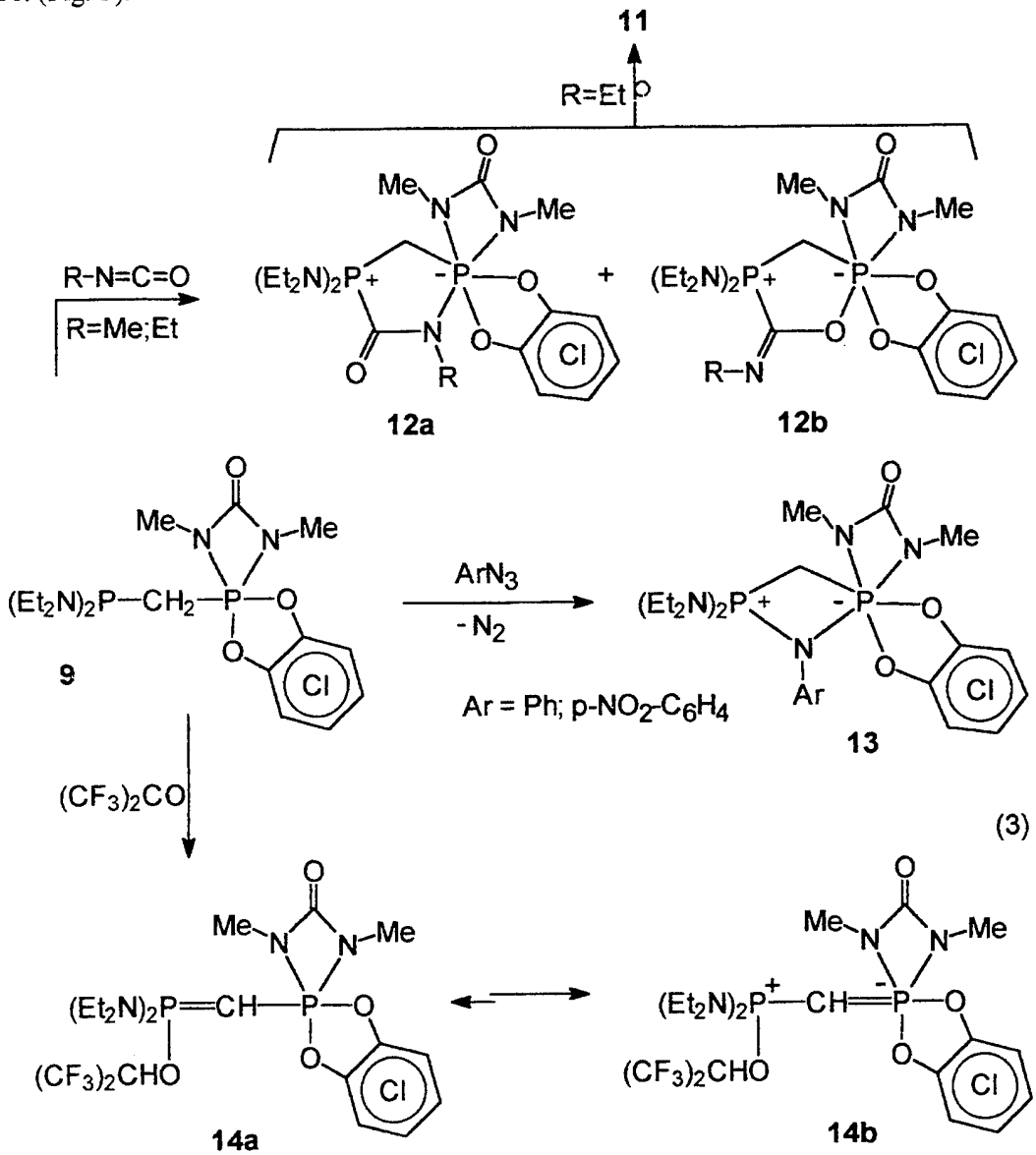
Chlorine atoms in **5** can be stepwise substituted by dialkylaminogroups to give derivatives **8** and **9**. Using PCl_3 it is possible to conduct the reverse transformations from **9** to **8** and then to **5**. Under the action of triethylamine **5** loses HCl and forms the C-spirophosphoranesubstituted phosphaalkene **10**. **10** is stable in solution within several hours and then dimerizes into **11**. (Fig. 2).

The methylenephosphinophosphorane **9** is especially interesting. It possesses unusual chemical properties. For example, it adds methyl- and ethylisocyanate to two


MeN NMe
Cl-P P-Cl
3
Cl
O
O
TOB
4
Me N N Me
Cl2P—CH2—P
5
MeN-C-NMe
Me3Si SiMe3
2
2
(1)
Cl2P-CH2-PCl2
1
TOB
Cl2P-CH2-PCl2
6
3 (R2N)3P
R=Me;Et
Cl⁻
R2N
R2N
P-NR2
7


5
Et2NH
PCl3
Et2N—P—CH2—P—O
Cl
8
R2NH
PCl3
(Et2N)2P—CH2—P—O
9
-HCl
Et3N
(2)
Et2N—P═CH—P—O
10
x2
Et2N
P—CH—P—O
O—P—HC—P
MeN NMe
NEt2
11

phosphorus atoms turning them into tetra- (λ^4P^+) and hexa-coordinate state (λ^6P^-) with formal opposite charges.[2] The reaction gives two structural isomers **12a** and **12b** in the ratio 7 : 1 which are in equilibrium. This is a new type of addition reaction in organophosphorus chemistry. The structure of **12a** was determined by X-ray analysis. The two bonds connecting the isocyanate fragment to the two phosphorus atoms are longer than expected. Accordingly the isocyanate fragment dissociates from the rest of the molecule in solution very easily. It is interesting that the isomers **12a,b** (R=Et) rearrange slowly in solution of chloroform at room temperature into the dimer **11**. This reaction obviously includes the intermediate formation of the monomeric phosphaalken **10**. (Fig. 3).



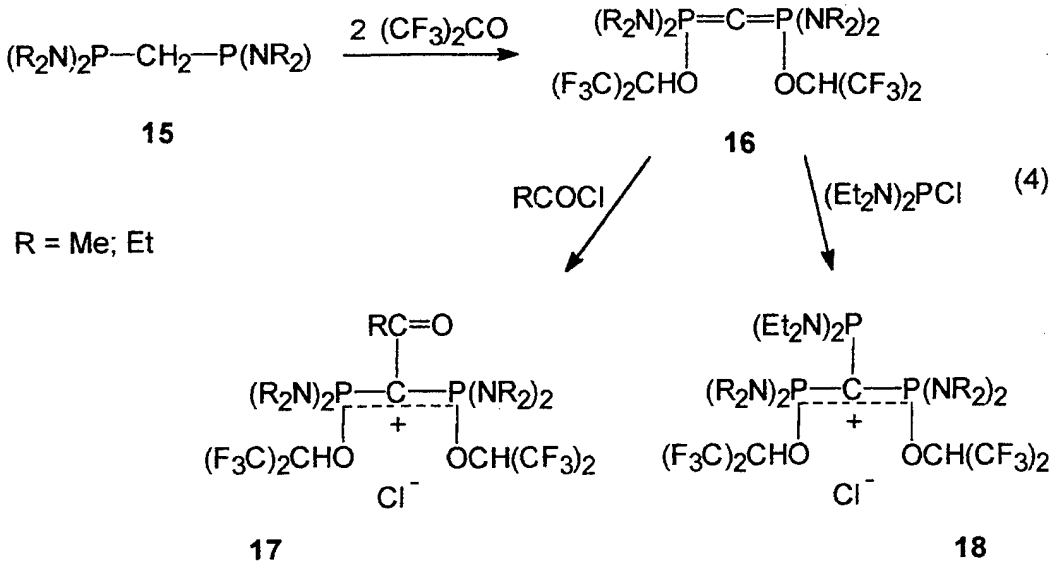
(3)

The interaction of **9** with azides is also unusual. It does not give the normal Staudinger reaction product. The reaction proceeds with the expected evolution of

nitrogen but again with the participation of both phosphorus atoms and leads to the zwitterionic product **13**.

The reaction of **9** with hexafluoroacetone (HFA) is very interesting. It does not lead not to the expected cyclic oxidation product but to compound **14**, which can be considered as an addition product of the P-H ylid, isomeric to **9**, to the carbonyl function of HFA.[3] Even if an excess of HFA was used, no other products except **11** were observed. X ray analysis of **14** showed that the λ^5P-C bond is even shorter than the ylidic λ^4P=C bond and that it has a pronounced double character. From these data the structure **14b** of negatively charged penta-coordinate phosphorus with a double bond can be postulated (Fig. 3).

It turned out, that HFA reacts in a similar way with some other phosphines as well. For example methylenediphosphine **15** easily adds two equivalents of HFA giving the double ylid **16** (Fig. 4). The reaction proceeds obviously in two steps, through the monoylid intermediate which cannot be detected as its further reaction with HFA is more rapid than its own formation. Compound **16** is stable in solution and can be prepared in good yield. It is readily available and presents an interesting starting material which can be derivatized in different ways. For example, it reacts with chloroanhydrides of carboxylic acids or with PCl_3 with the formation of salts **17** and **18** respectively.



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ENZYMATIC SYNTHESIS OF CHIRAL, NON-RACEMIC PHOSPHORYL COMPOUNDS

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Abstract: A series of phosphinyl-, phosphonyl- and phosphorylacetates was hydrolyzed in the presence of Pig Liver Esterase (PLE) to give the corresponding P-chiral phosphoroacetic acids and unreacted esters in a high enantiomeric purity (up to 100% ee).

Chiral phosphine oxides constitute a very important class of chiral phosphorus compounds which are widely used in synthetic and stereochemical studies. Chiral phosphine oxides are used as chiral auxiliaries in stoichiometric reactions[1] and they are the best precursors of chiral phosphines which, in turn, are usually applied as chiral ligands in transition metal catalyzed reactions.[2] Therefore, a search for new, efficient and general methods of the synthesis of chiral phosphine oxides continues.

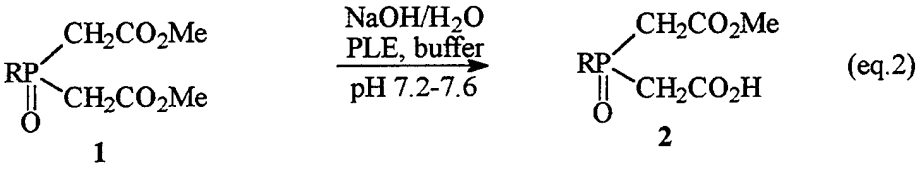
Recently, the enzyme-mediated hydrolysis reactions have been proven to be suitable for the generation of chiral heteroatomic centers. This approach was successfully applied to the synthesis of chiral sulfinyl carboxylates[3], hydroxymethylsilanes[4,5] and hydroxymethylgermanes.[6] Our recent work has demonstrated that enzyme-promoted hydrolysis of prochiral sulfinyldiacetate $(MeO_2CCH_2)_2SO$, is also very effective (ee up to 92%) in the preparation of both enantiomers of the corresponding carboxy-sulfoxide.[7]

These results prompted us to extend our investigations to phosphorus compounds having a stereogenic phosphinyl group. In the first instance, we decided to study the enzymatic hydrolysis of prochiral phosphinyldiacetates **1**. These compounds were obtained by a Reformatsky-type reaction of dichlorophosphines with alkyl bromoacetates.[8]

$$RPCl_2 + 2BrCH_2CO_2R^1 \xrightarrow[45\text{-}64\%]{\text{1. Zn}\ \text{2. [O]}} \underset{\underset{O}{\|}}{RP(CH_2CO_2R^1)_2} \quad \textbf{1} \qquad \text{(eq.1)}$$

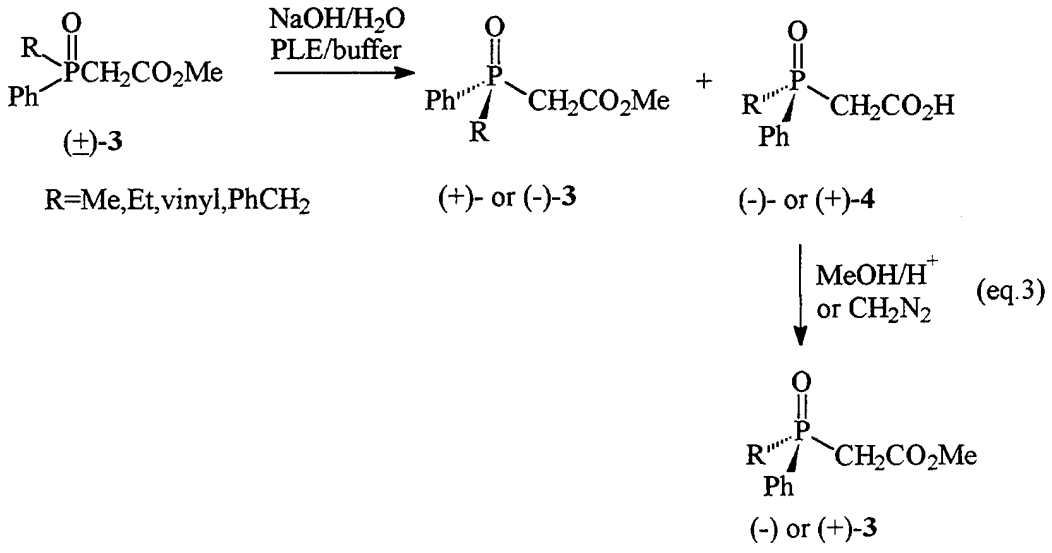
R=Ph,Et,BuO
R^1=Me,Et

However, in contrast to prochiral sulfinyldiacetates, the PLE-catalyzed hydrolysis of prochiral phosphinyldiacetates **1** was found to proceed slowly and with very low enantioselectivity affording the products **2** with enantiomeric excess values not exceeding 10%.



1 **2** (eq.2)

Therefore, we turned our attention to a different type of phosphinyl substrates, namely racemic phosphinylacetates **3**. In this case, the enzymatic hydrolysis was performed under kinetic resolution conditions, that is it was stopped after ca. 50% conversion. It was gratifying to find that the PLE-promoted hydrolysis of **3** proceeded smoothly and gave both the unreacted ester **3** and the corresponding acid **4** in good yields and with high enantioselectivity (ee up. to 100%).[9]



(±)-**3**

R=Me,Et,vinyl,$PhCH_2$ (+)- or (-)-**3** (-)- or (+)-**4**

(-) or (+)-**3** (eq.3)

By means of chemical correlation and circular dichroism (CD) spectra we were able to determine absolute configuration of the chiral products **3** and **4**. It turned out that all the recovered esters **3** have the same spatial arrangement of substituents around chiral phosphorus (as depicted in equation 3). This means that within the series of substrates investigated, enantiomers of the same spatial structure are recognized by PLE.[9]

Although the X-ray crystal structure of PLE is not known, extensive studies of Jones and his coworkers[10] on the PLE-catalyzed reactions of chiral and prochiral substrates led them to propose the active-site model of Pig Liver Esterase. Application of this model to our case requires that the methoxycarbonyl group should be located within the spherical locus of the catalytically active serine function (Fig.1). Taking into account the chirality at phosphorus in the ester **3**, which undergoes hydrolysis, the phenyl group should be accommodated in the large hydrophobic pocket (H_L), the alkyl group in the small hydrophobic pocket (H_S) and the phosphoryl oxygen in the back polar pocket (P_B) (Fig.1a). The alternative binding mode (Fig.1b) required for hydrolysis of the ester **3** with opposite configuration at phosphorus would change the position of the phosphoryl oxygen from the H_B- to H_F-pocket. The reason why the first binding mode is strongly preferred is not clear now.

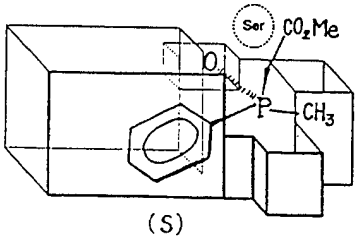


Fig **1a**

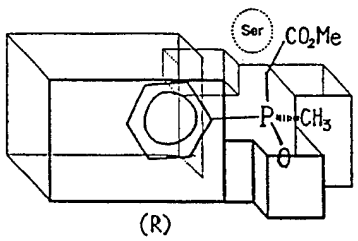
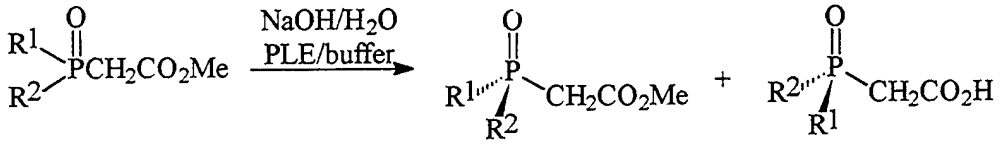


Fig **1b**

To broaden the spectrum of chiral phosphorus substrates, our investigations were extended to phosphonyl- and phosphorylacetates **5**. It was found that in the majority of cases the PLE-mediated hydrolysis is enantioselective and affords the products in good yields.

However, enantiomeric excess values of the chiral products **5** and **6** are generally lower, an exception being **5a** (ee~95%). Determination of the chirality at phosphorus in these compounds is under way.



(±)-5 (+)- or (-)-5* (-)- or (+)-6*

Substrate	R^1	R^2	pH	Time [h]	Ester 5*			Acid 6*		
					Yield [%]	$[\alpha]_D$ (MeOH)	ee [%]	Yield [%]	$[\alpha]_D$ (MeOH)	ee [%]
5a	Ph	MeO	7.5	15	40	-16.1	~9 5	44	+9.1 +10.8[a]	~64
5b	Ph	EtO	7.2	48	46	-11.3	~67	40	+13.1 +11.8[a]	~71
5c	Et	MeO	7.2	1.5	50	+8.5	~38	34[a]	-10[a]	42
5d	Et	EtO	7.2	48	40	+1.9	-	60[a]	-14[a]	-
5e	Et_2N	MeOH	7.5	7	20	-21.7	~90	58	+5.8	-
5f	PhO	EtO	7.1	45	66	-3.0[b]	~20	22	+8.7[b]	52

a) after reesterification
b) in $CHCl_3$

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o-PHOSPHINOPHENOLES - SYNTHESIS AND REACTIVITY

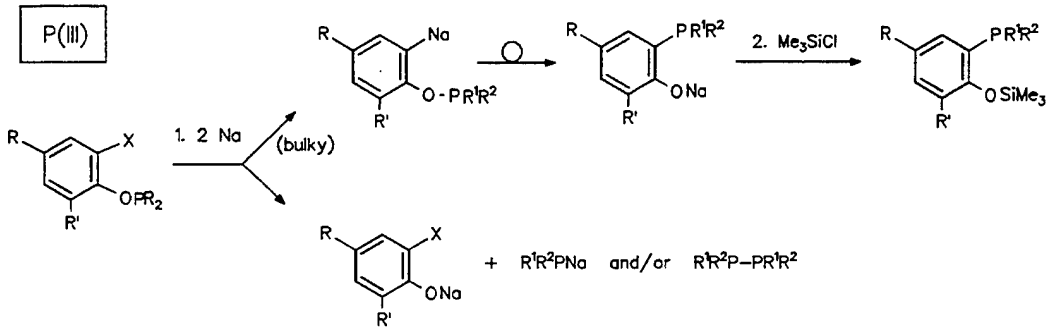
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Abstract Single and bulky substituted o-phosphinophenoles, -naphtholes, -diphenyl-2'-oles and -dinaphthyl-2'-oles are prepared and their preferred conformations studied. Substitution reactions at OH- and PH-groups, cyclization reactions to give P-E-O and P=E-O heterocycles as well as formation of nickel chelate complexes are described.

Keywords: hydroxyaryl phosphine ligand, heterocycle, phosphen, aroxydiphosphine

By reaction of appropiate dilithium reagents with chlorophosphines, subsequent treatment with Me_3SiCl and alcoholysis or by a metallation rearrangement procedure of o-bromo-aroxyphosphines (Scheme 1) a number of o-phosphinophenoles, -naphtholes as well as some diphenyl-2'-oles and dinaphthyl-2'-oles were prepared. Problems by side reactions and limits of the methods are discussed.

Scheme 1



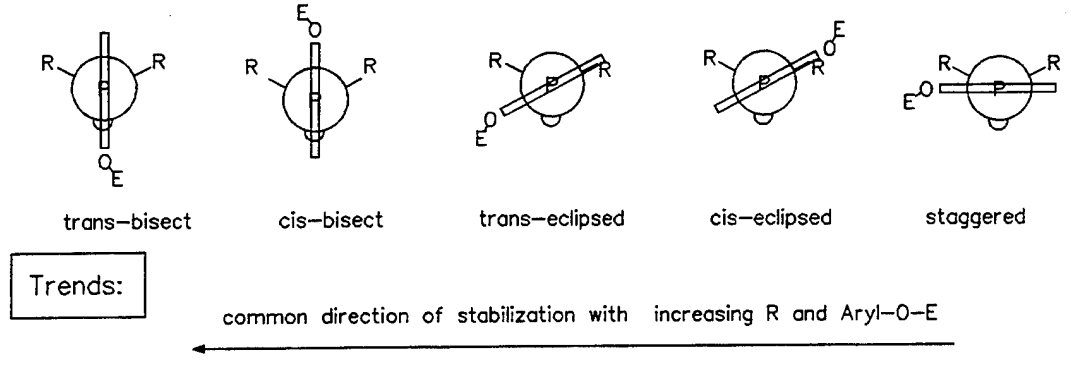
yields of phosphinophenoles:

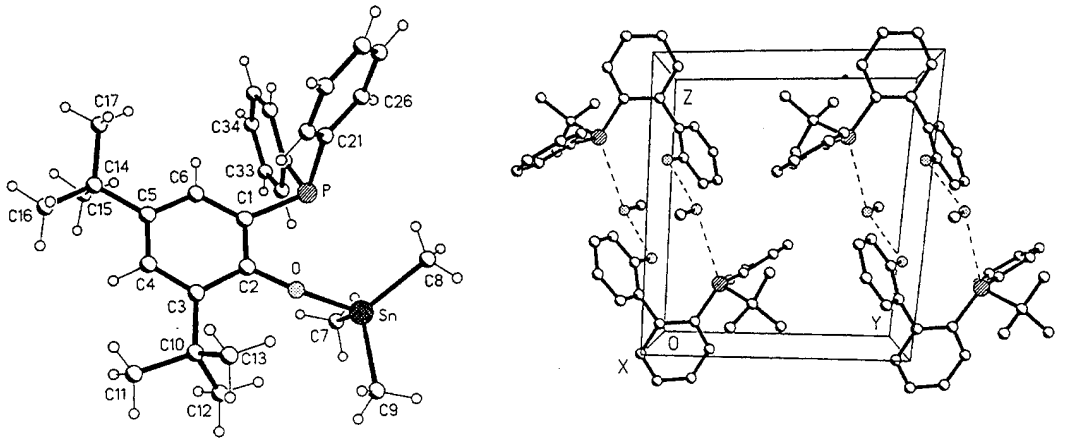
R=R = t–Bu $(NMe_2)_2$ NMe_2Ph (>80%)

R=R = H $(NMe_2)_2$ (80%) > t–BuMe $(i–Pr)_2$ (65%) > $(Et)_2$ (50%) > Me_2 (25%) > Ph_2 (–)

Special structural features were found for bulky derivatives. Simple phosphinophenoles and their silyl ethers prefer trans-conformations (Scheme 2) as shown by the ^{13}C-^{31}P coupling constants of the vicinal carbons (average at 25°C: $^{2}J_{PC1}$ 22-14, $^{2}J_{PC3}$ 0-5 Hz), the hindered 2,6-di(t-butyl)derivatives favour for the free phenoles cis-bisect (e.g. $P(NMe_2)_2$: $^{2}J_{PC1}$ 9, $^{2}J_{PC3}$ 40 Hz) and for O-substituted derivatives severely distorted trans-conformations (e.g. **A**) with trans-annular interactions. These cause strong P-CC-OE coupling constants ($^{4}J_{PP}$ ca. 140-150 Hz; $^{4}J_{PSn}$ ca. 160 Hz) and even $^{6}J_{PSiMe3}$ couplings. In the 1-phosphinonaphth-2-oles the steric stress comes from the opposite site (CH8) and turns the favored conformations to trans-bisect for OH- and cis-bisect for O-$SiMe_3$-compounds in solution as well as in the crystals. The peculiarity of the 2-phosphinodiphenyl-2'-oles is the formation of methanol adducts by strong hydrogen bonds to OH and weakly to PR_2 and the nearly perpendicular distortion of the phenyl planes leading to diastereoisomers for P-asymmetric species (e.g. **B**) [1].

Scheme 2

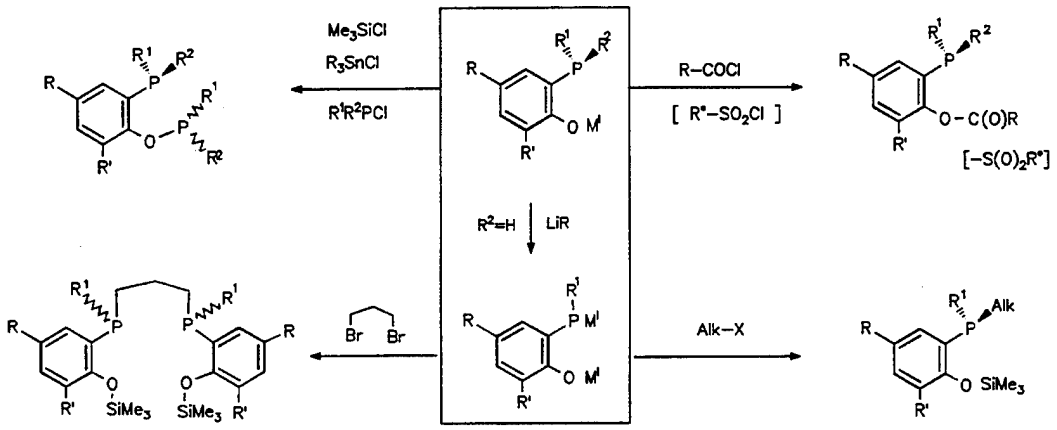




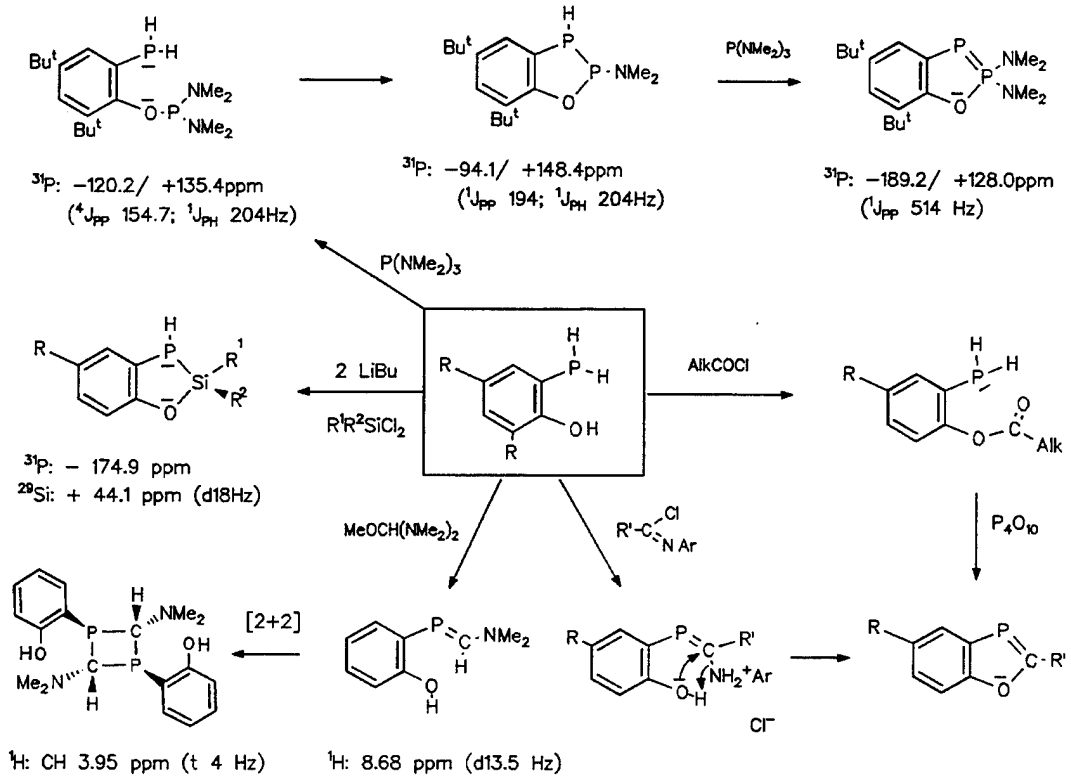
o-Hydroxyarylphosphines are ambident ligands with a hard and a soft Lewis-base center. After monometallation most electrophiles react at oxygen (Scheme 3). Alkylation proceeds in acceptable yields only on dimetallation or substitution of oxygen. The dilithium-phosphidophenolates were also tried to synthesize heterocycles but were found

to be here of limited use only. Heterocycles were obtained, however, by the more selective condensation of free P-H/O-H derivatives with element amides. Primary phosphinophenoles thus allow the synthesis of cycles with low-coordinated phosphorus like the earlier studied benzoxaphospholes [2] or the new benzoxadiphospholes with a $P^{III}=P^{V}$ [3] structural unit (Scheme 4).

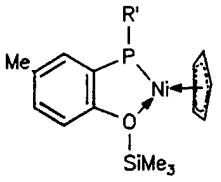
Scheme 3



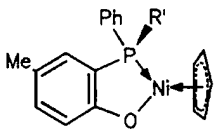
Scheme 4



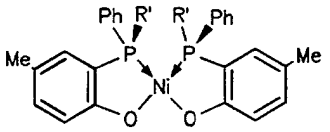
P-Tertiary [4], but also secondary o-hydroxyarylphosphines tend to form stable chelate complexes. From phosphinocresoles and nickel salts or ionic complexes we obtained green, but diamagnetic bis(chelate) complexes, probably in trans-configuration. $Ni(acac)_2$ reacts to give orange-brown soluble cis-bis(chelate) complexes while nikkelocene allows the mono- and bis-substitution to give CpNiL or cis-NiL_2 [5].



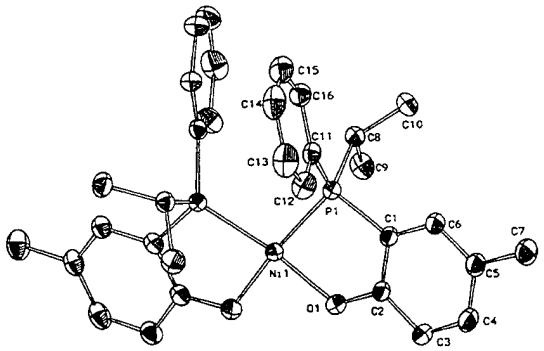
δ ^{31}P: − 88.9 ppm
($\Delta\delta$ = − 52.8 ppm)



δ ^{31}P: + 26 to +57 ppm
(R =Alk: $\Delta\delta$ = 75–81 ppm)
(R = Ph: $\Delta\delta$ = 61 ppm)



δ ^{31}P: + 21 to +51 ppm
(R =Alk: $\Delta\delta$ = 70–75 ppm)
(R = Ph: $\Delta\delta$ = 57.5 ppm)



Complexes formed from alkylarylphosphinophenoles and $Ni(COD)_2$ were found to be usable as homogenous catalysts for the polymerization and oligomerization of ethylene [6]. $Rh(CO)_2$acac and P-asymmetric o-hydroxyarylphosphines give catalysts that allow the hydroformylation of vinylacetate [7], the separation of the ligands and the enantioselectivity remains to be studied.

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SYNTHESIS AND ^{17}O NMR SPECTROSCOPY OF A SERIES OF ^{17}O LABELED TRIARYLPHOSPHINE OXIDES

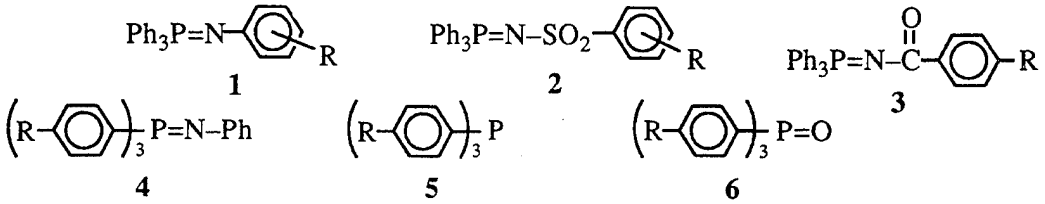
MARTIN POMERANTZ,* MICHAEL S. TERRAZAS, YANG CHENG, AND XIAOMIN GU
Department of Chemistry and Biochemistry, Box 19065, The University of Texas at Arlington, Arlington, Texas 76019-0065, USA

Abstract. A series of nine ^{17}O labeled triarylphosphine oxides [(*p*-R–$C_6H_4)_3PO$] was synthesized, ^{17}O NMR spectroscopic studies were carried out (toluene solvent / 95 °C and $CDCl_3$ / 60 °C) and the spectrum was fit with two Lorentzian peaks. The chemical shifts range from δ 51.8 to 55.7 in toluene and δ 44.8 to 48.9 in $CDCl_3$, while $^1J_{PO}$ varies from 159.6 to 168.6 Hz in toluene. The data were fit to the Taft DSP and Hammett equations and related to other NMR parameters for this system and the analogous λ^5-phosphazenes [(*p*-R–$C_6H_4)_3PNPh$]. Using the Taft DSP equation the ^{17}O substituent chemical shifts gave ρ_I and ρ_R with opposite signs which is different from what is observed with the λ^5-phosphazenes. $^1J_{PO}$, on the other hand correlates best with the Hammett σ_p^+ constants. The data are consistent with a triple bond contribution to the PO bonding.

Key Words: Triarylphosphine oxides, O-17 NMR spectroscopy

INTRODUCTION

For a number of years we have been interested in the synthesis and properties of phosphorus and nitrogen compounds, in particular λ^5-phosphazenes ($R_3P{=}N{-}R'$; phosphinimines) and related molecules. We have carried out considerable ^{31}P, ^{15}N and ^{13}C NMR spectroscopic studies of several series of λ^5-phosphazenes, **1-4** [1-8], phosphines **5** and phosphine oxides **6** [7,8]. Using the NMR data along with PRDDO



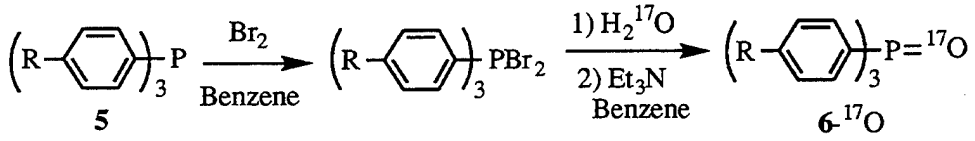
molecular orbital calculations, we described the electronic structure in terms of charge densities and induced dipoles and suggested that pπ-σ* bonding between phosphorus and nitrogen [using a σ* P-C(phenyl) orbital] was an important factor in the PN bonding. Systems **4** and **6** were similar to each other [7,8] in that changes in R resulted in essentially the same changes in the chemical shifts of the substituted ring carbon, but the phosphorus

chemical shift in **6** was twice as sensitive as that in **4** to changes in R [7,8]. This, we believe, is the result of the *N*-phenyl ring in **4** being able to delocalize charge. We have now turned to the synthesis of ^{17}O labeled phosphine oxides **6**, for ^{17}O NMR spectroscopic studies, in order to attempt to better understand the bonding in the oxides and how series **6** relates to series **4**. Since the parent **6**, Ar = C_6H_5, had been prepared previously with an ^{17}O label and its ^{17}O NMR parameters reported [9-11], we did not anticipate problems with the synthesis or NMR spectroscopy.

RESULTS AND DISCUSSION

We have synthesized the series of triarylphosphine oxides **6**-^{17}O with an approximately 10% ^{17}O label and have obtained the ^{17}O NMR spectra, which provided the chemical shifts and ^{17}O–^{31}P coupling constants. The synthesis is presented in Scheme 1. ^{17}O NMR

Scheme 1



5 **6**-^{17}O

a: R = $N(CH_3)_2$ **b:** R = OCH_3 **c:** R = CH_3 **d:** R = H **e:** R = F **f:** R = Cl **g:** R = CO_2CH_3 **h:** R = CF_3 **i:** R = CN

spectra are generally quite broad due to the rapid quadrupolar relaxation [12] and we have found that rather elevated temperatures (95 °C / toluene solvent) and deconvolution using two overlapping Lorentzian bands were required to resolve the spectra into two peaks. However, with $CDCl_3$ solvent at 60 °C several of the compounds showed a single broad peak and resolution into two peaks was not very accurate. It is well known that higher temperatures and lower viscosity solvents help in sharpening up the peaks [12]. Table 1 gives the ^{17}O NMR spectral data for series **6**-^{17}O.

Analysis of the data for **6**-^{17}O (toluene / 95 °C) provided the following relationships: ^{17}O SCS = $2.93\,\sigma_I - 5.37\,\sigma_R^\circ$ ($f = 0.160$) and $^1J_{^{17}O-^{31}P} = 3.71\,\sigma_p^+ + 165.9$ ($r = 0.976$) [13]. Perhaps the most interesting aspect of these data is that the Taft DSP treatment of the ^{17}O SCS data gives opposite signs for ρ_I and ρ_R° which is in marked contrast to the situation with **4** where ρ_I and ρ_R are both negative [7]. Thus the resonance effect in both systems appear similar (similar negative ρ values, –5.37 and –4.65 respectively) while the inductive effect in the two systems is opposite (ρ values of +2.93 and –1.99 respectively). This difference is consistent with a triple bond contribution to the PO bond where electron donation / withdrawal to the oxygen can occur via both inductive and resonance effects through two different pπ- σ* / pπ-dπ orbitals [14]. That is, a substituent such as dimethylamino might donate electrons by a resonance effect onto the oxygen through a π-bond (pπ- σ* or pπ-dπ) while at the same time electron density can be withdrawn from the oxygen (which now has an excess of electron density because of this resonance effect) through the perpendicular π-bond and into the sigma system of the phenyl ring(s). It should be mentioned that the ^{17}O–^{31}P coupling constant correlation with a positive slope

TABLE 1. ^{17}O NMR chemical shifts and coupling constants for series **6**-^{17}O.

		Chemical Shift (δ)	^{17}O–^{31}P Coupling Constant (Hz)	Chemical Shift (δ)
Compound	Solvent / R =	Toluene	Toluene	$CDCl_3$
6a-^{17}O	$N(CH_3)_2$	54.65	159.6	48.9
6b-^{17}O	OCH_3	54.97	163.1	48.1
6c-^{17}O	CH_3	52.77	163.6	45.4
6d-^{17}O	H	51.90	166.6	44.8
6e-^{17}O	F	55.73	165.9	48.7
6f-^{17}O	Cl	53.89	167.1	46.8
6g-^{17}O	$COOCH_3$	51.84	167.6	46.6
6h-^{17}O	CF_3	52.52	167.1	45.4
6i-^{17}O	CN	52.86	168.6	46.0

also stands in contrast to the negative slope of the corresponding ^{15}N–^{31}P coupling constant in **4** ($^1J_{^{15}N-^{31}P} = -2.15\ \sigma_p + 33.4$ ($r = 0.927$) [7]. This again is consistent with a different type of PO and PN bonding. The chemical shifts in toluene span the range of δ 51.8 to 55.7 and these are deshielded relative to those in $CDCl_3$ which are δ 44.8 to 48.9. As expected, the chemical shifts are to higher field in chloroform [11], in agreement with the observations that more polar or hydrogen bonding solvents shield the oxygen [11], presumably due to the stabilization of greater negative charge on the oxygen. The coupling constants from the $CDCl_3$ experiments at the lower temperature, where they could be measured, however, were much less accurate than those from the toluene experiments. The peaks were broader and so the resolution of the doublets was much poorer and with several compounds single, broad peaks were observed.

There are two reports of the ^{17}O NMR spectral parameters of triphenylphosphine oxide, **6d**, in the literature. In the first, $CDCl_3$ solvent, 30 °C, δ is given as 43.3 and $^1J_{PO}$ as 160 ± 2.4 Hz [10] and in the other, CD_3CN solvent, 70 °C, δ is given as 47.7 and $^1J_{PO}$ as 153.9 Hz [9]. While the chemical shifts seem to agree reasonably well with those obtained here, the coupling constants do not. A reasonable explanation for the differences, particularly in the latter study at 70 °C [9], is that with two broad overlapping peaks, peak fitting is required. This can be seen in Figure 1 (**6b**-^{17}O, R = OCH_3, toluene solvent, 95 °C) where the doublet is only partially resolved and the fitted peaks show a greater separation (larger coupling constant) than the peak maxima from the original spectrum.

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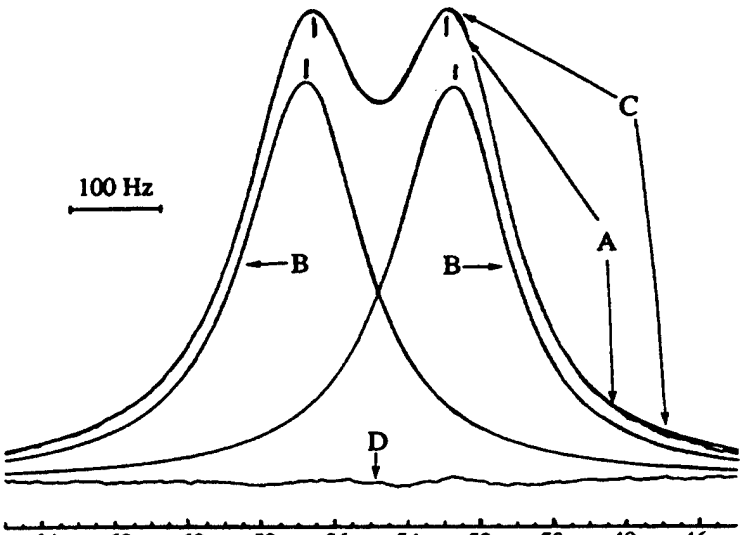


FIGURE 1. ^{17}O NMR spectrum of tris(*p*-methoxyphenyl)phosphine oxide-^{17}O (**6b**-^{17}O, toluene solvent / 95 °C)

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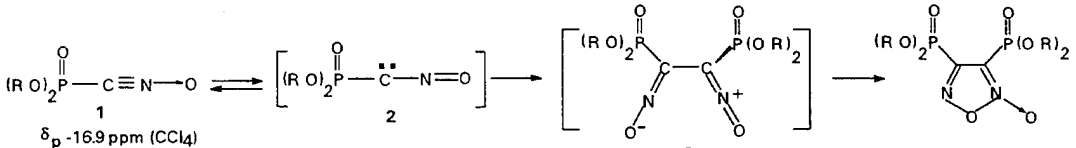
SYNTHESIS OF FUNCTIONALIZED HETEROCYCLES BEARING PHOSPHONATE MOIETY VIA PHOSPHORYLNITRILE OXIDES. STEREOCHEMISTRY AND UNUSUAL CYCLOADDITIONS.

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Abstract. C-(Dialkoxyphosphoryl)nitrile oxides, due to their availability and high reactivity, make it possible to conduct reactions of indirect phosphorylation of heterocyclic systems and to use them as a convenient "instrument" in studying the stereochemistry of cycloaddition and chemical transformations of labile compounds.

The interest to 1,3-dipolar cycloaddition reactions going with participation of oxides of nitrile is explained by the fact, that the application of "nitrile oxide strategy" of synthesis with the involvement of a wide range of dipolarophiles into cycloaddition reactions is often the only possible way to obtain various heterocyclic systems containing different functional groups, including phosphorus-containing moiety.

The information on nitrile oxides containing phosphoryl unit came to view recently [1]. We for the first time obtained (dialkoxyphosphoryl)nitrile oxides **1** by treatment of (dialkoxyphosphoryl)formylhalogenide oximes with bases [2]. The obtained dipole **1** quickly produces dimers and polymers at ambient temperature. Lowering of temperature below 0 °C slows the process down and makes it possible to obtain and keep for quite a long time a pure solution of **1**. Maintenance of a low concentration of **1** in the solution at room temperature promotes the formation of bis(dialkoxyphosphoryl)furoxan **4** despite quite a strong steric hindrance of nitrile oxide **1** [3]. AM1 Calculations testify that dimerisation is a stepwise process[4]. At the first stage, interaction of two molecules of nitrile oxide in nitroso-carbenic form **2** takes place. Transition state at the first stage of dimerisation is *gosh*-conformation of dimeric structure **3** forming *cis*-isomer of dinitrosoethylene.



1
δ_p -16.9 ppm (CCl_4)
R =Pr, i-Pr, S-Bu

2

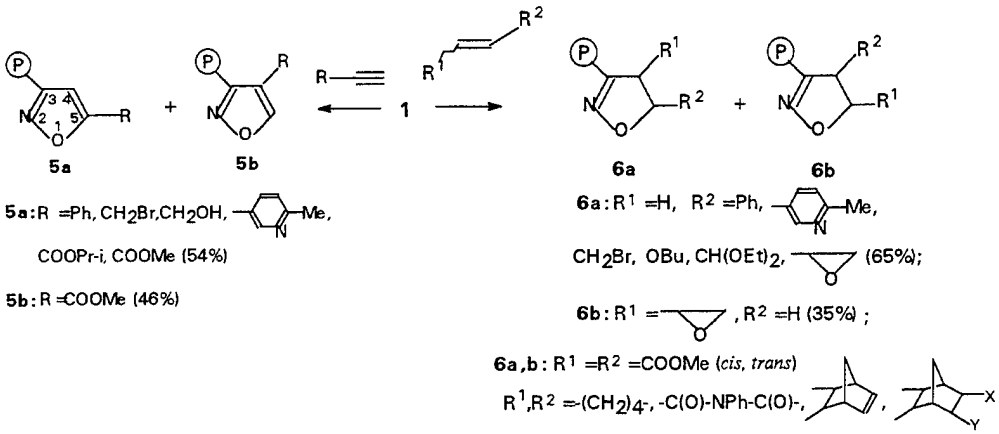
3

AM1 Calculation

Angles	NCC	PCC	PCCP	NCCN	NCCP
Degrees	114.2	105.1	95.3	88.7	-89.7

4
δ_p -3.32, -4.69 ppm
$^3J_{pp}$ 3.1 Hz ($CDCl_3$)

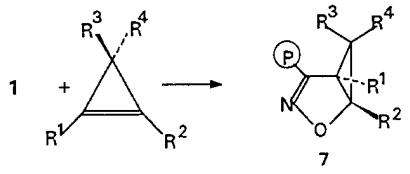
The presence of phosphoryl substituent in nitrile oxides **1** makes these synthons to the indispensable agents of indirect phosphorylation and allows to plan the synthesis of heterocycles bearing phosphonate moiety. Phosphorylnitrile oxides **1** easily enter the cycloaddition reactions with unsaturated compounds. 3-C-Phosphoryl-5-R-isoxazoles **5a** have been obtained with alkynes[3]. Interaction with terminal olefins leads to the corresponding 3-dialkoxyphosphoryl-5-R-isoxazolines **6a**[3]. Cycloaddition goes in regiocontrolled manuer. Here, the main role is played by steric factor, caused by capacious dialkoxyphosphoryl group of nitrile oxide. Regiospecificity of the process is broken only in the case of small-volume electron-acceptor substituents in dipolarophile. Then electronic factors compete with steric factors leading to two regioisomers.



Cycloaddition (at -60 °C) of dimethylfumarate gives a pure *trans*-diastereomeric product, but dimethylmaleate adds not stereospecifically leading to the mixture of *cis*-(27%) and *trans*-(73%) stereoisomeric isoxazolines[3] . Non-stereospecific occurence of the reaction with dimethylmaleate is probably explained by the balance between cycloadducts caused by tautomeric transition. Here, the decrease of the energetic barrier is supported by the presence of a phosphoryl group that easies formal migration of proton and promotes the formation of *trans*-diastereomeric cycloadduct. The cyclic alkenes have been also involved into cycloaddition with **1**[3] . Interaction with norbornene dipolarophiles yields with high stereoselectivity cycloadducts with *exo*-orientated isoxazoline cycle.

Thus, dialkoxyphosphorylnitrile oxides, being element substituted nitrile oxides, are comparable with alkyl - and arylnitrile oxides by the type of chemical behaviour. Evaluation of the reactivity of phosphorylnitrile oxides in approximation of MO perturbation theory with taking into account the contributions of orbital interactions into the energy of stabilization of *dipole-dipolarophile* reaction pairs have showed that (dialkoxyphosphoryl)nitrile oxides, despite the lowering energy of HOMO as compared with benzonitrile oxide by approximately 1.7 eV, should be classified with electron-donating agents in which interactions with participation of LUMO can influence regioselectivity of cycloaddition. In doing so, phosphorylnitrile oxides are close to trifluoroacetonitrile oxide as for the type of orbital interactions[5].The electron-donating property of dialkoxyphosphorylnitrile oxides is the consequence of the inertness of phosphoryl moiety rather, than its influence. This follows from the fact that the separation of phosphoryl group and nitrile oxide fragment by methylene link in dialkoxyphosphorylacetonitrile oxide has a little influence on changing the character of FMO's and chemical properties of nitrile oxides.

The reactions with participation of strained cycloalkenes such as cyclopropenes go ambiguously. The cycloaddition of **1** to some substituted cyclopropenes occurs as a typical dipolar addition to the π-bond of alkene, to give bicyclic adducts **7** with three-carbon ring being unchanged[6] . The stereochemistry of addition is controlled by a competitive influence of steric and electronic effects (ratio of stereo- and regio-isomers).

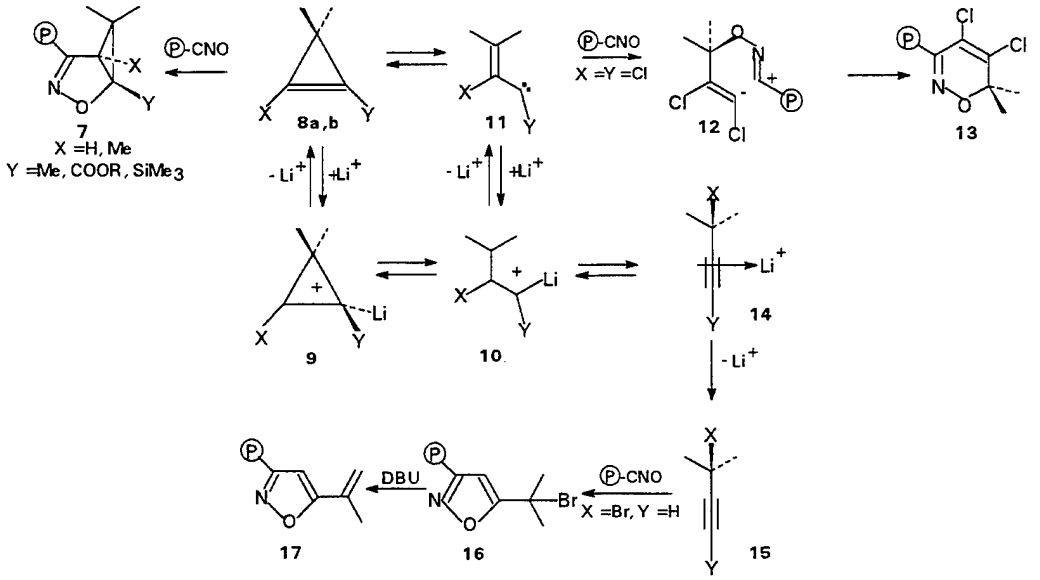


R1 =R2 =H: R3 =Me, R4 =Ph (80 %)
R3 =Ph, R4 =Me (20 %)
R3 =Me, R4 =CN (100 %)
R3 =R4 =Me, R1 =H: R2 =H, Me, SiMe3, COOMe (81%), COOEt (86%)
R3 =R4 =Me, R1 =COOMe: R2 =H (19 %), Me (100%)
R3 =R4 =Me, R1 =COOEt: R2 =H (14 %), Me (100%)
R3 =R4 =Me: R1 =Me, R2 =SiMe3 (82%); R1 =SiMe3, R2 =Me (18%)

The reaction of 1,2-dichloro-3,3-dimethylcyclopropene **8a** with **1** leads to 3-phosphoryl-1,2-oxazines **13**[7]. This reaction is quite different from the above addition to simple cyclopropenes. It is known that some cyclopropenes (such as **8a**) ring-open at ambient temperature to produce vinylcarbenes **11** or undergo rearrangement into alkynes[8] . In the given example the reaction went at T °C -60 in the presence of methyl lithium and lithium salts. This was the catalysing factor promoting cyclopropene ring-opening at such a low temperature.

Destruction of lithium-vinylcarbene complexes **10** during the reaction causes reverse cyclisation of vinylcarbenes **11** to mother cyclopropenes **8** which interacting with **1** give cycloadducts **7**.

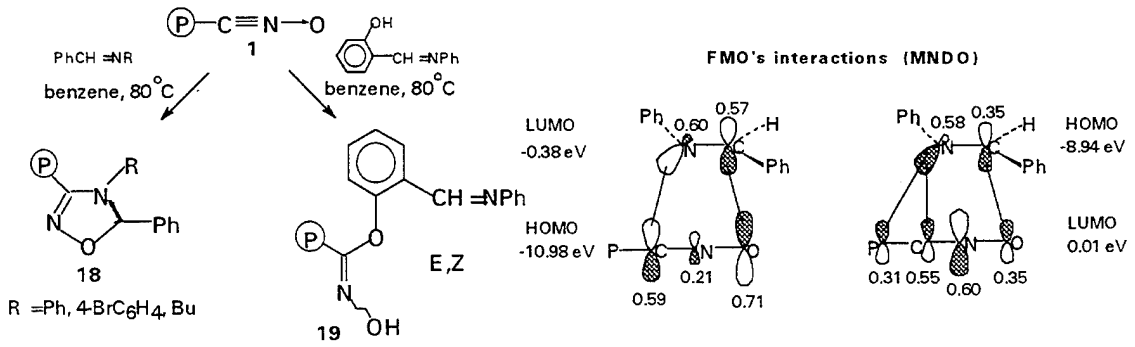
The formation of 1,2-oxazine could formally occur by 3-centre plus 3-centre cycloaddition of the intermediate singlet vinylcarbene **11** to the nitrile oxide **1**. Although it is not clear as yet whether this process occurs in a stepwise or concerted manner.



Under the same conditions catalytic isomerisation of 1-bromo-3,3-dimethylcyclopropene **8b** does not stop at the corresponding lithium-vinylcarbene complex **10**, but yields thermodynamically beneficial bromobutyne **15** which interacts with nitrile oxide **1** to produce isoxazole **16**.

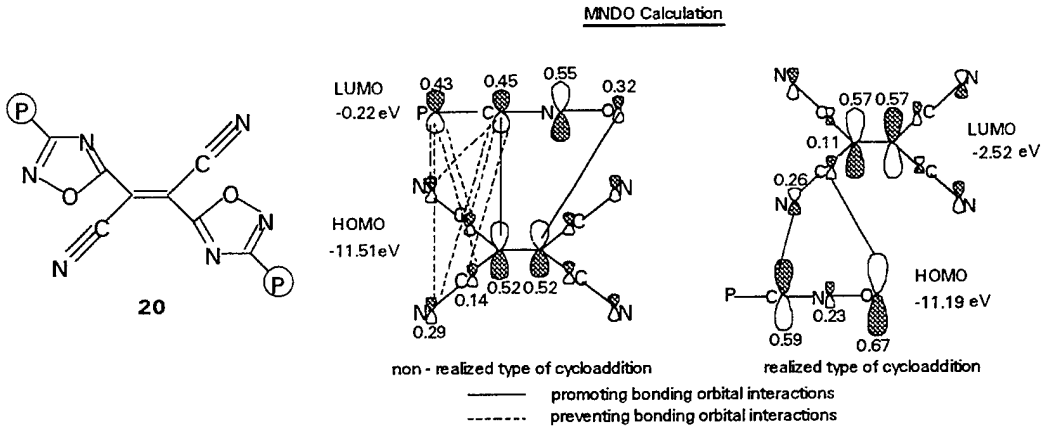
Thus phosphorylnitrile oxide **1** possessing the property to easily enter cycloaddition reactions with dipolarophiles has been used as a convenient and universal trap for both cyclopropenes and intermediates and products of their isomerisation.

Reactions of dipolar cycloaddition of phosphorylnitrile oxides were extended on dipolarophiles with carbon-heteroatom multiple bonds. 1,2,4-Oxadiazolines **18** have been synthesized with Schiff bases[9]. The reaction occurs in a highly regiocontrolled manner. This is explained by dissimilarity of the constitution of LUMO of dipole and HOMO of dipolarophile at reaction centres. Nucleophilic activity of oxygen in hydroxyl in 2-hydroxybenzylidene-aniline is higher than dipolarophilic activity of azomethin-bond. The result is 1,3-nucleophilic addition with formation **19**.



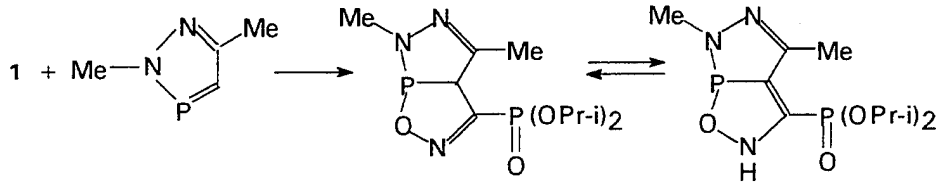
Bond C≡N is a much poorer dipolarophile than C=C and C=N. The attempt to conduct the cycloaddition with excess of acetonitrile with reflux did not give positive result. However, the crystalline bisadduct **20** containing two oxadiazole rings was isolated in the reaction

with tetracyanethylene. Here, C=C bond did not react because of the secondary orbital interactions occurring at initial orientation of the addends.



20

Unlike arylnitrile oxides[10], diisopropoxyphosphorylnitrile oxide adds to the P=C bond of 1,2,3-diazaphosphole with the phosphorus becoming bonded to the oxygen and not to the nitrile carbone. It happens probably because a new σ -bond of **P** with **O** is more energetically beneficial. Besides, stereochemistry of cycloaddition can be determined by stereoelectronic control of the reaction. The forming bicyclic adduct **21** exists probably in tautomeric form **22** (NMR).



21 22

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SYNTHESIS AND BINDING PROPERTIES OF PHOSPHORUS-CONTAINING CALIXARENES AND CALIXRESORCINARENES

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Abstract Full and regioselectively phosphorylated calix[4]arenes and calix[4]resorcinarenes were synthesized by Nickel catalyzed Arbuzov reaction of para-bromosubstituted calixarenes as well as by reaction of the hydroxyl-derivatives with chlorophosphates. Stereochemistry, chemical transformations, and complexation of the titled phosphorus-containing macrocycles were examined.

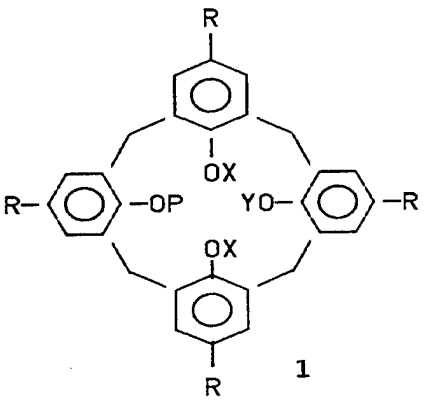
INTRODUCTION

Calix[4]arenes and calix[4]resorcinarenes due to their original bowl shaped molecular architecture are versatile starting material for design of novel 'host' molecules capable to separation of metal cations and particularly neutral organic molecules[1]. Continuing our studies of phosphorus-containing macrocycles[2] we have synthesized and investigated a number of calixarenes and calixresorcinarenes functionalized with exocyclic phosphoryl groups. This presentation summarizes methods of phosphorylation of titled macrocycles as well as properties of the compounds obtained.

SYNTHESIS OF PHOSPHORYLATED MACROCYCLES

Nickel catalyzed Arbuzov reaction of para-bromosubstituted calixarenes as well as interaction of polyoles with chlorophosphates or system dialkylphosphite/Et_3N/CCl_4 were used for synthesis of full and regioselectively substituted

upper-rim and lower-rim phosphorylated macrocycles 1,2 [3-5]. By subsequent treatment of the dialkoxyphosphorylderivatives of calixarenes and resorcinarenes with trimethylbromosilane and methanol the water-soluble hydroxyphosphorylderivatives 1,2 (P = $P(O)(OH)_2$) were obtained[6]. Mannich reaction of the tetraphosphorylated resorcinarenes 2 (R = $P(O)(OAlk)_2$, X = Y = H) leads to bis aminomethyl derivatives 2 (Y = CH_2-NRR').



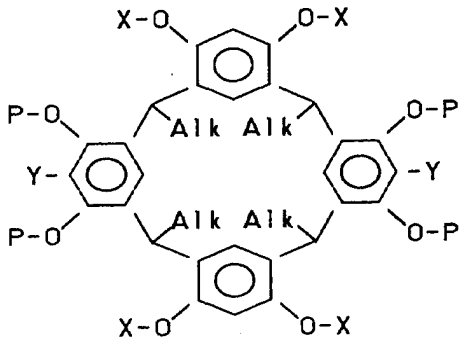
1

a R = $P(O)(OAlk)_2$, $P(O)Ph_2$; X = Y = P = Alk, H

b R = H, t-Bu; P = X = Y = $P(O)(OAlk)_2$, $P(O)(OH)_2$

c R = H, t-Bu; X = H; P = Y = $P(O)(OAlk)_2$, $P(O)(OH)_2$

d R = H, t-Bu; Y = H; P = X = $P(O)(OAlk)_2$

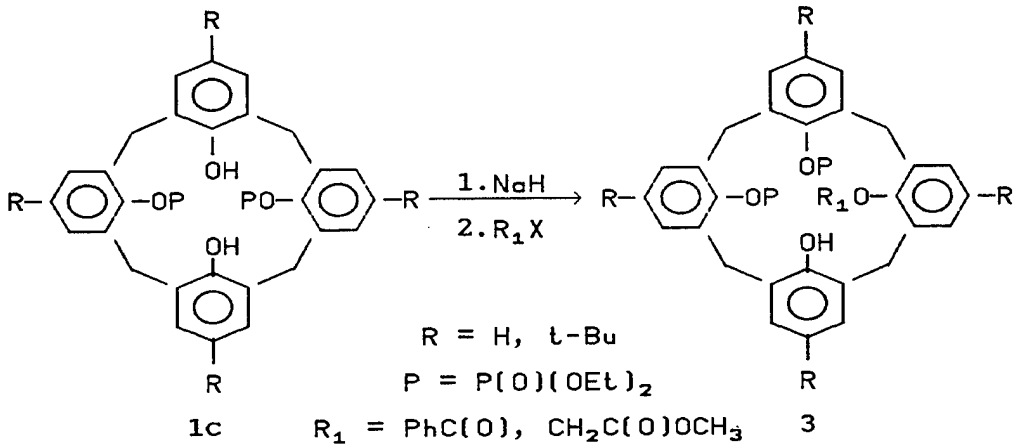


2

a P = X = $PO(OAlk)_2$, $P(O)(OAr)_2$; Y = H

b P = $PO(OAlk)_2$, $P(O)(OAr)_2$, $P(O)(OH)_2$; X = H, C(O)Me, SO_2-BENZO-15-CROWN-5; Y = H, CH_2-NMe_2, CH_2-NH-PROLINE-l

Chiral calix[4]arenes 3[7] were synthesized with good yields by one-pot procedure consisted in successive treatment of 1,3-bis(diethoxyphosphoryl)calix[4]arenes 1c[5] (P = Y = $PO(OEt)_2$, X = H) (*cone* conformation) with sodium hydride and benzoyl chloride or methylmonobromoacetate. The key step of this process is the O,O-phosphorotropic rearrangement conditioned by advantageous spatial orientation of the phenolate anione oxygen for the intramolecular nucleophilic attack of phosphorus atom.



1c 3

STEREOCHEMISTRY

Two steroisomeres *cone* (all up benzene rings orientation) and *1,2-alternate* (two up and two down neighbouring rings orientation) were isolated in the case of diphosphate 1c[4] [R = t-Bu, X = H, P = Y = $(EtO)_2PO$]. All other di-, tri- and tetraphosphorylated calixarenes 1 exist in *cone* conformation. Spatial structure and conformational stability of the conformers were examined by NMR and X-Ray analyses. The *cone* conformers are stereochemically rigid, in contrast to which the *1,2-alternate* one is flexible.

The NMR spectra as well as X-Ray analyses have confirmed that all phosphorylated calix[4]resorcinarenes 2 exist in a *boat* conformation where two opposite benzene rings (nonsubstituted in case of tetraphosphates) are coplanar to the main plane of a molecule and two others are perpendicular to it. As follows from the data of ^1H NMR spectra, the conformational mobility of the phosphorylated calix[4]resorcinarenes 2 depend on the nature of the substituents placed at the upper rim of macrocycle as well as solvent nature[8].

COMPLEXATION

All phosphoryl groups of the tetraphosphorylated calix-

arenes **1b** [P = X = Y = $(EtO)_2PO$] are conveniently preorganized for complexation of a metal cations, particularly for lithium one. Stability constants in tetrahydrofuran solutions are 5.43 for lithium, 4.40 for sodium and 3.89 for potassium.

Calix[4]resorcinarene **2** [P = $P(O)(OH)_2$, X = H, Alk = C_5H_{11}] forms complexes with aromatic molecules (toluene, xylenes, anysole, phenol, phenylalanine etc.) in water solutions. The constant of association of the tetraphosphoric acid **2** with phenol is 1.5 and with phenylalanine is 75 M^{-1}.

ACKNOWLEDGMENTS

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PHOSPHORUS DENDRIMERS: A NEW CLASS OF MACROMOLECULES

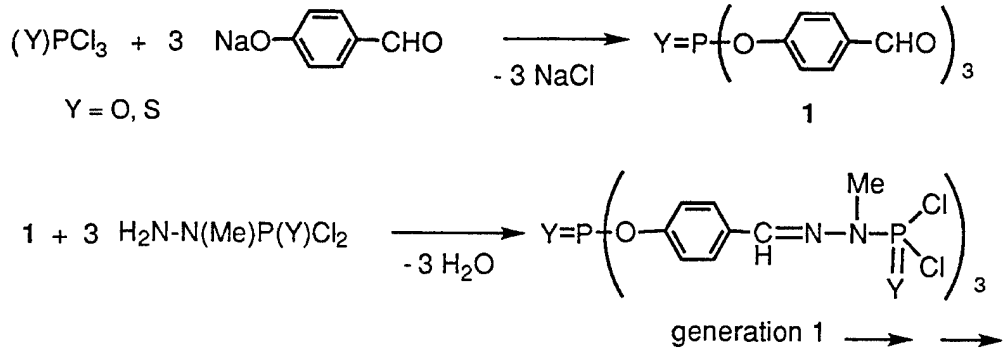
ANNE-MARIE CAMINADE, MICHAEL SLANY, NATHALIE LAUNAY, MARIE-LAURE LARTIGUE, JEAN-PIERRE MAJORAL*
Laboratoire de Chimie de Coordination du CNRS, 205 route de Narbonne, 31077 Toulouse Cedex, France

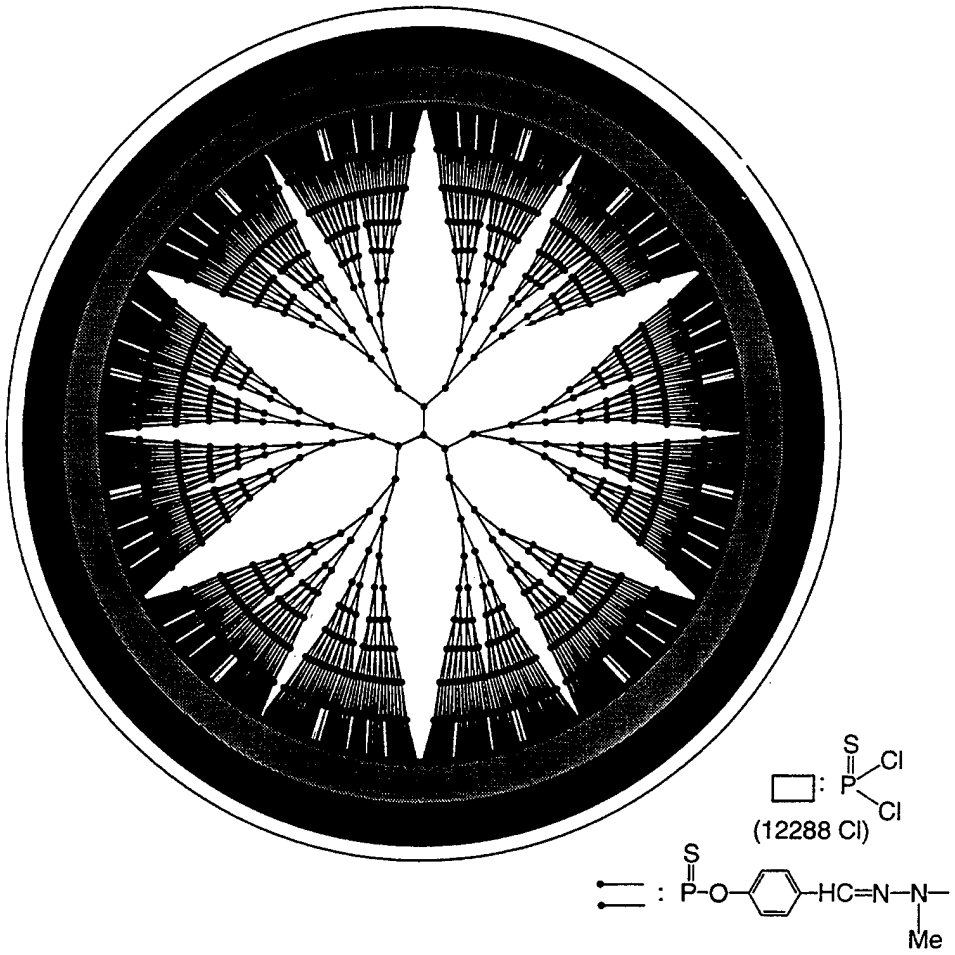
Abstract Two ways of synthesis of phosphorus dendrimers are elaborated up to the twelfth generation for one of them, to give a molecule which possesses 12288 functions. Examples of the reactivity of some dendrimers are described.

INTRODUCTION

Dendrimers are high molecular weight, highly branched multifunctional molecules which incorporate structural repetitions in an ordered manner.[1] Despite the fact that a variety of organic dendrimers have been synthesized in the past few years,[1a,b] only one phosphorus dendrimer (cationic)[2] was described before our work. We published last year the divergent synthesis of the first neutral phosphorus dendrimer,[3] and we described very recently a second approach.[4] A few recent papers concern dendrimers having cyclotriphosphazene in the cascade structure[5] and the formation of small organophosphine dendrimers.[6]

The first phosphorus dendrimers we reported[3] were built by a simple two steps synthesis, which gives alternatively P-Cl and aldehyde functions on the surface of the molecules.[7] Reiteration of the same sequence of reactions now allows us to elaborate dendrimers up to the twelfth generation, which is the highest generation currently known for a dendrimer. This compound possesses 12288 chlorine at the periphery, a molecular weight of more than 3 millions, and a diameter of roughly 190 Å.

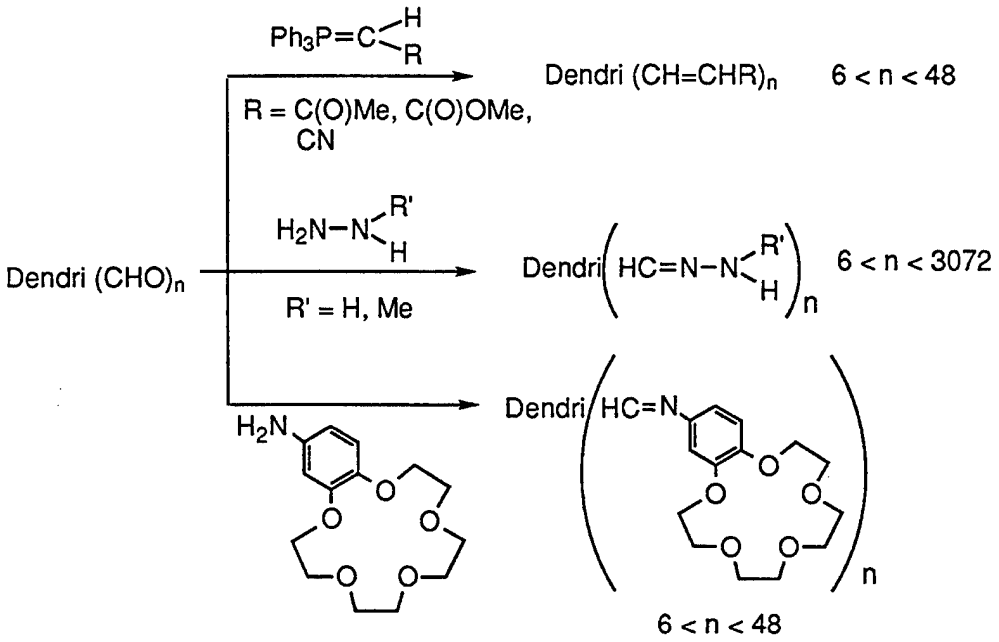




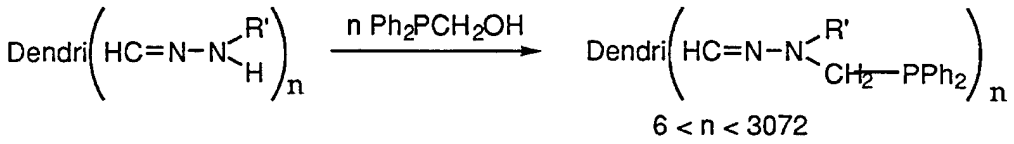
Schematic drawing of the twelfth generation of the dendrimer

Our second way to obtain phosphorus dendrimers consists in a three steps synthesis which gives alternatively aldehyde, NH, and phosphine functions at the periphery. Dendrimers were elaborated in this way up to the third generation, with either up to 24 phosphines at the periphery starting from a tridirectional core, or up to 48 aldehyde functions starting from an hexadirectional cyclotriphosphazene core.[4]

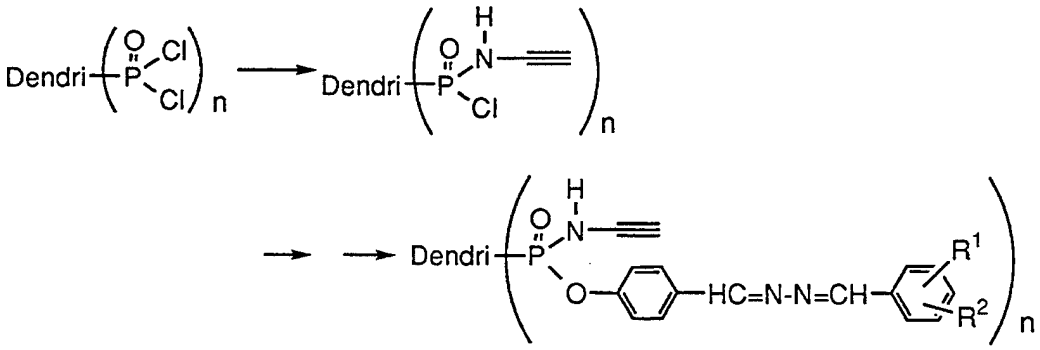
The presence of reactive functions at the periphery of dendrimers prompted us to study the reactivity of these highly functionalized molecules and to graft new functions able to meet precise requirements. Starting from aldehyde functions, we performed Wittig reactions, as well as condensations with hydrazines or imines which gave for example a compound with up to 48 crown-ether functions.[7]



NH and NH_2 functions react with Ph_2PCH_2OH leading to polyphosphines which are isolated up to the tenth generation. This is the largest polyphosphine of defined structure ever known (3072 phosphines!) which can be complexed with 3072 gold atoms.[8]



Starting from $P(S)Cl_2$ functions, we can selectively substitute only one chlorine on each phosphorus, in order to obtain dendrimers which have for the first time two, three, four or even five different and compatible functions at the periphery.



Studies on physical and chemical properties, and potential applications of these new families of macromolecules are underway.

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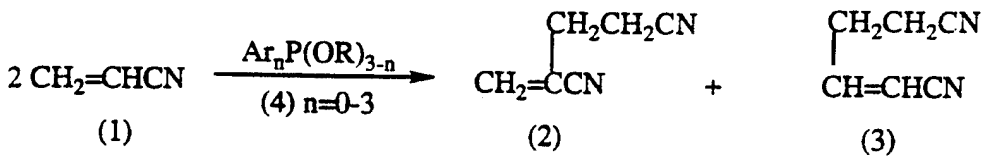
THE KINETICS AND MECHANISM OF THE PHOSPHORUS-CATALYSED DIMERISATION OF ACRYLONITRILE

C. DENNIS HALL*, NICHOLAS LOWTHER*, BRUCE R. TWEEDY*
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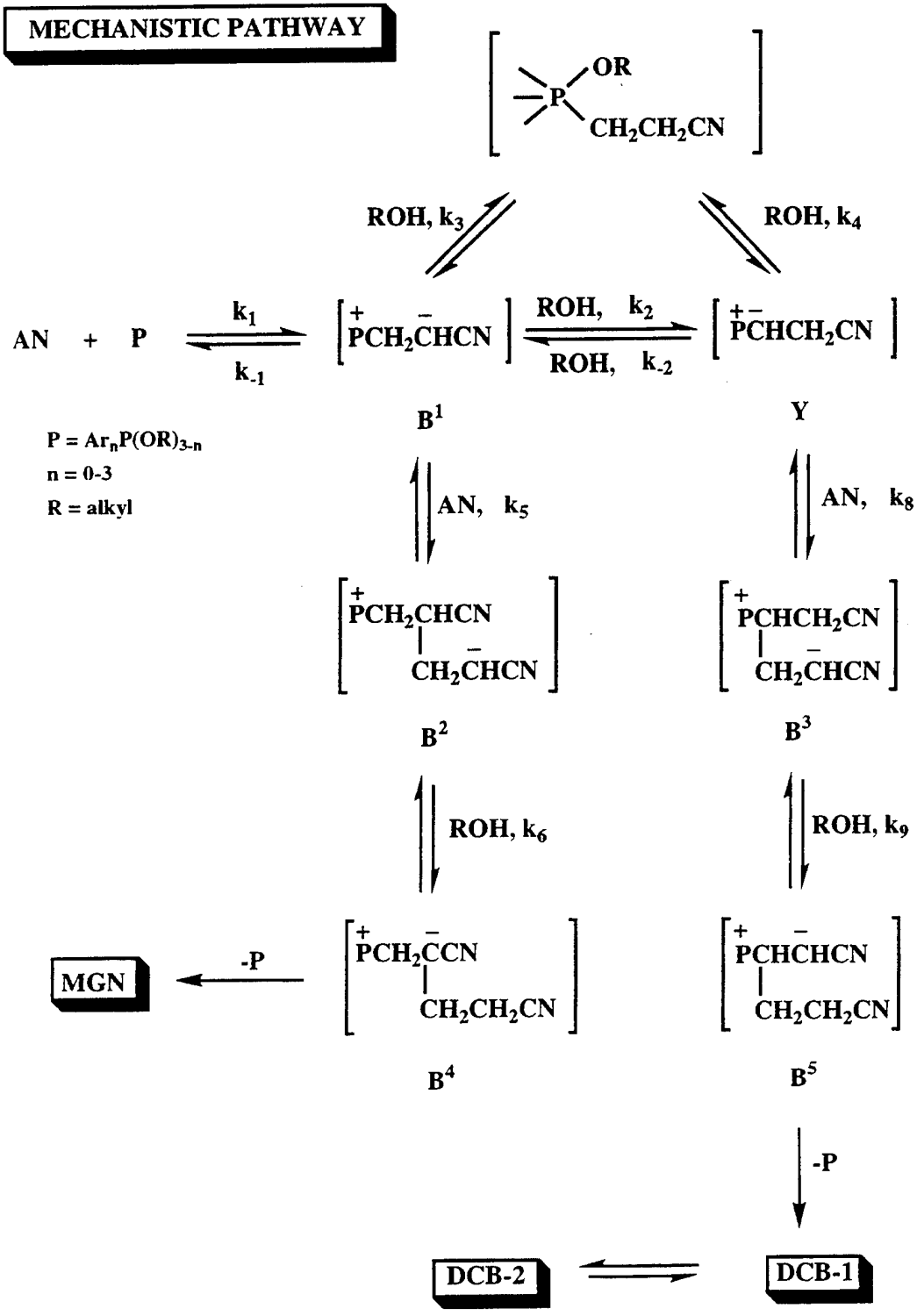
Abstract. The kinetics and mechanism of the phosphinite-catalysed dimerisation of acrylonitrile to 1,4-dicyanobut-1-ene and 2,4-dicyanobut-1-ene are presented and discussed.

INTRODUCTION

The dimerisation of acrylonitrile (AN,1) gives either 2,4-dicyanobut-1-ene (MGN, 2) or *cis/trans* 1,4-dicyanobut-1-ene (DCB, 3) as the principle products and hydrogenation of the latter leads to hexamethylene diamine, a vital intermediate en-route to Nylon. Thus the *selective*, catalysed dimerisation of AN and DCB is potentially a very important process which has been achieved using a variety of tricoordinate organophosphorus compounds (4) as homogeneous catalysts[1].



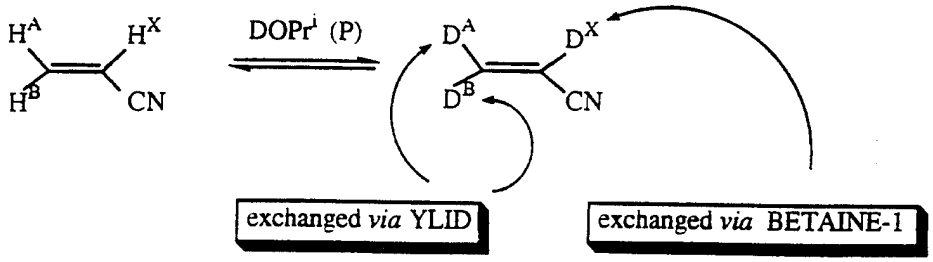
The successful exploitation of the dimerisation reaction as a commercial process, however, depends upon a knowledge of the optimum combination of rate, selectivity and turnover for the catalyst system. This paper describes the structural and kinetic studies to elucidate the mechanism of the reaction and hence define the operational window for maximum catalytic efficiency.


MECHANISTIC PATHWAY
OR
P
CH2CH2CN
ROH, k3
ROH, k4
AN + P
k1
k-1
+ −
PCH2CHCN
ROH, k2
ROH, k-2
+ −
PCHCH2CN
B1
Y
P = ArnP(OR)3-n
n = 0-3
R = alkyl
AN, k5
AN, k8
+
PCH2CHCN
−
CH2CHCN
+
PCHCH2CN
−
CH2CHCN
B2
B3
ROH, k6
ROH, k9
+ −
PCH2CCN
CH2CH2CN
+ −
PCHCHCN
CH2CH2CN
MGN
-P
B4
B5
-P
DCB-2
DCB-1

Scheme 1

RESULTS AND DISCUSSION

The mechanistic pathway proposed for the formation of dimers (2) and (3) is shown in Scheme 1. In addition the reaction affords a number of by-products including 1,4-dicyanobut-2-ene, a variety of trimeric species and a crystalline hexamer $\{(CNCH_2CH_2)_2C(CN)CH{=}CHC(CN)(CH_2CH_2CN)_2\}$ in quantities dependent upon the reaction conditions and the catalyst used. Although no betaine (B) or ylid (Y) intermediates were observed by nmr, the intermediacy of the ylid species was established by trapping the latter with benzaldehyde[1b]. The kinetics of the reaction were studied by monitoring the rate of disappearance of AN and the rate of appearance of DCB or MGN by gas liquid chromatography (glc) on a capillary column which was also capable of analysing the reaction mixtures quantitatively for trimers. Any crystalline hexamer formed was filtered off and estimated gravimetrically. Independent experiments showed that hexamer was derived from either DCB-1 or DCB-2 and that the trimers (and oligomers) were derived in a consecutive fashion from dimers and AN rather than in a parallel manner from B^2 or B^3 plus AN (see Scheme 1). Thus it was possible to correct the concentrations of AN, DCB or MGN at any time, t, for the formation of hexamer or trimers. Thereafter, plots of ln f[AN], ln f {DCB] and ln f [MGN] *vs* time all gave excellent linearity ($r>0.99$) with slopes = $2k_1$ [P] where [P] is the concentration of catalyst used. Thus the reaction was shown to be first order in AN and first order in [P], - Table 1, which indicates the excellent agreement found between the three experimental parameters used to monitor the rate. The value of K_2k_8/k_5 was taken as the ratio of DCB/MGN found in the product and is seen to be essentially *independent* of the concentration of catalyst used. The value of K_2 was estimated independently from the ratio of H^A (or H^B) to H^X incorporated into unreacted D_3-AN or the incorporation of D into unreacted AN over a range of conversions from 2 to 40%. It was found to be about 2 for Ph_2POPr^i but to vary with



the nature of the catalyst (Table 2). Values for k_1 also varied with the catalyst (Table 2) and Hammett plots revealed ρ values (against σ) of -2.3 (for k_1) and +0.4 for K_2. These data, together with the activation parameters (Table 3) identify k_1 as the rate-limiting step of the reaction with K_2 controlling the selectivity to DCB as the substituents in the aryl groups are changed.

Table 1. k_{obs} *vs* [P] *via* [AN], f[MGN] and f[DCB] data
Temperature = 60°. 10 : 3 : 1 (v/v) toluene : AN : IPA, Ph_2POPr^i catalyst.

[CATALYST] mol l^{-1}	K_2k_8/k_5	$10^5 \times k_{obs}$ (s^{-1}) *via* [AN]	f[MGN]	f[DCB]
0.0426	18.9	1.06	0.904	0.904
0.0515	20.6	-	1.28	1.28
0.0618	18.9	1.52	1.67	1.67
0.0741	18.8	1.71	1.75	1.75
0.0754	20.8	2.18	1.91	1.91
0.124	19.9	3.23	3.19	3.19
0.146	18.9	3.72	3.57	3.57

Table 2. Average k_1 and K_2 values for a series of phosphinite catalysts $(XC_6H_4)(X'C_6H_4)POPr^i$ in 10 : 3 : 1 toluene : AN : IPA at 333K

CATALYST	K_2	k_8/k_5	$10^4 k_1$ ($l\ mol^{-1}\ s^{-1}$)
X = X' = *p* -F	2.29	10.1	0.636
X = H' = H	2.02	9.4	2.57
X = X' = *m*-Me	1.55	9.9	4.85
X = H, X' = *p*-Me	1.65	10.1	5.34
X = H, X' = *p*-MeO	1.35	10.5	8.16
X = H, X' = *p*-Pr^iO	1.47	9.4	7.20
X = H, X' = *p*-Et_2N	1.01	7.5	77.1
X = X' = *o*-MeO	1.37	0.96	3.6

Table 3. Activation parameters for k_1 (10 : 3 : 1) at [CAT] = 0.073 M

CATALYST	$10^4 k_1$ (60°C) $l\ mol^{-1}\ s^{-1}$	E_A (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal $mol^{-1}\ K^{-1}$) (298 K)
(*p*-$Me_2NC_6H_4)_2$ $POPr^i$	2300	10.3	-33
(*p*-$MeOC_6H_4)_2POPr^i$	27.1	6.8	-52
(*p*-$MeC_6H_4)_2POPr^i$	3.91	6.0	-56
Ph_2POPr^i	2.57	5.0	-64

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ON THE SCENT OF SPHERICAL DENDRIMERS: CYCLOPHOSPHAZENIC DANDELION DENDRIMERS UP TO THE EIGHTH GENERATION

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Abstract **Preparation of spherical dendrimers up to the eighth generation from D_{3h} cyclophosphazenic hexadangling cores (coded as sexapus) involves two repetitive steps: aminolysis of hexachlorocyclotriphosphazene, $N_3P_3Cl_6$ 0, by long-chain aliphatic diamines (such as 1,6-Diaminohexane and higher cousins) leading to sexapus cores with dangling diamino groups followed by a grafting of $N_3P_3Cl_5$ flagstones as 5-fold growing multipliers on these amino endings. Dendrimers of the first (compounds 1a, b) to the eighth (compounds 8a, b) are described. Dendrimer of the eighth generation, 8b, possesses 2,343,750 terminal (P-Cl) functions (molecular weight 228,977,179).**

Dendrimers, the most highly branched functionalized molecules that exist, constitute a definite breakthrough into generations of new materials and they are attracting considerable attention in organic, supramolecular, and/or polymer chemistry [1]. Among these huge **monomeric** architectures, only few incorporate phosphorus [2] and only phosphorus dendrimers **having charges** within the cascade structure had been described [2] till the very recent past where two kinds of **neutral** phosphorus dendrimers were reported concomitantly by Majoral [3] and by ourselves [4]. Majoral's dendrimers have a cauliflower structure with $SPCl_3$ as the core and they possess 46 pentavalent phosphorus atoms and 48 terminal functions [aldehydic groups or phosphorus-chlorine bonds (molecular weight : 11268 or 15381)]. The synthesis of further generations having up to 384 functional groups (molecular weight 94146) was recently reported by Majoral's group [5].

Dendrimers from our own are **spherical** architectures which could be designed thanks to the previous skillful synthesis of D_{3h} cyclophosphazenic cores. Indeed, we recently reported [4] on the neat synthesis of pure cyclophosphazenic hexapodanes (coded as **sexapus** by reference to an octopus with six tentacles) through a regiospecific peraminolysis of hexachlorocyclotriphosphazene, $N_3P_3Cl_6$ **0**, by long-chain diamines, $H_2N\text{-}(CH_2)_n\text{-}NH_2$ ($n \geq 6$), on **ALPOT [50:11]**, i.e. on alumina impregnated with a certain amount of potassium hydroxide [6]. These sexapus are **3-dimensional polyfunctional** cores suitable for generating cyclophosphazenic **spherical** (i.e. aesthetically similar to the structure of a **dry dandelion flower** and not of a **cauliflower**) dendrimers.

Amino endings of tentacles in **sexapus 1a** are accessible to further nucleophilic attacks. Our strategy for dendrimers design lies on a two-step process. The first step consists of the grafting of $N_3P_3Cl_5$ flagstones (**pentafunctional** fans) at the extremity of each tentacle (giving compounds **1b** or **first-generation**) and the second step results of a subsequent persubstitution of chlorine atoms from the $N_3P_3Cl_5$ flagstones by a new set of long-chain diamines, $H_2N\text{-}(CH_2)_n\text{-}NH_2$ ($n \geq 6$) as linkers (giving compounds **2a**). In other words, the linkage of such $N_3P_3Cl_5$ flagstones on **sexapus** cores leads to **first-generation** dendrimers, the number of linkers for further extension being **multiplied by five** with respect to the starting situation in $N_3P_3Cl_6$ itself. Thus, every two-step performance from **1b** yields a **new generation** and we reported recently on the synthesis of such generations up to the fifth one [7].

The present contribution reports on the synthesis and structural investigation of dendrimers elaborated to the eighth generation [8] which possesses 2,343,750 phosphorus chlorine bonds (molecular weight 228,977,179). Moreover, the preliminary study of the chemical properties of dendrimers of the first (**1b**) and second (**2b**) generations is under investigation in our Laboratory with the aim of knowing more about the point where steric congestion and/or loss of solubility would eventually prevent further growth of the dendrimer.

Every generation of dendrimers was obtained through a careful stepwise growth of successive phosphorus-containing layers. The synthesis of each generation necessitates two repetitive steps: aminolysis of hexachlorocyclotriphosphazene, $N_3P_3Cl_6$ **0**, by long-chain aliphatic diamines (such as 1,6-Diaminohexane and higher cousins) leading to cores with dangling diamino groups followed by a grafting of $N_3P_3Cl_5$ flagstones as 5-fold growing multipliers on these amino endings.

In each step, reactants are introduced quantitatively according to the suitable stoichiometry. The only by-products are hydrogen chloride and the related $Et_3N.HCl$ hydrochloride ! All the compounds of the generations (i.e. **1b** to **8b**) are stable and perfectly soluble in a wide variety of organic solvents (chloroform, ethyl ether, etc.). All the intermediate compounds (i.e. **2a** to **8a**) with amino groups at the periphery are no more soluble in the previous organic solvents but are rather soluble in water. All the dendrimers were characterized by NMR and IR spectroscopy, and elemental analysis. Mass spectrometry (FAB or Electrospray) was useful for dendrimers up to **2b**. Vapor Pressure Osmometry (VPO) was useful for dendrimers up to **3b**.

The **second-generation dendrimers 2b** are obtained through 1) a nucleophilic substitution of the 30 Cl atoms of the **first-generation 1b** by 30 diamino groups (leading to **2a**) and 2) a subsequent grafting of 30 $N_3P_3Cl_5$ moieties on the ends of the 30 new tentacles. We used the classical pathway where Et_3N was employed for scavenging HCl, a polar solvent such as Et_2O being used. Reactions take 48 h and yield light yellow syrupy oils which are actually Et_2O-clathrates. A magnetic stirring (one night) of these oils with large excess of n-heptane leads to the declathrated species as white powders.

Further **precursors** and **generations** of dendrimers from **sexapus** cores may be synthesized till the **eighth generation** [8], the amount of impurities (i.e. of non completely substituted species) increasing gently but steadily with the size of molecules. An efficient approach for circumventing this difficulty is based on the following remark: the three steps consisting into the successive graft of **n** linkers + **n** $N_3P_3Cl_5$ fans + **5n** linkers are strictly identical, from a structural point of view, to the unique graft of **n sexapus** molecules ! Recent works illustrated this

approach, compounds **5a**, which are precursors of **5b**, having been synthesized from compounds **3b** in this way [7]. Such a procedure decreases sharply the risk of generating impurities. Anyhow, single SiO_2 column chromatographies with n-hexane/ethyl ether (2:1) as the eluant lead to **pure fourth to eighth generations which are now crystallizing.**

The saga of dandelion dendrimers is currently going on and it seems that the chemical process for their design looks endless. These monomeric monsters, that we called previously UFO (Unsual Fascinating Objects) [7], will probably take the place of common polymers on the next century, both for *in vitro* and *in vivo* applications. Up-to-now, no clear technological use was evidenced in literature for such dendrimers, cauliflowers or dandelions, but Epistemology shows that Beauty leads always to Benefits for Mankind ...

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SYNTHESIS OF ENANTIOMERIC AMINOPHOSPHONIC ACIDS AND PEPTIDES

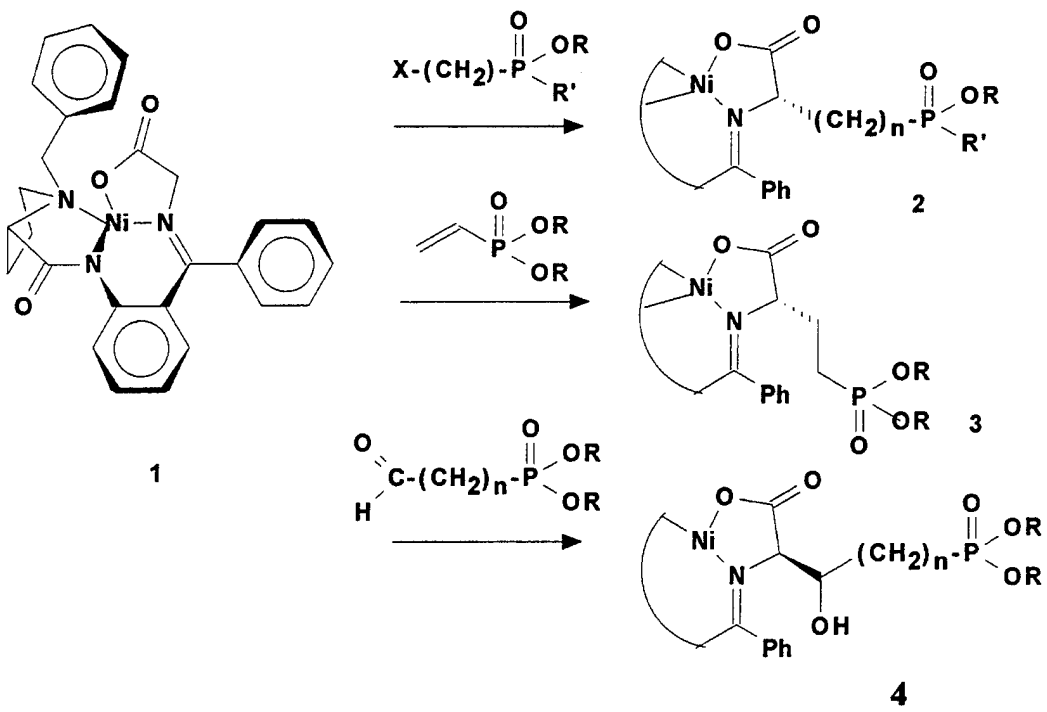
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Institute of Bioorganic Chemistry and Petrochemistry, NAS of Ukraine

Abstract Synthesis of enantiomeric amino phosphonic acids APA is described by using chiral auxiliary reagent or enzymatic resolution of racemic mixtures of APA phenacyl derivatives. Peptides with APA residue were obtained by application of trimethylsilyl derivatives or condensation in the presence of enzyme-papain

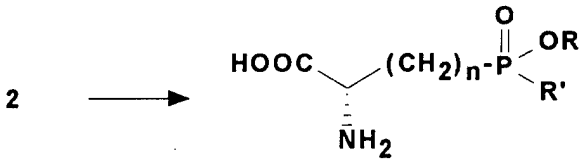
Key Words : aminophosphonic acids, enantiomers, peptides, enzymes

Today the most interest point in preparation of aminophosphonic acids , as in many other cases for bioactive compounds, is synthesis of stereochemically individual substances. To prepare enantiomers of amino acids with phosphonyl and phosphinyl groups in ω-position we have applied chiral auxiliary reagent containing glycine fragment. Started Ni-complex **1** could be easily obtained by reaction (*S*)-N-benzylprolyl-*o*-aminobenzophenone with glycine and $Ni(NO_3)_2$ in methanol solution. In the complex the acidity of C-H bond on glycine residue is enough to generate carbanion under action of organic or inorganic bases such as triethylamine or sodium methylate. We found the complex **1** is easy alkylated with haloalkylphosphonates and -phosphinates in acetonitrile solution of potassium hydroxide in presence of phase-transfer catalyst $Bu_4N^+ Br^-$. As a result of reaction the diastereomeric mixture of new complexes **2** and its diastereomer is formed in ~ 65 % yield and 10:1 ratio. Complexes were isolated from reaction mixture by preparative chromatography on silica.

Relatively high C-H acidity of glycine fragment in chiral auxiliary complex **1** allows to realize Michael addition of vinyl phosphonate (or phosphinate) in presence of bases and aldol condensation with corresponding phosphorus-containing aldehydes to yield chiral phosphorus-containing amino acids by other reactions. Unsubstituted phosphorus containing analogs of asparaginic , glutamic, homoglutamic acids, phosphinothricine and β-hydroxy APA are obtained from corresponding complexes .

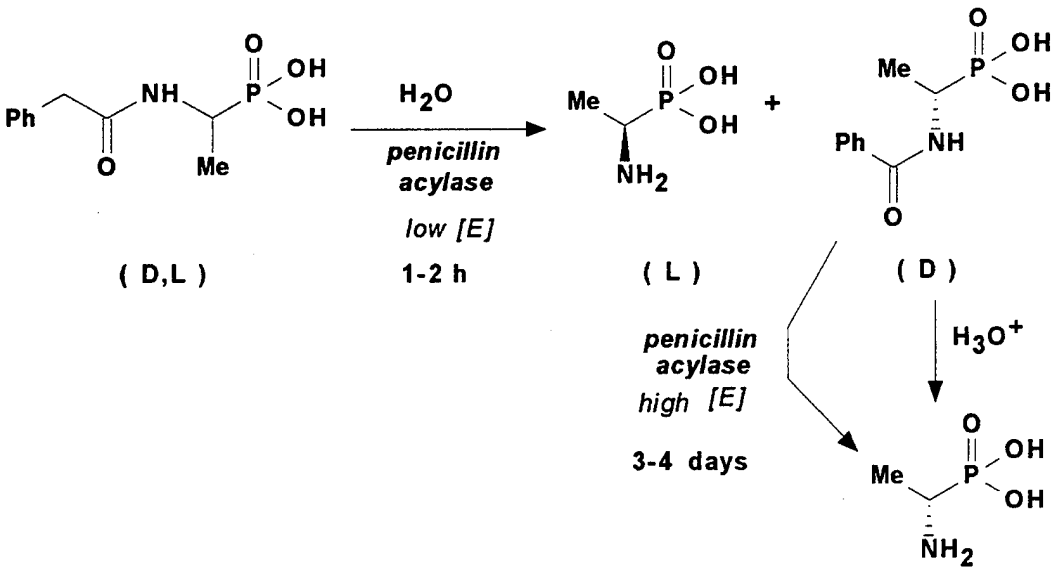


Absolute configuration of α-amino-containing center in obtained complexes has been estimated by ORD spectra. At action of 2N HCl solution in methanol the complexes are transformed into corresponding esters of amino acids and chiral auxiliary reagent - (*S*)-N-benzylprolyl-*o*-aminobenzophenone, for example :



Free amino acids were obtained by hydrolysis with HCl and ammonia. Proposed method of synthesis for ω-phosphonic analogs of dicarboxylic amino acids opens the possibility to obtain desired substances of this type in high yield.

We developed also effective method for the preparation of optically active 1-aminoalkylphosphonic acids with application of enzyme -penicillin acylase. The methods includes a biocatalytic step followed by chromatographic separation of the L-aminophosphonic acid from unreacted D-1-(N-phenylacetylamino)-alkylphosphonic acid and acid hydrolysis of the latter to D-aminophosphonic acid.

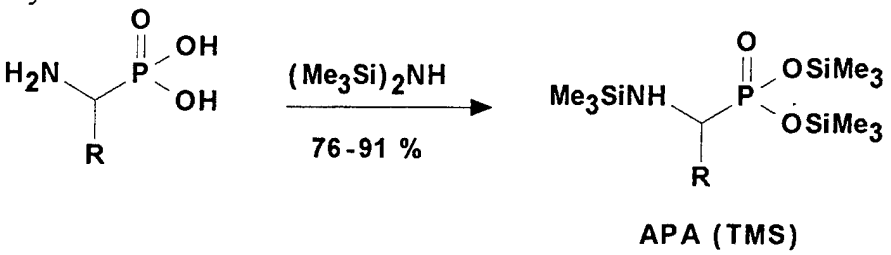


The computer simulation of the process indicates that an increase in enzyme concentration can result in drop of APA optical purity up to 0 as consequence of a significant increase in the rate of D-enantiomer hydrolysis. Indeed, when D-PhAc-Ala^P was incubated with a high enzyme concentration in 50-100 times as large as that used for L-Ala^P preparation over 3-4 days, D-Ala^P was isolated in good yield and excellent optical purity (ee >99%). Thus, owing to the high enantioselectivity of the process, the enzymatic hydrolysis of racemic PhAc-Ala^P can be carried out in two separate stages without any special precautions - at low enzyme concentration only the L-enantiomer of the substrate is hydrolyzed, the D-enantiomer can be hydrolyzed with noticeable velocity only by enhanced amounts of the enzyme.

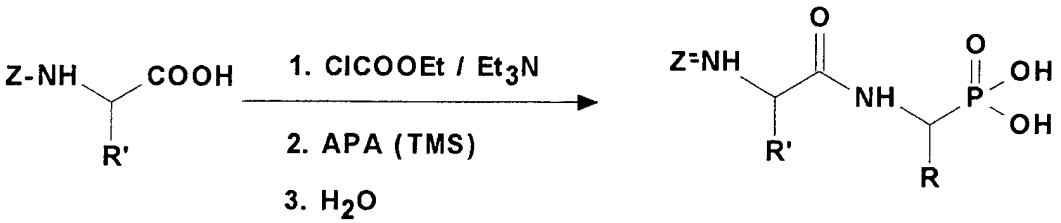
In comparison with N-acylated Ala^P, the hydrolysis of 1-(N-phenylacetylamino)ethylphosphonous acid (PhAc-Ala$^{P\text{-}H}$) by penicillin acylase proceeds with moderate enantioselectivity (E = 1440 in comparison with E = 58 000 for Ala^P), the rate of D-substrate hydrolysis being relatively high (K_D= 1.37 ·10^4 M^{-1}s^{-1}).

1-Aminoalkylphosphonic acids as natural amino acid analogs could be used as components in peptide synthesis. We shown that esters of 1-aminophosphonic acid react easily with mixed anhydrides of N-protected amino acids and pivalic acid obtained in situ from N-acyl amino acids and pivaloyl chloride in the presence of tertiary amine to give phosphonopeptides in good yield. We developed the method allowing to use effectively free aminophosphonic acids for the synthesis of phosphonopeptide with P-terminal aminophosphonic residues. At heating with hexamethyldisilazane APAs easily and in high yield give tris-trimethylsilyl derivatives, which are able to form amide bond

by acylation reaction. In such case the method of mixed anhydrides could be used effectively.

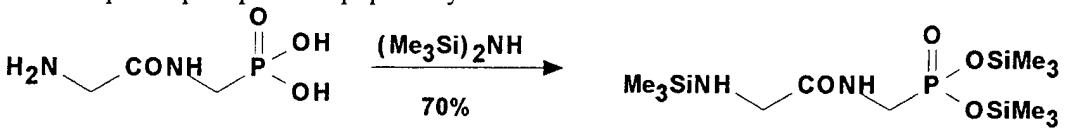


APA (TMS)

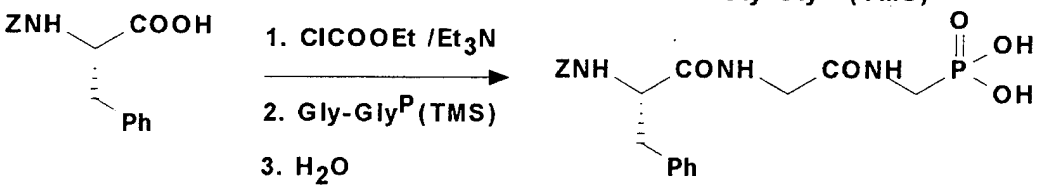


R'/R = H/H, Me/Me, $PhCH_2$/Me, H/$PhCH_2$, Me/$PhCH_2$, i-Bu/$PhCH_2$

Total removing trimethylsilyl group proceeds under standard process of workup with aqueous solution to give N-protected phosphonopeptides with free phosphonic residue. Silylation could be realized and in the case of phosphonopeptides with following application of trimethylsilyl derivatives in peptide synthesis, as it was shown on example of phosphonotripeptide synthesis.



Gly-Gly^P (TMS)



Z-Phe-Gly-Gly^P

Developed method was successfully applied for synthesis of phosphonic analogs of virus replication inhibiting peptide.

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SUBSTRATE RELATED *O,O*-DIALKYLDIPEPTIDYLAMINOPHOSPHONATES, A NEW TYPE OF THROMBIN INHIBITOR

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Abstract The facile reduction of *O,O*-dialkyl 1-hydroxyiminoalkanephosphonate precursors, using $LiBH_4/Me_3SiCl$ in THF at ambient temperature, conveniently affords *O,O*-dialkyl 1-aminoalkanephosphonates in good yield and high state of purity. *O,O*-Dialkyl 1-aminobenzylphosphonates may be prepared in high yield and purity from catalytic hydrogenolysis of their 1-benzylaminobenzylphosphonate precursors. These biologically active aminophosphonates, when coupled to substrate derived dipeptides, produced a range of novel phosphonotripeptides based upon the 'fibrinogen-like' sequence H-D-Phe-Pro-Arg; where the phosphorus structural units replace the 'P1'Arg. These tripeptides showed a marked inhibitory specificity towards the trypsin-like serine protease thrombin, a ubiquitous enzyme that plays a crucial role in the cardiovascular system. The compounds possess an initial K_i *in-vitro* in the micromolar range against thrombin. Further enzyme kinetic analysis of the compound Z-D-Dpa-Pro-$Pgl^P(OiPr)_2$ (IC_{50} 11.7 micromolar), showed that it displayed competitive inhibition characteristics toward thrombin, in contrast to the two stage slow-tight binding kinetics that had been shown by the analogous *O,O*-diphenyl derivative.

Key Words: Aminophosphonates, phosphonotripeptides, thrombin inhibition, anti-thrombotic agents.

INTRODUCTION

Cardiovascular disease is a prevalent cause of mortality across the world; recorded cases being higher than that of cancer. Advanced stages of the disease state such as myocardial infarcation, stroke, peripheral arterial occlusion and venous thromboembolic disease have been found to be as a result of formation of thromboembolic clots[1]. The anatomy of the disease state, and in particular clot formation is moderated by the coagulation serine proteases which are also responsible for the normal haemostatic equilibrium of the blood[2]. However, reversible inhibition of thrombin, a centrally acting multifunctional serine protease, and penultimate enzyme in the blood coagulation cascade, facilitates amelioration of thrombotic events that would

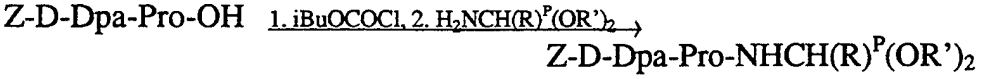
otherwise be extremely debilitating or potentially fatal[3]. Thrombin has the essential role of cleaving fibrinogen to liberate fibrin, which initiates blood clot formation; and stimulates platelet aggregation at the onset of vessel wall injury[4]. As a result of its pivotal role, thrombin is an ideal target for the development of an anticoagulant protease inhibitor.

Phosphorus containing inhibitors such as diisopropyl phosphorofluoridate[5], have often been used to characterise the physiological properties of hydrolytic enzymes. Furthermore Oleksyszyn and Powers showed that peptide derivatives of (α-aminoalkyl) phosphonic acids had the greatest potential for affording selective serine protease inhibitors, since they are closely related analogues of α-amino carboxylic acids. They prepared a number of peptidyl (α–aminoalkyl)phosphonate diphenyl esters with substrate related sequences, which in fact were potent and specific irreversible inactivators of a range of serine proteases; forming very stable derivatives with the enzymes[6,7]. This prompted our investigation into the synthesis and use of novel phosphorus-containing peptidomimetics as potentially useful antithrombotic agents.

RESULTS AND DISCUSSION

Earlier work had shown that mixed anhydride coupling of *O,O*-diphenyl α–aminoalkanephosphonates to Z-D-Dpa-Pro-OH efficiently generated phosphonotripeptides modelled on the 'fibrinogen-like' sequence H-D-Phe-Pro-Arg. Here the positively charged side chain of 'P1' Arg could be replaced with a neutral side chain protected by a phosphorus nucleus without a serious loss of inhibition[8]; and the 'P3' Phe could be replaced by the hydrophobic Dpa (ß,ß–diphenylalanine) to effect better interaction with the apolar binding site of thrombin. Although thrombin is known to cleave exclusively Arg and Lys bonds it was interesting that good inhibition could be obtained with a 'P1' structural unit having a neutral side chain, and that this contributed toward producing enhanced selectivity for thrombin. Initial K_i's were found to be in the micromolar range, and with 1h pre-incubation of the enzyme and inhibitor, these values improved, falling to the nanomolar range. The compounds showed two stage slow-tight binding behaviour, suggesting that the mechanism maybe ordered by hydrolysis of one of the phenyl ester groups to give a more stable enzyme-inhibitor complex[9].

An examination was later made to ascertain whether *O,O*-dialkoxy groups in $P(O)(OR)_2$ would interact with the catalytic triad of residues Asp, His, Ser in the active site of thrombin more favourably than the diphenyl groups of the earlier series (particularly as the free phosphonic acid derivatives were found to be less potent against thrombin). *O,O*-Dialkyl 1-aminoalkanephosphonates derived from the facile reduction of *O,O*-dialkyl 1-hydroxyiminoalkanephosphonate precursors, using $LiBH_4/Me_3SiCl$ in THF at ambient temperature[10]; and *O,O*-dialkyl 1-aminobenzylphosphonates derived from catalytic hydrogenolysis of their 1-benzylaminophosphonate precursors, were similarly coupled to Z-D-Dpa-Pro-OH, to form a new range of *O,O*-dialkyldipeptidylaminophosphonates (Scheme 1).



Scheme 1

TABLE 1

O,O-DIALKYLDIPEPTIDYLAMINOPHOSPHONATE INHIBITORS OF THROMBIN

entry	R	R'	K_i (μM)	$\delta^{31}P(CDCl_3)$/ppm
1	CH_2CH_3	CH_2CH_3	27.2	25.23, 25.59
2	CH_2CH_3	$CH(CH_3)_2$	18.1	23.43, 23.58
3	CH_2CH_3	$(CH_2)_3CH_3$	4.7	25.23, 25.65
4	$(CH_2)_2CH_3$	CH_2CH_3	3.65	25.48, 25.98
5	$(CH_2)_2CH_3$	$CH(CH_3)_2$	1.18	23.68, 23.97
6	$(CH_2)_4CH_3$	CH_2CH_3	0.944	25.39, 25.93
7	$(CH_2)_4CH_3$	$CH(CH_3)_2$	2.8	23.65, 23.93
8	$(CH_2)_4CH_3$	CH_2CH_2Cl	18.6	26.09, 26.84
9	$(CH_2)_4CH_3$	C_6H_5	0.854	27.66, 28.54
10	C_6H_5	CH_2CH_3	1.5	21.91, 22.07
11	C_6H_5	$(CH_2)_2CH_3$	11.2	21.86, 22.04
12	$4\text{-}CH_3OC_6H_4$	CH_2CH_3	4.9	22.15, 22.31
13	$4\text{-}CH_3OC_6H_4$	$CH(CH_3)_2$	30.0	20.42, 20.55
14	$3,4,5\text{-}(CH_3O)_3C_6H_2$	CH_2CH_3	42.7	21.68, 22.13
15	$4\text{-}FC_6H_4$	CH_2CH_3	insoluble	21.60, 21.81
16	$4\text{-}CF_3C_6H_4$	CH_2CH_3	560.0	20.87, 21.20
17	$3\text{-}CF_3OC_6H_4$	CH_2CH_3	7.04	20.90, 21.13
18	$4\text{-}CF_3OC_6H_4$	$CH(CH_3)_2$	22.2	19.42, 19.67
19	C_6F_5	$CH(CH_3)_2$	19.2	16.22
20	C_6F_5	$(CH_2)_3CH_3$	10.6	18.41

The *O,O*-dialkyldipeptidylaminophosphonates prepared (see Table 1) were purified by flash chromatography through sephadex LH 20 (MeOH eluant). All the compounds were fully characterised by ^{1}H, ^{13}C, ^{31}P and where appropriate ^{19}F N.M.R. spectroscopy; FABMS, electrospray MS and C, H, N analysis. ^{31}P N.M.R. spectroscopy showed that the tripeptides were isolated for the most part, as a mixture of diastereoisomers. The compounds when assayed (apart from **9** and **15**) displayed competitive inhibition toward thrombin[11]. The use of different dialkoxy groups in the 'P1' position did not have a detrimental effect on the potency and innate specificity of the inhibitors. It is envisaged that resolution of chirally 'pure' products and further structural modification, may generate phosphonotripeptides that would be extremely useful therapeutic agents for use as antithrombotic drugs.

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RADICAL-PAIR INTERMEDIATES IN THE PHOTOLYSIS OF ARYLMETHOXY GROUPS ATTACHED TO THREE- COORDINATE PHOSPHORUS

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Abstract. Stereochemical and product studies of the photochemistry of the title compounds is interpreted in terms of concerted as well as singlet and triplet radical-pair mechanisms.

Key Words: Radical pairs, photo-Arbuzov rearrangements, stereochemistry

Early work from this group demonstrated the high-yield conversion of benzyl phosphite **1** to the corresponding benzylphosphonate (**3**) in a photo-Arbuzov reaction.[1,2] A yield of bibenzyl of about 1% was formed which suggested either a largely concerted process or one in which radical pair intermediates (**2**, Ar = C_6H_5) are very short lived and undergo rapid, near-exclusive combination to **3**. The synthetic utility of this process for the synthesis of acyclic nucleoside-based phosphonates has been demonstrated.[3,4]

$$ArCH_2OP(OMe)_2 \xrightarrow{h\nu} [\,(MeO)_2P(O)\cdot \;\cdot CH_2Ar\,] \longrightarrow (MeO)_2P(O)CH_2Ar$$

1 Ar = C_6H_5 **2** **3** Ar = C_6H_5
4 Ar = *p*-$CH_3COC_6H_4$ **5** Ar = *p*-$CH_3COC_6H_4$

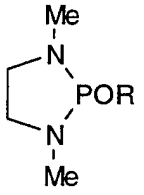
We now report that direct irradiation of 0.02 M dimethyl *p*-acetylbenzyl phosphite (**4**) in benzene at 335 nm yields only 12% of the photo-Arbuzov product (**5**) (quantum yield, ϕ, = 0.07) and major amounts of the dimer of the *p*-acetylbenzyl radical (**6**) (ϕ = 0.14; chemical yield 48%, based on moles of arylmethyl radicals

6 *p*-$CH_3COC_6H_4CH_2\cdot$

potentially available from **4**). $(MeO)_2P(O)\cdot$ from cage escape attacks benzene to

give products of trapping of the resulting cyclohexadienyl adduct with radical **6**. This result is consistent with rapid crossover, typical of ketones, of the initially formed excited singlet state of **4** to the triplet (presumably π,π^*) excited state. Triplet **4** then yields caged, triplet, radical pairs (**2**, Ar = *p*-$CH_3COC_6H_4$) that undergo diffusion more rapidly than intersystem crossing to singlet pairs and combination to **5**. Addition of appropriate amounts of PhSH diverts the carbon-centered radicals to *p*-$CH_3COC_6H_4CH_3$ and the dimethylphosphonyl radicals to $(MeO)_2P(O)H$ and greatly reduces the yield of **5**. The triplet nature of the excited state of the photoreaction of **4** also was demonstrated by CIDNP and CIDEP studies.[5] By inference, photorearrangement on direct irradiation of **1** proceeds from the singlet excited state.

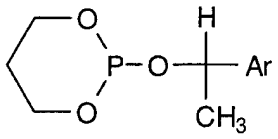
A survey of the photoreactions (254 nm) of a series of phosphoramidites, illustrated by **7**, showed that in acetonitrile or cyclohexane 65-70% yields of



7 R = $PhCH_2$, 1-naphthylmethyl

phosphonates resulted. Significantly, these photoprocesses were accompanied by the formation of 10-25% of 1,2-diarylethanes (accountability of arylmethyl radicals potentially formed) that obviously arise from dimerization of free arylmethyl radicals that diffuse out of the initial solvent cage.

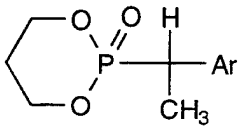
Stereochemical studies of these reactions, with 2-arylethyl analogs of known configuration at the carbon stereogenic center, also are in accord with the idea that increased amounts of products of radical diffusion result from relatively long-lived radical pairs. Earlier, we reported results of a proton NMR study that employed the



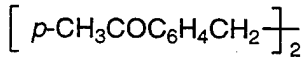
R-**8** Ar = C_6H_5
R-**9** Ar = *p*-$CH_3COC_6H_4$

chiral shift reagent *tert*-BuPhP(S)OH to demonstrate that phosphite *R*-**8** yields near-

quantitative amounts of phosphonate with at least 90% retention of configuration at the stereogenic carbon center in **10**.[1] This result has now been confirmed by HPLC on a CHIRACEL column. Photorearrangement of **8** (*R*/*S* = 97/3) in acetonitrile or cyclohexane yielded **10** with *R*/*S* = 85/15. Not surprisingly, 40% of the carbon-centered radicals potentially formed on direct irradiation (λ>320 nm) of the acetyl-substituted phosphite **9** (55 and 97% conversions) is accounted for as dimer **11**. Product phosphonate **12** was



R-**10** Ar = C_6H_5
R-**12** Ar = *p*-$CH_3COC_6H_4$



11

nearly racemic at carbon (*R*/*S* = 50/50-54/46). Clearly, the long-lived, triplet, free-radical pairs initially formed (**13**, Ar = *p*-$CH_3COC_6H_4$) undergo rapid stereochemical equilibration (**13** ⇌ **14**) on diffusion out of the initial radical cage and perhaps also within the cage. (The relative contributions of stereorandomization before and after escape from the solvent cage are currently being determined)



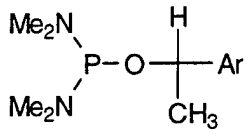
13 **14**

phosphonate (retention) phosphonate (inversion)

The stereochemistry of the phosphoramidite photorearrangements is typified by **15**. Starting with a 98/2 *R*/*S* ratio, a phosphonate ratio reduced to 65/35 (*R*/*S*) was encountered; and 20% of the potential 1-naphthylmethyl radicals appeared as dimer. This suggests that the amino substituents promote reaction via relatively long-lived free radical pairs. The most straightforward rationale is that a portion of

the photoreactions of **15**, and other phosphoramidites, proceed via triplet caged

15



radical pairs (**13** and **14**, Ar = C_6H_5 or Np). Either intersystem crossing of the singlet excited state is promoted by the amino substituents or initially formed singlet radical pairs equilibrate rapidly with their triplet counterparts in competition with their coupling to product phosphonate. To help better define the origins of the increased amounts of products of radical diffusion encountered in the phosphoramidite photoreactions, experiments with appropriate triplet quenchers and sensitizers are underway, along with collaborative CIDNP and CIDEP studies with the group of Professor N.J. Turro, Columbia University.

ACKNOWLEDGMENT.

We are most grateful for support of this research by grants from the National Science Foundation, and the Public Health service (CA 11045 and GM 53309)

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NUCLEOPHILIC ADDITION-OXIDATION REACTIONS OF σ^3, λ^3 DIALKYL(SILYLAMINO)PHOSPHINES WITH MONO AND DISUBSTITUTED ACETYLENES

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Abstract: Dialkyl(silylamino)phosphines R_2PNT_2 undergo a nucleophilic addition-oxidation reaction with either mono- or di-substituted acetylenes which is followed by a silyl migration to form phosphoranimines with unsaturated substituents. The reaction route depends on the substituent on the acetylenic carbon atom. Reactions of the acetylenes with dialkyl(silylamino)phosphines show high chemo and regio selectivity for addition to the triple bond in the formation of the alkene phosphoranimines. The reaction of (silylamino)-phosphines with α,β-acetylenic carbonyl compounds is more complicated; the reaction route depends critically on the substituents at both the carbonyl and the β-acetylenic carbon atoms.

INTRODUCTION

It is well known that σ^3, λ^3 phosphines are good nucleophiles and their reactions with a variety of organic compounds have been studied in detail.[1] The first step of the reaction is nucleophilic attack of P^{III} at the electrophilic center of the organic substrate. In the second step an addition or elimination reaction occurs to form stable product.[1] Thus, primary and secondary phosphines add to activated acetylenes to yield tertiary alkenyl phosphines.[2-4]

$$R_2PH + R^1C{\equiv}C{-}R^2 \longrightarrow R_2PC(R^1){=}CHR^2$$

$R = H$ or Ph; R^1, $R^2 = H$ or Ph

Tertiary phosphines react with acetylenes to give alkenylphosphonium salts [2-6]

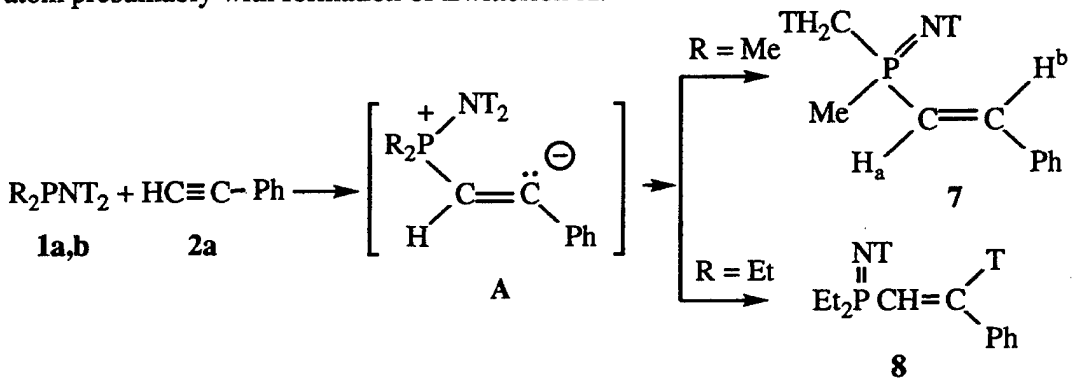
$$Ph_3P + RC{\equiv}CR' \xrightarrow{HX} [Ph_3P^+{-}C(R){=}CHR']\ X^-$$

In the past 20 years simple syntheses of secondary and tertiary silylaminophosphines have been developed[7] and this has stimulated the study of their reactivity with organic compounds containing different functionalities. These phosphines are good nucleophilic reagents which react easily with polar compounds. The reactions are accompanied by silyl group elimination or migration to give stable σ^4,λ^5 phosphoranimines[7-10]

In view of the fact that phosphines react with triple bonds, it was of interest to investigate the reactivity of silylaminophosphines with mono- and disubstituted acetylenes as a route to unsaturated phosphines. Herein we describe the results obtained for reactions of dialkyl(silylamino)phosphines **1a-e** with phenylacetylene **2a**, trimethylsilylacetylene **2b**, phenylpropargylaldehyde **3**, 4-phenyl-3-butyn-2-one **4**, 3-butyn-2-one **5** and ethylpropiolate **6**.

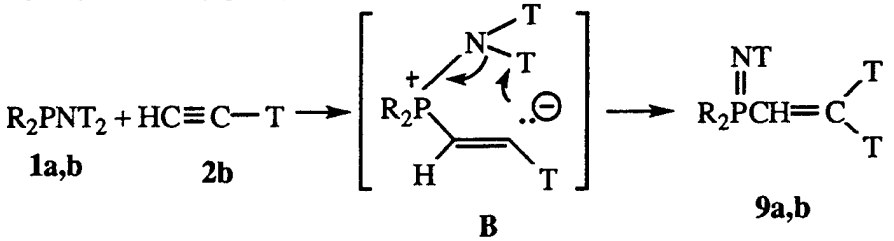
RESULTS AND DISCUSSION

Me_2PNT_2 **1a** and Et_2PNT_2 **1b** react very slowly with phenylacetylene **2a** at room temperature reaching completion only after 30 days. The first step of the reaction appears to be nucleophilic attack of phosphorus on the unsubstituted acetylenic carbon atom presumably with formation of Zwitterion **A**:



1a,b **2a** **A** **7** **8**

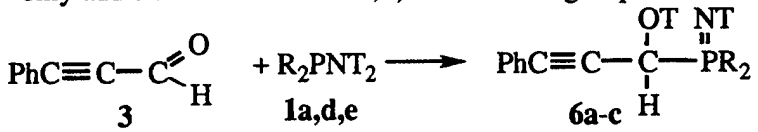
In the second step, **1a** and **1b** gave different oxidation products; in the case of **1a** the proton migration from one of methyl groups at phosphorus to the carbanion of **A** occurs and, after Me_3Si group migration from the N-atom to the methylene group at phosphorus, the alkene phosphoranimine **7** was obtained. In the case of **1b**, direct migration of the Me_3Si group from the nitrogen to the terminal carbon of the carbanion **A** gave the alkene phosphoranimine **8**. The structures of **7** and **8** were established by NMR spectra and elemental analysis. The reaction of Me_2PNT_2 **1a** and Et_2PNT_2 **1b** with trimethylsilylacetylene **2b** is an addition-oxidation process with migration of the Me_3Si from the nitrogen to the terminal carbon of the carbanion **B** and dialkyl 2,2-bistrimethylsilyl-1-ethenylphosphoranimines **9a,b** was obtained:



1a,b **2b** **B** **9a,b**

This reaction was carried out without solvent in a sealed ampoule at 120°C. After 30 days heating the phosphoranimines **9a,b** were obtained in good yield (75-80%). The structures of **9a** and **9b** were elucidated by NMR and elemental analysis.

The reaction of (silylamino)phosphine with acetylene carbonyl compounds is more complicated. The route depends on the substituents at the carbonyl and the β-acetylenic carbon. Dialkyl (silylamino)phosphines **1a,d,e** were reacted with phenylpropargylaldehyde **3** in CH_2Cl_2 at -78°C. As was shown for other carbonyl compounds[12] only addition-oxidation of **1a,d,e** to the C=O group was observed:

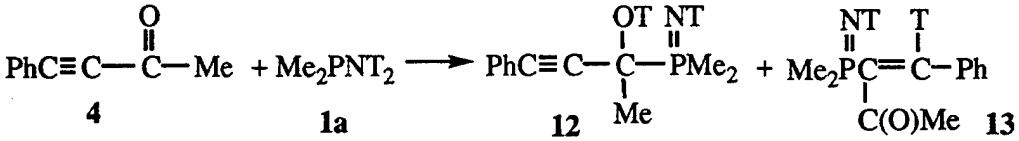


3 **1a,d,e** **6a-c**

R: (**a**) Me; (**d**) ^{i}Pr; (**e**) TCH_2

Structures of the acetylenic phosphoranimines **6a-c** were deduced from NMR and elemental analysis. This reaction is again **1a,d,e** highly chemo-, regio-, and stereoselective.

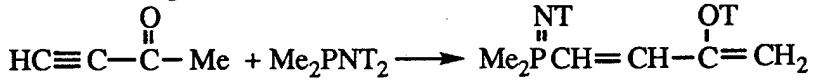
The formation of a similar acetylenic phosphoranimine (**12**) was also found in the reaction of 4-phenyl-3-butyne-2-one (**4**) with (silylamino)phosphine **1a** at -78°C. In this case, however, the main product (**13**) resulted from the addition of **1a** to the α-acetylenic carbon atom with subsequent migration of the trimethylsilyl group to the β-acetylenic carbon atom:



4 **1a** **12** **13**

The ^{31}P NMR spectrum of the crude product showed three signals at 19.2 ppm, 3.7 ppm and 2.6 ppm respectively for **12** and the (E) and (Z) isomers of **13**. These two examples show that the reaction path strongly depends on the particular substituents at β-acetylenic and carbonyl carbon atoms. The reaction is neither chemo-, regio-, nor stereoselective.

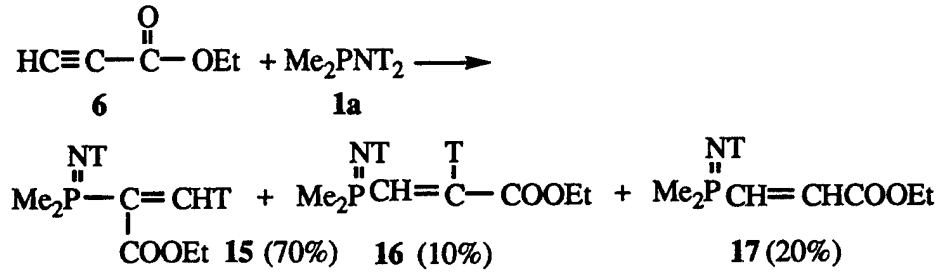
The reaction of **1a** with 3-butyne-2-one **5** yields a different product because the electron donating CH_3 group decreases the electrophilicity of the carbonyl carbon atom facilitating the addition of **1a** to triple bond. At -78°C in CH_2Cl_2 the reaction of 3-butyne-2-one **5** with **1a** was accompanied by polymerization. The polymerization process continued during distillation and so **14** was isolated only in low yield:



5 **1a** **14**

The structure of 1,3-butadienyl phosphoranimine **14** was also deduced from ^{1}H, ^{13}C and ^{31}P NMR spectra.

To evaluate the influence of a substituent at C=O on the reaction, we studied the reactivity of **1a** with ethyl propiolate **6**. In diethyl ether at -50°C a mixture of products was obtained:



The main product of the reaction was the phosphoranimine **15**, which arises from nucleophilic addition of **1a** to the α-acetylenic carbon atom. The structure of compound **15** is in accord with the NMR spectral data. Finally, the phosphoranimine **17** probably results from the presence of a trace of water or the abstraction of proton from the solvent in the first step of the reaction. Reacting **1a** with **6** in dichloromethane gave only **17**.

The phosphines **1d-e** reacted with **3** in the same fashion as **1a**. Individual products however could not be isolated from the reaction of **1d** or **1e** with **4**, **5** or **6** because the reaction mixture polymerized very rapidly.

CONCLUSION

The investigations described herein illustrate the reactivity of the dialkyl(silylamino)phosphines toward variously substituted acetylenes. For the first time we have shown a nucleophilic addition-oxidation reaction of σ^3, λ^3 (silylamino)phosphines to the C≡C triple bond. Extensions of these reactions will provide new approaches for the synthesis of alkenylphosphoranimines.

We thank the Natural Sciences and Engineering Research Council of Canada for support.

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ORGANOLITHIUM DISPLACEMENT OF ARYL ANIONS FROM TERTIARY PHOSPHINE DERIVATIVES OF DIPHENYL ETHER[1,2]

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Abstract Methyllithium displaces a phenyl anion from 10-phenyl-10H-phenoxaphosphine to produce a 70:30 mixture of 10-methyl-10H-phenoxaphosphine and starting phosphine. Butyllithium gives 50% conversion to 10-butyl-10H-phenoxaphosphine. These reactions could take place either by a one-step nucleophilic displacement or by ring cleavage followed by recyclization. To show the feasibility of the two-step process, non-heterocyclic lithiated tertiary phosphines were generated and shown to cyclize to phenoxaphosphines. For example, reaction of 2-phenoxyphenyldiphenylphosphine with phenyllithium produced 10-phenyl-10H-phenoxaphosphine (by lithiation ortho to oxygen followed by cyclization) along with triphenylphosphine (by direct displacement of 2-lithiodiphenyl ether). Other compounds prepared in this work: 2,2'-bis(diphenylphosphino)-diphenyl ether, bis(2-phenoxyphenyl)phenylphosphine, tris(2-phenoxyphenyl)phosphine, 4-carboxy-10-phenyl-10H-phenoxaphosphine, and the oxides and sulfides of the phosphines.

Key Words: nucleophilic displacement, 10-phenyl-10H-phenoxaphosphine, methyllithium, butyllithium, phenyllithium.

INTRODUCTION

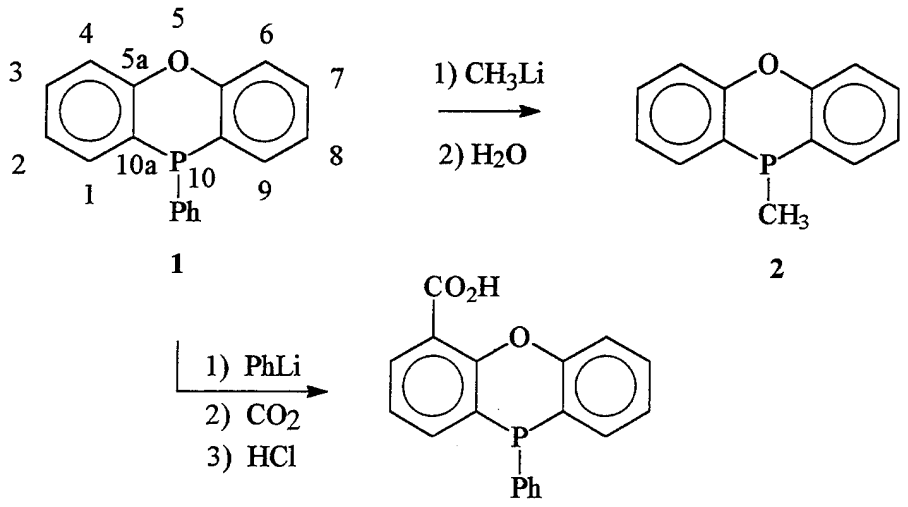
Nucleophilic displacement of good leaving groups from phosphines is well known, an example being the reaction of 2,2'-dilithiodiphenyl ether with phenylphosphonous dichloride to form 10-phenyl-10H-phenoxaphosphine (**1**).[3-7] In contrast, we have found only three previous reports of nucleophilic displacements of aryl anions from tertiary phosphines by alkyl anions of organolithium reagents and no previous reports of one aryl anion displacing another. Mathey[8] reported displacement of a phenyl anion of a phosphole by *t*-butyllithium; Kyba and Hudson[9] observed substitution of a phenyl of methyldiphenylphosphine by either an n-butyl or a *t*-butyl group; and Kyba[10] also determined that displacement of a benzyl group from optically active benzylmethylphenylphosphine by either n-butyl or *t*-butyl occurred with inversion of configuration.

RESULTS AND DISCUSSION

Reaction of 10-Phenyl-10H-phenoxaphosphine(1) with Lithium Reagents

Reaction of 10-phenyl-10H-phenoxaphosphine (**1**) with methyllithium cleanly produced after hydrolysis a 70:30 mixture of 10-methyl-10H-phenoxaphosphine (**2**) and the starting phosphine. 10-Methyl-10H-phenoxaphosphine[11] was identified by its ^{1}H, ^{13}C, and ^{31}P NMR spectra and by its mass spectrum. Reaction of **1** with butyllithium instead of methyllithium gave a 50% conversion to 10-butyl-10H-phenoxaphosphine.

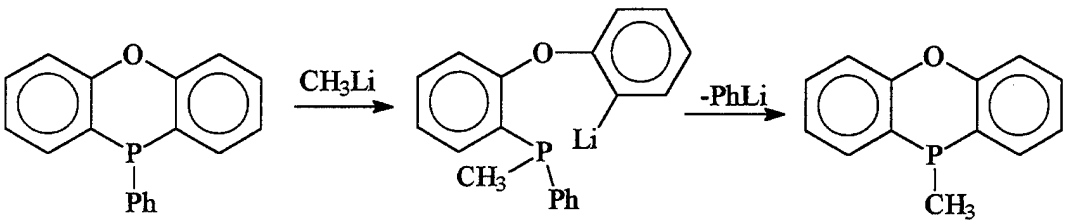
In these reactions any lithiation of **1** at the 4-position of the phenoxaphosphine ring system (abstraction of a proton ortho to the oxygen) or lithiation of the 10-alkyl group was reversed by hydrolysis in the workup. That deprotonation of the phenoxaphosphines had occurred was confirmed by hydrolysis of an aliquot of the reaction mixture with deuterium oxide and then examination of the mass spectrum of the product. Reaction of **1** with phenyllithium in the presence of tetramethylethylenediamine followed by carbonation gave after acidification 4-carboxy-10-phenyl-10H-phenoxaphosphine in 65% yield. When phenyllithium was employed for proton abstraction, any competing nucleophilic substitution simply replaced one phenyl group by another.



1 **2**

It was at first surprising that cleavage of the exocyclic C-P bond had occurred in the reaction of **1** with alkyllithiums, since alternative ring cleavage would have produced an *o*-lithiated diphenyl ether derivative (**3**) in which the negative carbon would have been

stabilized by the nearby oxygen. Ring cleavage is known to take place both in the reaction of hydroxide ion with 10-methyl-10-phenyl-10H-phenoxaphosphonium iodide, which formed methyl-2-phenoxyphenylphenylphosphine oxide, and in the reaction of hydroxide ion with 10,10-dimethyl-10H-phenoxaphosphonium iodide, which formed dimethyl-2-phenoxyphenylphosphine oxide.[11] In these reactions, in which ring cleavage occurred upon attack by hydroxide ion, protonation of the negative carbon of the ring-opened species by a hydroxyl-containing species probably occurred rapidly. In the reaction of **1** with methyllithium, however, there would not have been a sufficiently acidic group present to rapidly protonate **3**. Therefore, we propose that **3** could have been generated in our reaction of **1** with methyllithium but, if so, it then cyclized by an internal nucleophilic substitution reaction to form **2** plus phenyllithium.



1 **3** **2**

Synthesis of Tertiary Phosphines

We decided to test the two-step mechanism by synthesizing species similar to the proposed intermediate **3** in order to observe whether or not cyclization would occur spontaneously forming phenoxaphosphines. The phosphines needed were prepared by reaction of the appropriate chlorophosphines with 2-lithiodiphenyl ether. The yields were low because reaction of diphenyl ether with an equimolar amount of butyllithium gave a 7:3 ratio of monolithiated to dilithiated diphenyl ether, as determined both by hydrolysis with D_2O followed by mass spectral analysis and by reaction with diphenylphosphinous chloride followed by ^{31}P NMR analysis of the product mixture. Reaction of diphenyl ether with two moles of butyllithium as in the synthesis of **1** gave a good yield (58% after recrystallization) of 2,2'-bis(diphenylphosphino)diphenyl ether upon reaction with diphenylphosphinous chloride.

Reactions of 2-Phenoxyphenyldiphenylphosphine or Bis(2-phenoxyphenyl)phenylphosphine with Phenyllithium or Methyllithium

The reaction of 2-phenoxyphenyldiphenylphosphine with phenyllithium followed by hydrolysis was carried out to see if 10-phenyl-10H-phenoxaphosphine (**1**) would be produced as a result of abstraction of a proton ortho to the oxygen followed by cyclization through nucleophilic displacement of a phenyl anion. Indeed **1** was formed along with an approximately equal amount of triphenylphosphine, and both products support the feasibility of the two-step mechanism, **1** to **3** to **2**. The formation of triphenylphosphine in this reaction, which may represent the first example of nucleophilic displacement of an aryl anion from a phosphine by another aryl anion, is very similar to the displacement proposed as the first step of the two-step mechanism, and the conversion of 2-lithio-2'-diphenylphosphinodiphenyl ether to **1** is analogous to the second step of the two-step mechanism. Reaction of 2-phenoxyphenyldiphenylphosphine with methyllithium followed by hydrolysis gave the following relative amounts of products: **2** > **1** > triphenylphosphine > methyldiphenylphosphine. Reaction of bis(2-phenoxyphenyl)-phenylphosphine with phenyllithium or methyllithium gave mechanistically similar results and indicated that a diphenyl ether anion was displaced ten times more readily than a phenyl anion.

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1. Presented in part at the annual meeting of the North Carolina Academy of Science, March 26, 1994.
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INTRAMOLECULAR INTERACTION IN HETEROCYCLIC PHOSPHINES

Georgy N.NIKONOV, Anna S.BALUEVA, Andrey A.KARASIK

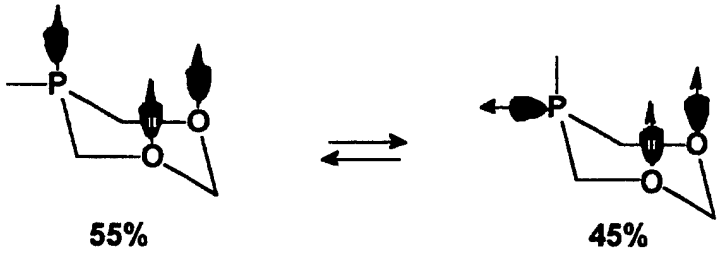
A.E.Arbuzov Institute of Organic and Physical Chemistry, Russian Academy of Sciencies, Kazan Scientific Centre, Kazan, Russia.

Some specific features of space structure, reactivity, complex formation and unusual physical properties of organic and organophosphorus compounds are due to univalent intramolecular interactions. Several intramolecular interactions observed in heterocyclic phosphines will be discussed in this current paper.

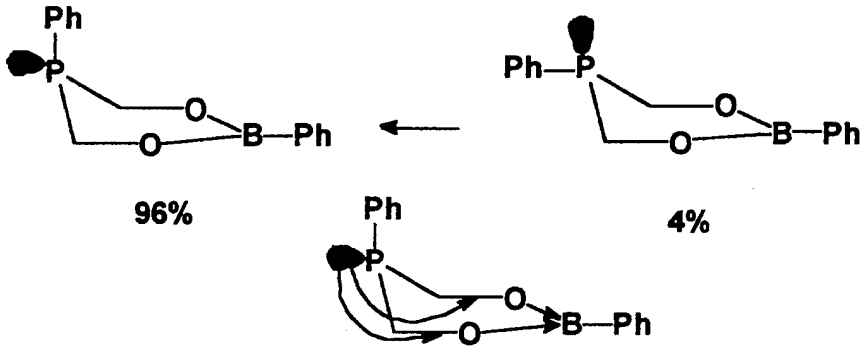
Heterocycles with the P-C-X fragments (X - heteroatom) are of interest regarding the interaction between phosphorus and the heteroatom and its influence on conformational behavior (substituent orientation, conformation of the ring, and inversion barriers). The quantity of conformers and stereoisomers of 1,3,5-dioxaphosphorinanes are in reasonably good agreement with dipole-dipole repulsion between lone electron pairs on phosphorus and oxygen. Moreover, the quantity of the conformer or stereoisomer with the axial orientation of substituents increases by substitutions of phosphorus lone pair on the oxygen, sulfur and selenium atoms. This correlates well with the increase of dipole-dipole repulsionion.

On the base of this theory the equlibrium of conformers of the 1,3,2,5-dioxaboraphosphorinanes the quantity of conformers with an axial orientation of the substituent on P-atom is bound to be smaller because the threecoordinated boron atom is a π-acceptor and the repulsion interaction must be smaller. However it has been found that the quantity of the conformer with an axial Ph group at the phosphorus atom is larger than in the above cases. This can be fairly well interpreted in terms of intramolecular donor-acceptor through-bond interactions (n-σ^*). In this case the electron

density is transferred from the phosphorus atom to vacant orbital C-O bonds, which are activated by the boron atom.

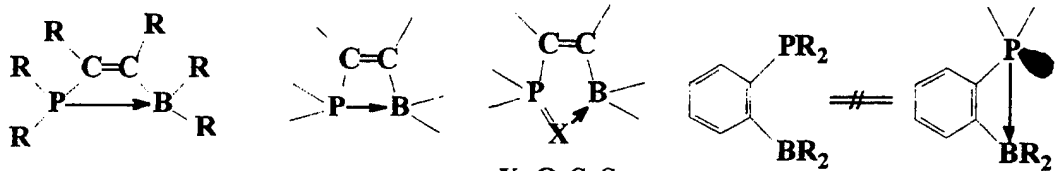


dipol-dipol interaction



n-σ * interaction

The next type of intramolecular interaction is a well known trans-annular donor-acceptor interaction. We are interested in compounds with P-C=C-B fragments. In these compounds the intramolecular trans-annular interaction are realised.

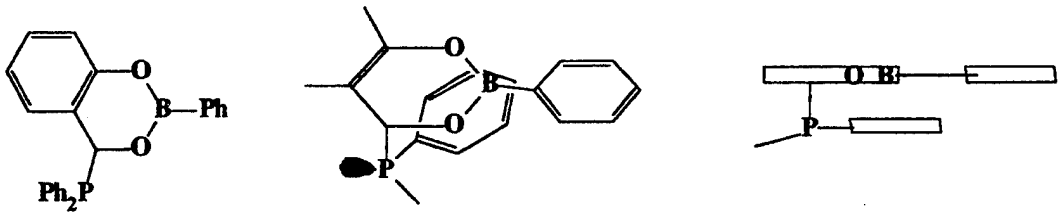


**Binger P., Koster R.
J. Organomet. Chem.,
1974, 73, 205**

During the past several years we carried out systematic studies of the properties of Z-1,2-borylphosphinoethenes. We have demonstrated that the

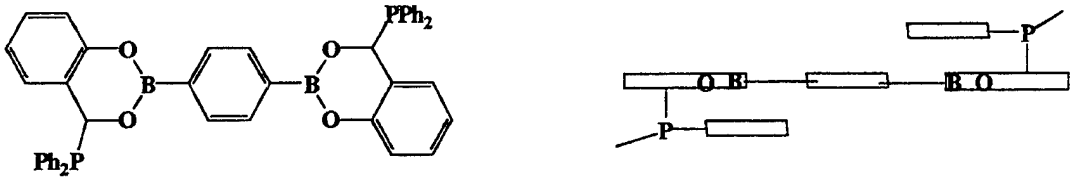
chemical shifts in ^{31}P NMR spectra, the dipole moments, and X-ray and mass spectral data all prove the existence of the P-B dative trans-annular intramolecular bond. The interaction in the oxides, sulfides and selenides is similar. In this case oxygen, sulfur and selenium atoms are donor centres. The o-borylphenylenphosphine is a structural analogue of borylphosphinoethenes. However it appears that the interactions between boron and phosphorus atoms are not observed in this system.

The dioxaborinanes with the exocyclic phosphine fragment were obtained by interaction of secondary phosphines, aromatic ortho-oxyaldehydes and boronic acid esters.



Dispersion Intramolecular Interaction
Overlapping stacks

However the properties of the compound that was obtained appeared to differ from those expected for compounds containing the P-C-O-B and P-C=C-B fragments. In contrast to these compounds, they exibit typical properties of tertiary phosphines and boronic acid, e.g. a high sensitivity to oxidation and hydrolysis, respectively. Parallel orientation of one of the phenyl substituents with the heterocyclic system should be mentioned, with short contacts (3.1 - 3.4 A) between the atoms of the phenyl ring and oxygen and boron atoms being observed in it crystal structure. Thus, there is no repulsion between the two planar fragments and the interaction between them are likely to result from dispersion forces. This is probably a first example of a "stacking interaction" of the cyclic boronic ester fragment. This interaction stabilizes the unusual conformation. The new substances were obtained from phenylendiboric acid with the aim to increase the number of interaction fragments. The properties of these compounds are analogous to properties listed above. In this case these may be a few structures in which stacking is available.

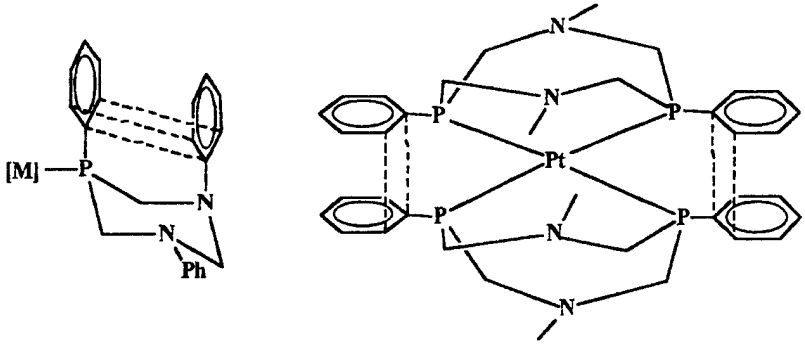


The planar nature of the dioxaborinane heterocyclic fragment determine the possibility of intramolecular interaction.

The computer simulations of 5-benzyl-1,3,2,5-dioxaboraphosphorinane shows, that the distance between the phenyl plane of axial benzyl group and O_2BC plane is equals nearles 3.2 A. The compound has been obtained in the crystal phase and was described by NMR and IR and Raman spectroscopy. This data have demonstrated that benzyl substitution have an axial orientation. There is reason to believe that staking takes place.

And finally a few words about the complexes of transiton metals with ligands which already possess a certain type of interactions. Intramolecular interactions may be observed in ligand, between the ligand fragment and the metal ion and between different ligands. For example, the six-membered ring ligands (1,3,5-diazaphosphorinane) possess a steric disadvantage conformation namely with two axial phenyl groups at phosphorus and nitrogen atoms, as shown for platinum and palladium complexes. Phenyl rings are parallel to one another and come within short distances of each other.

The stack between phenyl rings of two different ligands were observed in platinum(II) complexes of diazadiphosphacyclooctane.



The type of intramolecular interactions are far more numerous if works of other authers are taken into consideration.

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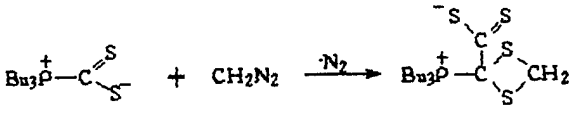
SYNTHESIS AND REACTIVITY OF NEW ORGANOPHOSPHORUS COMPOUNDS

Nickolay I. Tyryshkin, Alexander I. Konovalov,
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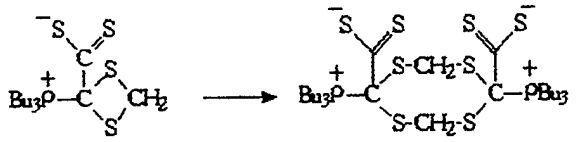
Abstract Synthesis of functionally substituted organophosphorus compounds on the basis of reactions of the tri-n-butylphosphine/carbon disulfide, tri-n-butylphosphine/phenylisothiocyanate, tris(dimethylamino)phosphine/phenylisothiocyanate adducts with a wide range of different dipolarophiles are reported. The development of application of S-Li tri-n-butylphosphonio-dithioformiate derivatives to the synthesis of new types of organophosphorus compounds are reported.

In 1861 A.W.Hofmann reported on the violently exothermic reaction between the newly discovered trialkylphosphines and carbon disulfide to give red crystalline adducts. Over the succeeding century the chemistry of this class of compounds was little studied. In 1971 Hartzler[1] reported on the formation of 2-alkylidene-1,3-dithioles as a result of interaction of the tributylphosphoniodithiofor-miate adduct with acetylene carbo-xylate in the presence of aromatic aldehyde. Cava[2] reported that the intermediate ilide can be stabilized by formation of stable phosphonium salt, if the reaction is carried out in the presence of absolute HBF. In 1992 the papers of R.A.Aitken[3] appeared on the reactions of the phosphoniodithioformiate cycloaddition to 1,3-dipolarophiles.

We have undertaken a detailed study of the cycloaddition reactions of adducts with a wide range of different dipolarophile. Reaction of diazomethane with tributylphosphoniodithioformiate proceeds at temperatures from 0 C to room temperatures for several minutes. The data NMR ^{31}P (48 ppm), ^{13}C (235 ppm CSS, 94 ppm P=C, 75 ppm CH_2). IR (1045 cm^{-1}, CSS^-) may correspond both to monomeric (1) or dimeric (2) products, but its molecular weight corresponds to dimeric form (2):

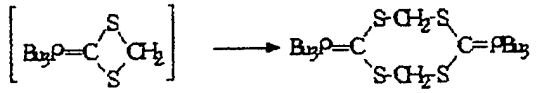


1



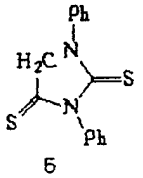
2

Reaction of tributylphosphoniodithioformiate with diazomethane at temperatures from -40 C to -20 C give somewhat different results. Yellow noncrystallizing oil is formed. In the NMR ^{31}P spectrum two signals are observed at +48 ppm similar to phosphonium salt (2) and at +44 ppm with the ratio 2:1. Obviously the latter signal may be assigned to phosphonium ylide (3) which most probably has also a dimeric form (4):

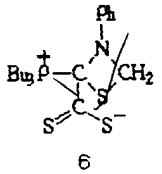


3 4

The reaction of tributylphosphoniophenylisothiocyanate with diazomethane proceeds differently from dithioformiate derivative. Nonphosphorus product (5) was isolated from the reaction mixture.



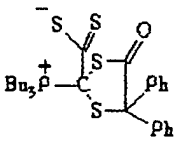
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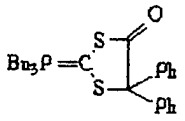
6

The remaining reaction mixture is a yellow viscous oil containing two compounds with the chemical shifts of +52 (tributylphosphineazine) and +49 ppm (phosphonium salt (6)) in the ratio 10:1.

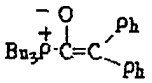
Interaction of diphenylketene with tributylphosphonio-dithioformiate preceeds analogously as interaction of diazomethane. Reaction proceeds at room temperature in several minutes. According to NMR ^{31}P and ^{13}C and IR spectroscopy the mixture of four phosphorus containing compounds is formed. These are phophonium salt (7) (+44 ppm), ylide (8), (+34 ppm), phosphonium salt (9) (+48 ppm) and tributylphosphine oxide.



7



8

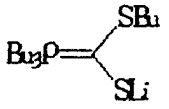


9

In both cases with diazomethane and diphenylketene, the formed ylides may serve as good Wittig reagents for formation of heterocyclic structures.

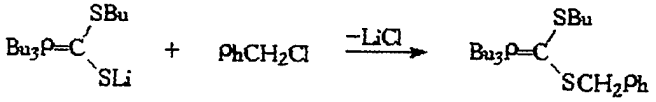
Analysis of literature shows that the interest to metallated phosphorus ylides is explained by their synthetic potential, by the possibility to regulate stereochemical aspects of Wittig reaction with aldehydes and ketenes.

Interaction of tributylphosphoniodithioformiate with butyllithium easily proceeds at temperatures from -70 to -40 C in several minutes. The reaction mixture shows one ^{31}P phosphorus signal at +40 ppm corresponding to phosphonium ylides. The obtained lithium derivative of tributylphosphoniodithioformiate is highly reactive, thus afterwards it was studied in situ without its isolation from the solution.



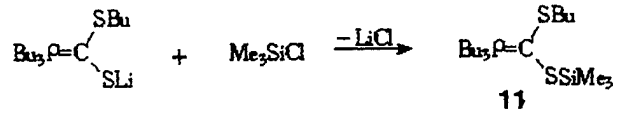
Our further study deals with synthetic application of the above lithium ylide.

Interaction of benzyle chloride with Li-ylide proceeds at -20 C with formation of the single product, transparent colorless oil, dithioalkyidenphosphorane (10) with the chemical shift +32.5 ppm.



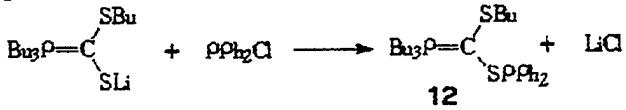
10

Interaction of lithium Li-ylide with trimethylchlorosilane gives ylide (11) with a quantitative yield, which is yellow liquid oil.



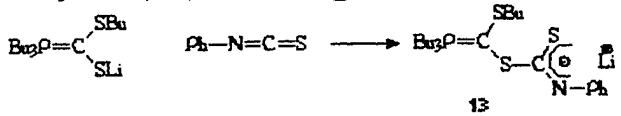
11

Reaction of Li-ylide with diphenylchlorophosphine results in formation of phosphonium ylide (12) with the yield 90% containing trivalent phosphorus atom, (δ_P 49 ppm, 28 ppm)



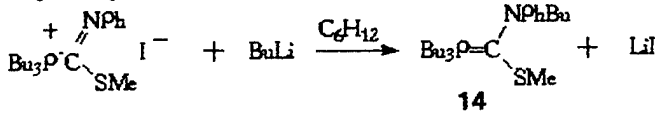
12

Ylide reacts with phenylisothiocyanate via pseudoacylation giving metallated ylide (13) with a high yield. (δ_P 41 ppm)



13

Phosphonium salt, obtained from tributylphosphoniophenylisocyanate and methyl iodide with small admixture of tributylmethylphosphonium iodide, gives phosphonium ylide (14) with the enamine nitrogen atom when treated by butyllithium.



14

Thus, the studies of metallation reactions of the tributylphosphine/carbon disulfide adduct, phosphonium salts with butyllithium allowed us to find a new convenient one-pot method of synthesis of functional alkylidenphosphoranes.

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Action of Nucleophilic Phosphorus Reagents on Heterocyclic *cis*-Disulfides

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As a contribution to previous studies of the reaction of phosphorus nucleophiles with heterocyclic *cis*-disulfides,[1,2] the reactivity of trialkyl phosphites **2** toward 5-p-chlorophenyl-4-cyano-1,2-dithiol-3-thione **1a**, 5-phenyl-1,2,4-dithiazol-3-thione **1b** and its 3-carbonyl derivative **1c** has now been investigated.

The reaction of the thione **1a** (0.01 mol) with trimethyl, triethyl or triisopropyl phosphites **2a-c** was found to proceed in the absence of solvent at 100 °C for ~10 h. Chromatographic separation of the reaction mixture produced two crystalline products **8** and **9**. The parallel trialkyl thiophosphate was also identified (^{31}P NMR) in the product-mixture in each case. Reaction of **1a** with **2a** produced in addition to **8a** and **9**, another crystalline yellow product assigned structure **7** (R=CH_3) (see table A).

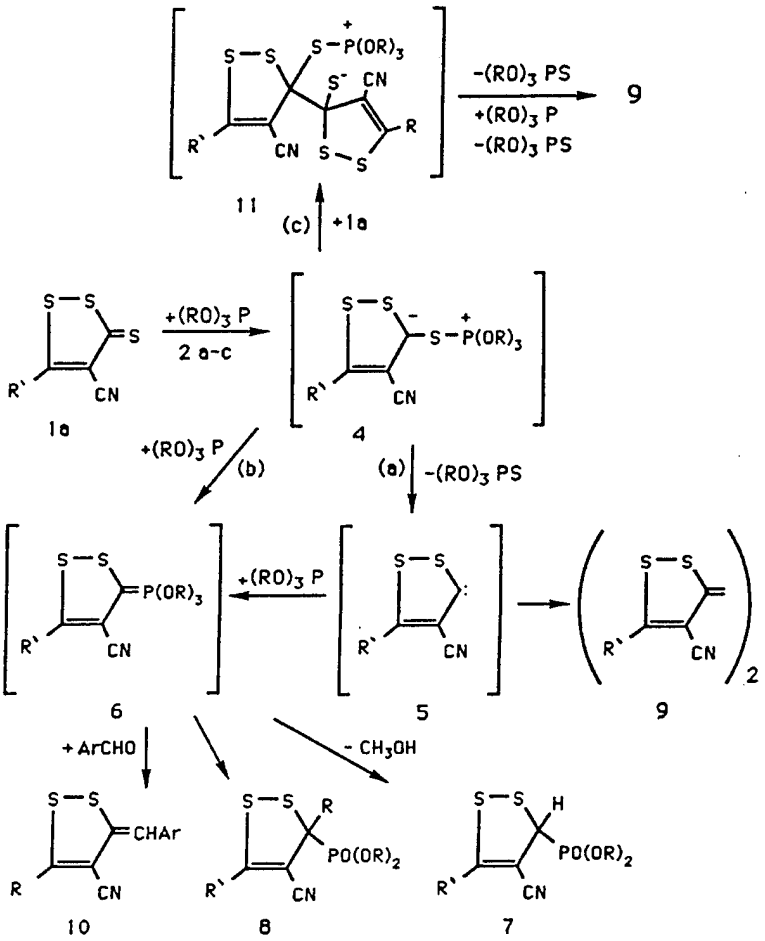
Table A : Reaction conditions and the products of the reaction of 1a with 2a-c.

Educt	Reaction Time (h)	Reaction products Compound (yield, %)[a]			
1a + **2a**	10	**7** (15)	**8a** (28)	**9** (15)	
1a + **2b**	10	–	**8b** (45)	**9** (16)	
1a + **2c**	8	–	**8c** (52)	**9** (20)	
1a + **2a** + ArCHO	8	**7** (10)	**8a** (15)	**9** (<5)	**10** (35)

a) yields are approximated.

Reasons for phosphonate structures **7** and **8** are: a) Satisfactory elemental analyses and molecular weight determinations (MS) were obtained for all new compounds. b) Their ^{31}P NMR spectra have chemical shifts at δ 28-30 ppm (vs. 85% H_3PO_4). c) In the ^{1}H NMR spectrum of **8a**, the methyl protons appear as a doublet at δ 1.96 ppm with $^{2}J_{HP}$ = 10.5 Hz. The presence of –C–CH_3 group was supported by a signal at δ 19.6 ppm in the ^{13}C NMR spectrum and a signal at δ 35.8 ppm (C.CH_3), a value which coincides with a chemical shift for the ring sp^3-carbon atom bearing a methyl group. The ^{1}H NMR of **7** lacked the signal due to the –C–CH_3 group, instead another doublet appeared at δ 4.45 ppm with $^{2}J_{HP}$=18.2 Hz, which attributed to the ring-methine proton.

* To receive any correspondence.



4-11, R` and R as in 1a and 2; Ar = C_6H_5

Scheme 1

d) The IR spectra of **7** and **8** showed -S-S- absorption band at 1275 cm^{-1}. Finally, on carrying out the above reaction in the presence of benzaldehyde, it yielded the phosphonates **7** (10%) and **8a** (15%), the dimeric product **9** (<5%) and 3-benzylidene derivative **10** as a major product (35% yield), which was identified by elemental analysis, mass and ^{13}C NMR spectroscopy.

3,3`-bi(1,2-dithiol-3H-ylidene) **9** was obtained as orange crystals, mp. 196 °C, m/e = 475 (M^+), calcd. = 475.46. The principle spectral features of **9** are its absorption at υ_{max} cm^{-1} 2215 (CN), 1275 (-S-S-) and 1622 (C = C).

The structure of 3,3`-bi(1,2-dithiol-3H-ylidene) **9** was presumed to be (E)- isomer since it is previously reported [3, 4] that Z-alkenes having electron - withdrawing group (CN, cf. **4** and **11**, Scheme 1) substituent α to the thiocarbonyl group of the substrate, isomerizes to the thermodynamically more stable E-isomer.

Scheme 1 presents the three kinds of pathways had been observed from the thiocarbonyl group in **1a** which is adjacent to α electron-withdrawing group (-CN)

substituent. Thus, the initial thiophilic addition is assumed, involving trialkyl phosphite and the thiocarbonyl group. The evoluted thiophilic addition product **4** can undergo desulfuration with formation of carbene **5** [path (a)]. Reaction of **5** with a second equivalent of phosphite [path (b)] or the substrate **1a** [path (c)] leads to the resulting products **8** and **9**, respectively. Formation of **7** was explained *via* the protonation-arbuzov type dealkylation of the ylide intermiate **6**.

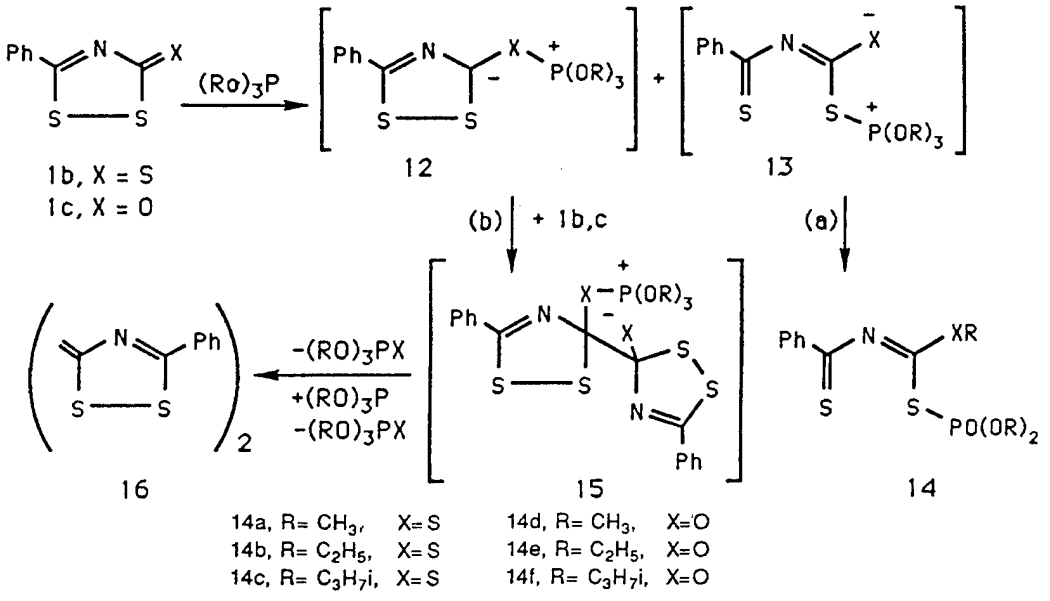
On the other hand, when **1b** or **1c** was allowed to react with trialkyl phosphites **2a-c** under the same experimental conditions used with **1a**, the reaction course takes another way to give **14a-f, 16** and the parallel trialkyl thiophosphate or trialkyl phosphate, respectively, (Scheme 2). This result is contrary to the previously reported[5] observations that, only, thioacyl isothiocyanates or thioacyl isocyanates and the corresponding thiophosphate were the reaction products, for the same reactions. Moreover, addition of benzaldehyde to the reactants **1b** or **1c** and trialkyl phosphite did not affect the result.

Table B : The reaction of 1,2,4-dithiazoles 1b and 1c with trialkyl phosphites 2a-c.

Product	X	R	Mp °C	Yield[a] (%)	Product	X	R	Mp °C	Yield[a] (%)
14a	S	CH_3	83[b]	33	**14d**	O	CH_3	66[d]	38
14b	S	C_2H_5	109[b]	47	**14e**	O	C_2H_5	71[d]	44
14c	S	C_3H_7-i	113[c]	55	**14f**	O	C_3H_7-i	81[d]	48

a) Yields are approximated. b) From ether / light petroleum ether (b.r. 40-60 °C).
c) From cyclohexane. d) From pentane.

Structural assignment for O,O-dialkyl S-phosphorothioate **14** was based on microanalyses and spectroscopic interpretations (MS, IR, ^1H, ^{31}P and ^{13}C NMR spectra), e.g., ^{31}P NMR chemical shifts for **14** are $\delta \sim 22.5$ ppm.



Scheme 2

The identity of 3,3`-bi(5-phenyl-3H-1,2,4-dithiazol-3-ylidene) **16** was confirmed by comparison with authentic specimen.[2] However, we were unable to assigne the (E)- or the (Z)-structure for the dimeric product **16** since the already available spectroscopic data can not decisively differentiate between the two isomers. X-ray crystallographic analysis will be undertaken and the data will be published in the forthcoming communication.

A possible explanation for the course of the reaction of **1b** and **1c** with trialkyl phosphites is shown in Scheme 2. We presumed the enhanced ability of -S-S-linkage to be disrupted due to the absence of the electron- withdrawing group substituent from

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PHOSPHORYLATED AND SILYLATED DERIVATIVES OF ALFA-MERCAPTOCARBONYL COMPOUNDS

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Abstract The phosphorylation and silylation of α-mercaptocarbonyl compounds have been investigated. Novel different cyclic and linear silicon(phosphorus) containing derivatives have been obtained.

Key words: α-Mercaptocarbonyl compounds, trimethylchlorosilane, chlorophosphites, phosphorylation, silylation, 1,3,2-oxathiaphospholenes, thiophosphites, siloxyalkenes.

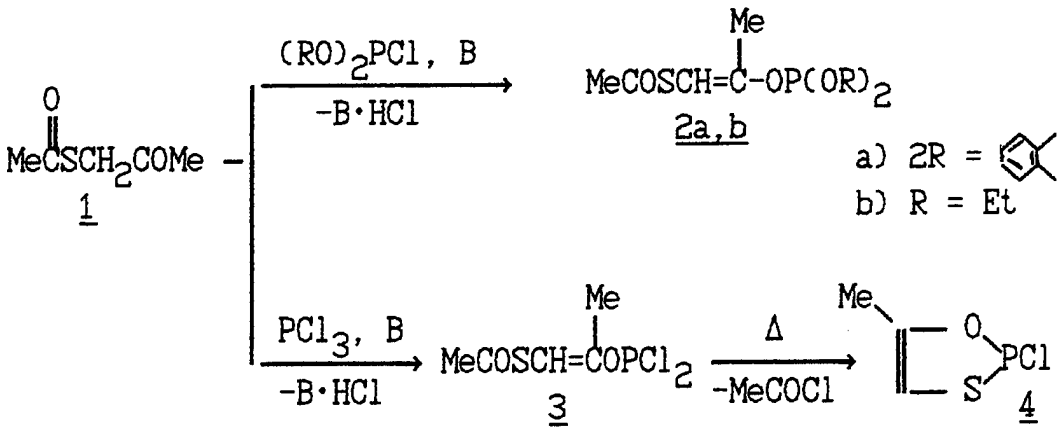
INTRODUCTION

The chemical behaviour of phosphorylated α-oxy- and α-aminocarbonyl compounds has been described in detail [1,2]. Meanwhile, the phosphorylation and silylation of α-functionally substituted mercaptanes has not been adequately investigated [3]. In this paper we would like to report on phosphorylated and silylated products of α-mercaptocarbonyl compounds and their use in elementoorganic synthesis.

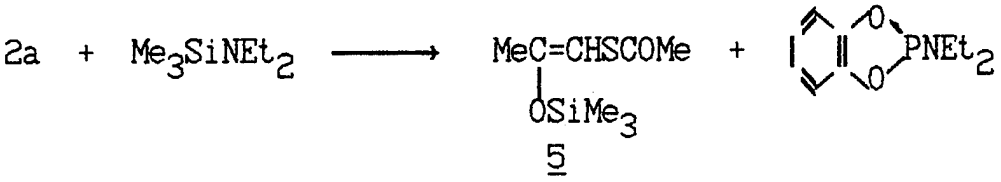
RESULTS AND DISCUSSION

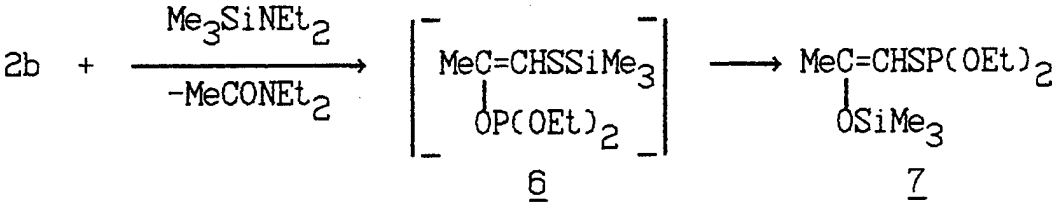
By the interaction of α-mercaptoacetone with acetylchloride ketone 1 was obtained. The interaction of 2-chloro-1,3,2-dioxabenzophospholene or diethylchlorophosphite with ketone 1 results in the formation of functionally substituted vinylphosphites 2a,b. When phosphorus trichloride is used in this reaction vinyldichlorophosphite 3 is formed,

which when heated is converted into 1,3,2-oxathiaphospholene 4 with the elimination of acetylchloride.



In the reaction of phosphite 2a with trimethylsilyldiethylamine the nucleophilic attack is directed to a highly electrophilic phosphorus atom with the elimination of 2-diethylamino-1,3,2-dioxabenzophospholene and formation of siloxyalkene 5. Meanwhile, when the electrophility of phosphorus atom is rather low, as in molecule 2b, the interaction with trimethylsilyldiethylamine is accompanied by elimination of N,N-diethylacetamide and formation of vinylphosphite 7.





This result is the consequence of the formation of vinylphosphite 6, which is converted into a final product 7 due to the internal 1,4 O-S exchange process.

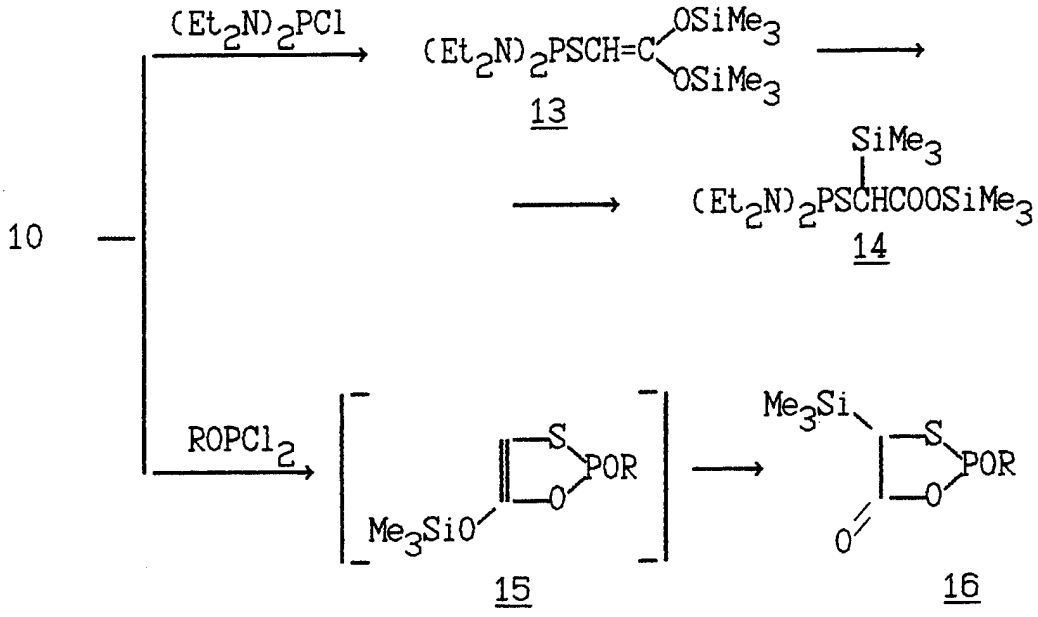
We also conducted the silylation of α-mercaptoacetic acid 8. At first trimethylsilyl(trimethylsilylthio)acetate 9 was obtained, which when acted upon by sodium or lithium bis(trimethylsilyl)amide and trimethylchlorosilane was converted into 1-trimethylsilylthio-2,2-bis(trimethylsiloxy)ethylene 10. As is known, the carbonyl group of carbonic acids is not subgect to enolization and therefore the strong base must be used for the rupture of C-H bond and introduction of trimethylsilyl group.

$$\underset{\underline{8}}{HSCH_2COOH} + 2\,Me_3SiCl \xrightarrow[-2B\cdot HCl]{2B} \underset{\underline{9}}{Me_3SiSCH_2COOSiMe_3} \longrightarrow$$

$$\xrightarrow[2.\ Me_3SiCl]{1.\ M\cdot N(SiMe_3)_2} \underset{\underline{10}}{Me_3SiSCH{=}C(OSiMe_3)_2}$$

The compound 10 is a novel organosilicon synton, which may be used for obtaining different organophosphorus compounds. Its interaction with diphenylchlorophosphine proceeds at room temperature and gives rise to thiophosphinite 11 which when distilled is converted into siloxythiophosphinate 12.

$$10 + Ph_2Cl \longrightarrow \underset{\underline{11}}{Ph_2PSCH{=}C(OSiMe_3)_2} \xrightarrow{\Delta} \underset{\underline{12}}{Ph_2P(S)OSiMe_3} + [Me_3SiOC{=}CH]$$



The interaction of siloxyethene 10 with tetraethyldiaminochlorophosphine is accomplished with the formation of thioamidophosphite 13, which when distilled or stored for a long time is rearranged into compound 14. The reaction of alkene 10 with alkyldichlorophosphites is unexpected. In this case the products of reaction are 2-alkoxy-4-trimethylsilyl-1,3,2-oxathiaphospholane-5-one 16. Apparently, reaction proceeds with the internal formation of oxathiaphospholenes 15, which under reaction conditions are isomerized into the final products 16.

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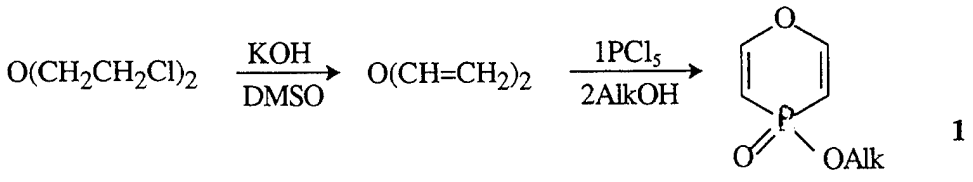
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A STEREOSELECTIVE SYNTHESIS OF TWO 2-DEOXY-3-PHOSPHASUGARS EPIMERIC AT PHOSPHORUS

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School of Chemistry, The University of New South Wales, Sydney 2052 Australia; Faculty of Science & Technology, Griffith University, Nathan, Queensland 4111 Australia

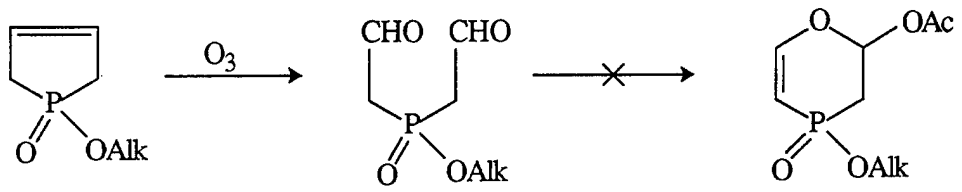
Abstract A synthetic route to 2-deoxy-3-phosphasugar derivatives utilising a stereoselective addition of a phosphinate to an aldehyde is described.

Monosaccharides are fundamental building blocks in all living systems. They are also stereochemically complex and not often targets of total synthesis with some notable and marvellously elegant exceptions [1]. Their biological ubiquity suggests that heterosugars should be attractive targets as biologically active molecules, particularly those that are isosteric or nearly so. Phosphasugars have attracted considerable attention over the past twenty years, particularly by Japanese [2] and more recently Polish [3] workers who have synthesised a wide range of derivatives in which the hemiacetal oxygen or C, of an existing sugar was replaced by P(O)R. The substituent, R, is often aryl or alkyl which would diminish any isosteric behaviour but which is synthetically more convenient. The best replacement for CHOH would be HP(O) but it would be technically difficult to carry this group through a synthesis. However, the conversion AlkOP(O)→HP(O) is known [4] and the ester group is more easily handled. We wished to development methods for the synthesis of phosphapentoses and hexoses in which CHOH was replaced by AlkOP(O) as a first step to isosteric phosphasugars, few of which are known. Initially we sought to use Sharpless's powerful stereoselective epoxidation route beginning with the readily available heterocyclic [5] (Figure **1**)

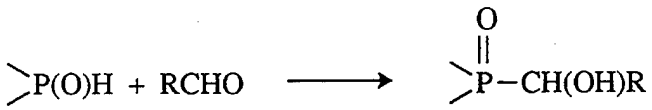


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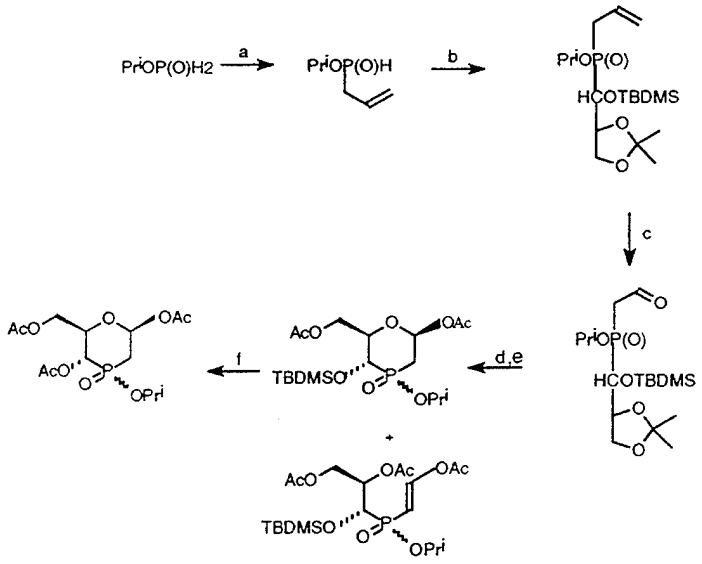
but this molecule turns out to be essentially inert under any of the oxidative conditions we examined. Attempts to prepare mono-unsaturated precursors eg



were also unsuccessful and we decided to examine the stereochemical consequences of the addition reaction:



in the hope of being able to control the stereochemical outcome by varying the substituents on the two components. After much trial and error, a successful pathway has been found and is outlined in the Scheme.



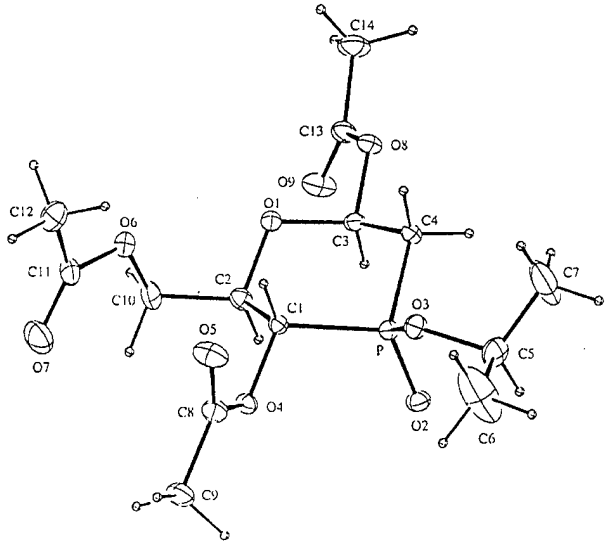
SCHEME a.$Et_3N,CH_2{=}CHCH_2Br$ b.Et_3N,(R)glyceraldehyde acetonide, t-$BuMe_2SiCl$ c.O_3,Me_2S d. CF_3CO_2H,H_2O,THF e. Ac_2O,Py,DMAP f. KF,18-crown-6,Ac_2O

Though chromatographic separations are necessary the route has a reasonable overall yield (20-30% based on R-glyceraldehyde) and optical purity is good, so it provides a practical route to 0.5-1.0g quantities of pure P-epimers as their acetates.

An interesting feature of the reaction sequence is the high stereoselectivity in the addition of the phosphinate to the aldehyde. Since we could only detect two P-epimers by

TLC and ^{31}P nmr we assume an *ee* of ≥95%. No steric preference occurs at phosphorus. Though the intermediate in the addition appears less crowded in the enantiomer leading to the S-isomer, such a high stereoselectivity seems surprising. Selectivity at C in the acetates is reasonably attributable to base-catalysed epimerisation to give the more stable equatorial acetate.

Overall stereochemistry in the sequence is confirmed by an X-ray structure of the only crystalline product obtained.



We hope to extend this study to other pentoses and hexoses and to a clearer understanding of the origins of selectivity in the addition step. We have examined many other additions with very little evidence of substantial selectivity.[6]

ACKNOWLEDGEMENT

We thank the Australian Research Council for financial support.

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NOVEL ORGANOPHOSPHORUS REAGENTS FOR THE SYNTHESIS OF AMINES

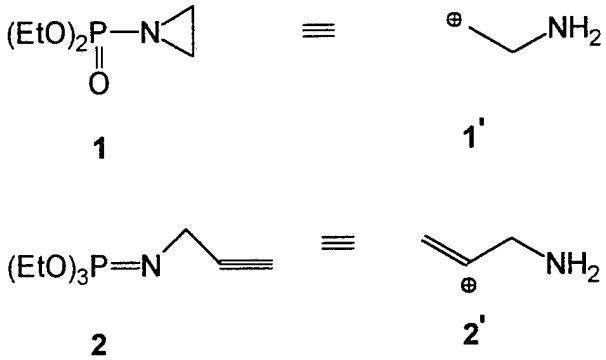
ANDRZEJ ZWIERZAK and KRYSTYNA OSOWSKA-PACEWICKA
Institute of Organic Chemistry, Technical University (Politechnika),
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Abstract: New organophosphorus equivalents of a^2 type N-protected amine synthons are presented.

Key Words: Aminoethylation of Grignard reagents, deprotection of P-N bond, homocuprates, allylamines.

INTRODUCTION

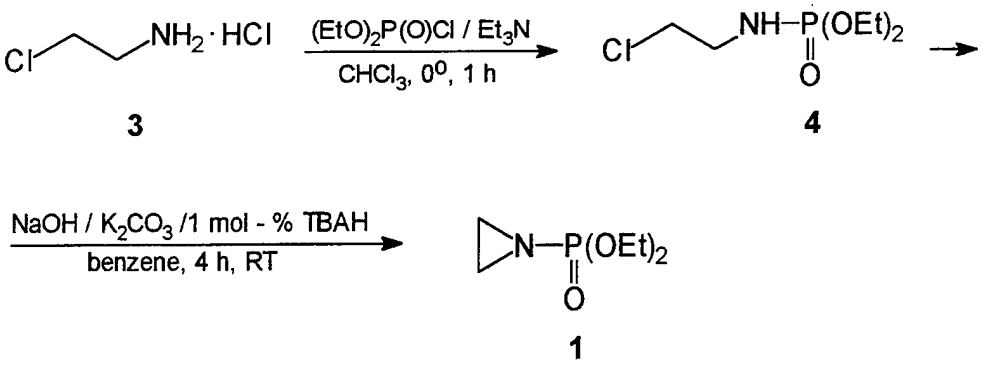
Considerable effort is still being expended toward the development of new effective procedures for the synthesis of amines. In the course of our studies on the use of diethoxyphosphoroyl group for protection of an amino function we have discovered two convenient equivalents **1** and **2** of acceptor type amine synthons **1'** and **2'** :



AMINOETHYLATION OF GRIGNARD REAGENTS:

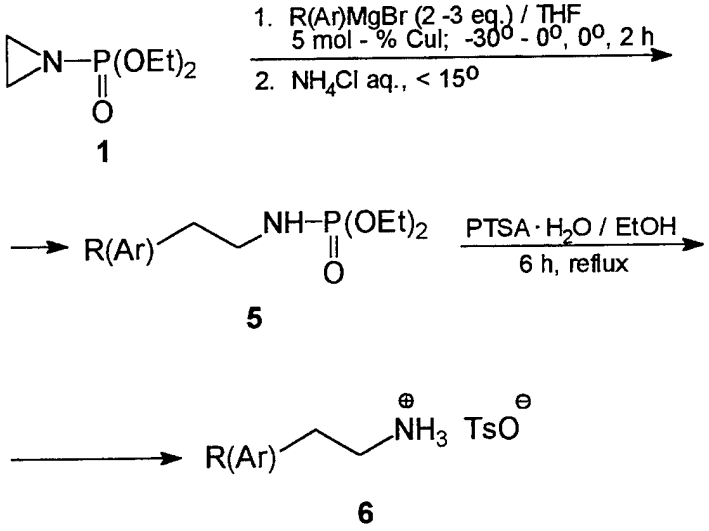
It was found that N-(diethoxyphosphoroyl)-ethyleneimine **1** can be conveniently applied for aminoethylation of Grignard reagents. Compound **1** was first prepared by

phosphorylation of strongly toxic ethyleneimine with diethyl phosphorochloridate [1]. We were able to overcome the use of ethyleneimine and to synthesize **1** according to the following sequence starting from commercially available 2-chloroethylamine hydrochloride **3**:



3 **4** **1**

Diethyl N-(2-chloroethyl)phosphoroamidate **4** was cyclized in crude state according to the previously described procedure [2] but in the presence of only 1 mol-% of tetrabutylammonium hydrogen sulfate as catalyst to give **1** (purified by distillation in vacuo) in 65% overall yield. Nucleophilic ring opening of **1** by means of 2-3 equivalents of organomagnesium bromides occurs smoothly and cleanly in the presence of 5 mol-% of CuI at 0° to give N-alkylphosphoramidate **5**. This compound can be easily deprotected [3] by refluxing with p-toluenesulfonic acid monohydrate in ethanol to afford the corresponding amine tosylate **6** (Table I):



1 **5** **6**

TABLE I Amine tosylates **6**

R (Ar)MgBr[a]	Yield (%)[b]	M.p.
Et (2)	90	118-120°
Bu (1.75)	70	125-127°
t-Bu-CH_2- (3)	52[d]	-
Me_2CH-CH_2-CH_2 (2)	69	107-109°
Ph-CH_2-CH_2 (1.75)	56	141-142°
CH_2=CH- (2)	70	103-104°
i-Pr (3)	75	99-101°
3-pentyl (3)	78[d]	-
cyclopentyl (2)	72	127-129°
Ph (2.5)	83	176-178°
1-naphthyl (3)[c]	81	185-187°
p-$CH_3$0-C_6H_4- (3)	83	148-150°
t-Bu (5)[e]	77	257-260°
CH_2=CH-CH_2-CH_2 (3)	73	111-113°

[a] Necessary equivalents of Grignard reagent securing full conversion of **1** are given in parentheses.

[b] Overall yield of pure amine tosylate **6**.

[c] 15 mol-% of CuI was necessary to complete opening of **1**.

[d] Isolated as free amine.

[e] 10 mol-% of CuI was used.

SYNTHESIS OF 2-ALKYLALLYLAMINES

N-Propargyltriethoxyiminophosphorane **2**, easily obtained by azidation of propargyl bromide followed by Staudinger reaction with triethyl phosphite [4], was found to be a useful reagent for the preparation of 2-alkylallylamines. Homocuprates prepared by the action of 2 moles of alkylmagnesium bromides on 1 mole of CuBr at -60° readily undergo nucleophilic addition to the triple bond of **2**. Protic work-up of the adducts (NH_4Cl aq.) followed by dephosphorylation of **7** (PTSA.$H_2$0 in refluxing ethanol [3])

affords 2-alkylallylamines **8** in moderate yields (Table II):

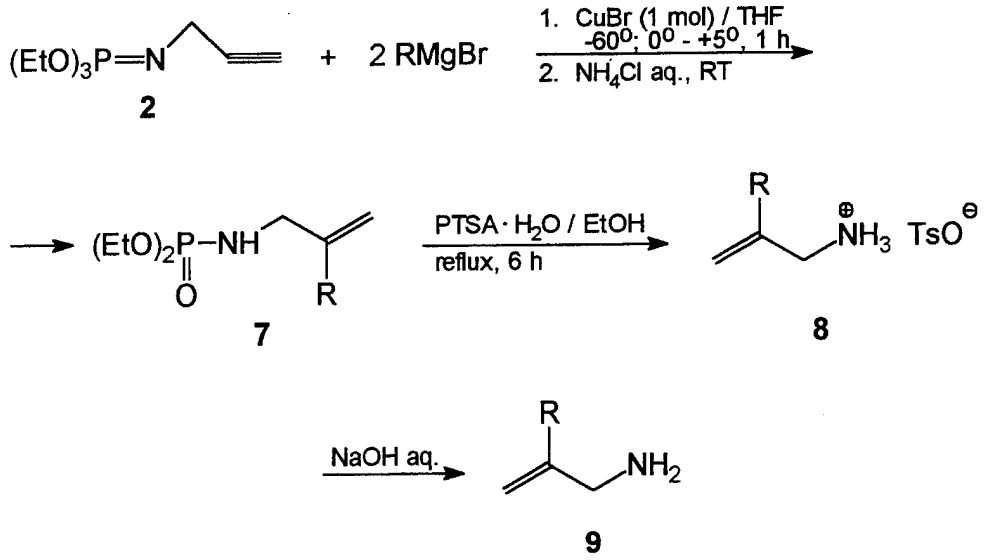


TABLE II 2-Alkylallylamines

R	Yield of **7** (%)	Yield of **7**→ **8** or **9** (%)	M.p. of **8** or b.p. of **9**
Et	46	90 (8)	101-102°
Bu	48	50[a]	166-168°
i-Bu	50	88 (9)	126-128°
i-Pr	50	70 (9)	115-116°
s-Bu	51	73 (9)	123-125°
c-C_6H_{11}	50	90 (8)	92-94°

[a] Yield and m.p. of amine hydrochloride.

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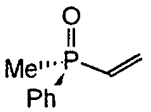
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STEREOSELECTIVE SYNTHESIS AND RESOLUTION OF P-CHIRAL PHOSPHINE CHALCOGENIDES.

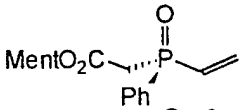
K. MICHAŁ PIETRUSIEWICZ
Department of Organic Chemistry, Maria Curie-Skłodowska University, ul. Gliniana 33, 20-031 Lublin, and Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Sienkiewicza 112, 90-363 Łódź, Poland

Abstract New synthetic methods and resolution procedures securing ready access to the resolved P-chiral phosphinoylethenes, phosphinoylacetates and secondary phosphine oxides of diversified structures have been developed. The methods are based on processes employing stereoselective nucleophilic displacement at phosphorus, asymmetric deprotonation, immolative vinyl and chirality transfer from sulfur to phosphorus, chemical and enzymatic kinetic resolution, resolution via covalent diastereoisomers, as well as direct resolution of racemates by classical resolving agents and by chromatography on chiral stationary phases.

Rapidly growing utility of resolved P-chiral phosphorus compounds stimulates interest in the development of convenient methods for their preparation.[1] In recent years enantiopure methylphenylvinylphosphine oxide (**1**), readily available from the spontaneously resolving menthyl phenylvinylphosphinoylacetate (**2**),[2] was shown to serve as an organophosphorus chiron whose resolved stereogenic P-center could be incorporated into a large diversity of chemical structures by virtue of the versatile chemistry of its pendant double bond functionality.[1,3]



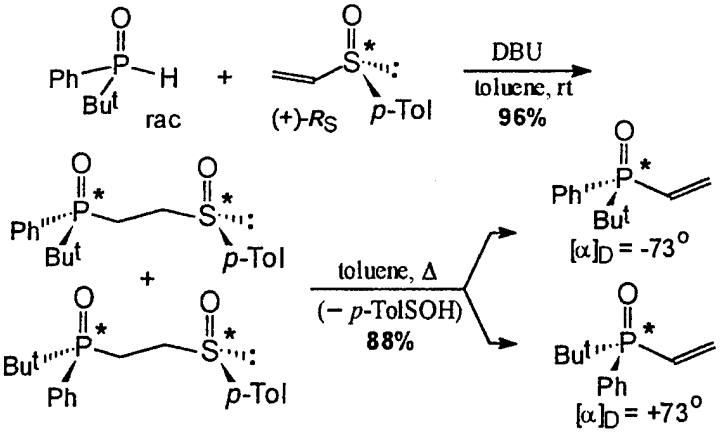
S_P-1



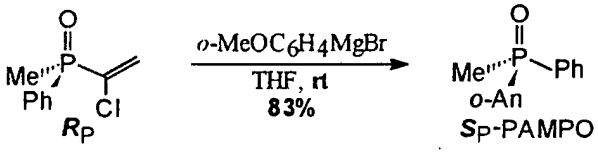
S_P-2

In an effort to further expand the synthetic potential of this approach we have focused our attention on the development of procedures allowing relatively easy access to enantiopure vinyl phosphine oxides of different structures including also the corresponding cyclic systems. One of such procedures has originated from the idea of employing sulfur instead of the conventional carbon as the chirality source. The developed procedure involves immolative vinyl and chirality transfer from enantiopure *p*-tolylvinylsulfoxide to nonsymmetrical secondary phosphine oxides and is illustrated

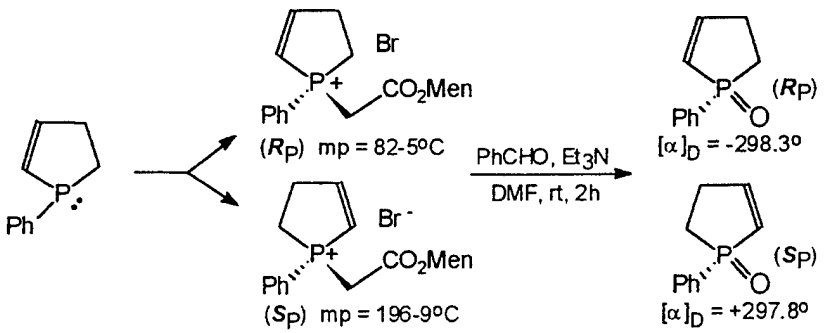
below with the preparation of the two enantiomers of *t*-butylphenylvinylphosphine oxide.[4]



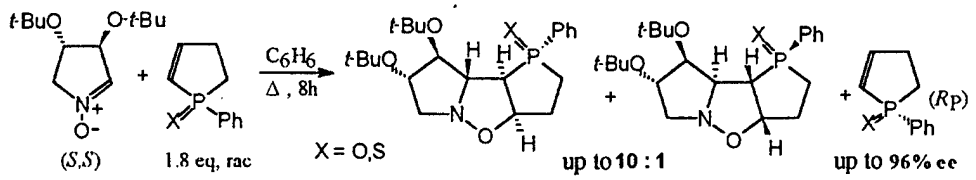
Pursuing further the fruitful combinations and parallelism of sulfur and phosphorus chemistry we have capitalized on the recent observation by Naso et al., that the α-chlorovinyl group at sulfur can be readily substituted by Grignard reagents with clean inversion of configuration at S.[5] In expected analogy, treatment of enantiopure α-chlorovinylmethylphenylphosphine oxide[6] with aryl and vinyl Grignard reagents led to substitution of the α-chlorovinyl group by an aryl or substituted vinyl group with 100% inversion of configuration at P.[7] The substitution process is very facile and accomodates easily ortho substituents in the entering aryl groups as demonstrated by the synthesis of the renowned (*S*P)-*o*-anisylmethylphenylphosphine oxide (PAMPO) in 83% yield.[7]



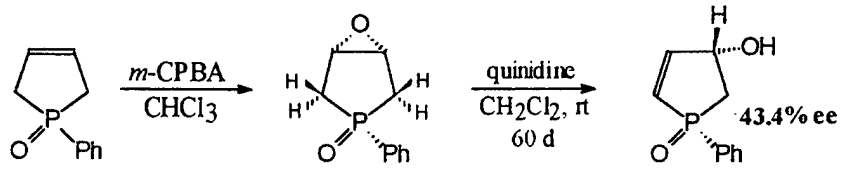
Larger quantities of PAMPO can be conveniently obtained by the menthyl phosphinoylacetate route developed earlier for the large scale preparation of **1**. The two P-epimeric menthyl *o*-anisylphenylphosphinoylacetates are expeditiously separable as in this particular case only one of them is crystalline at ambient temperature.[8] Analogously facile separations of P-epimeric (menthoxycarbonylmethyl)phosphonium bromides led



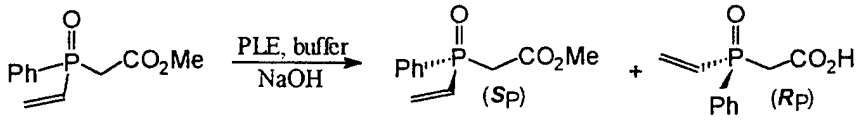
in turn to the development of an efficient synthetic route to enantiomers of 1-phenyl-2-phospholene 1-oxide, a cyclic congener of **1**.[9] 1-Phenyl phospholene derivatives of high enantiomeric purity are also accessible by kinetic resolutions of the corresponding racemates subjected to the highly enantioselective (k_S/k_R ratio up to 14) cycloadditions with enantiopure nitrones derived from tartaric acid.[10]



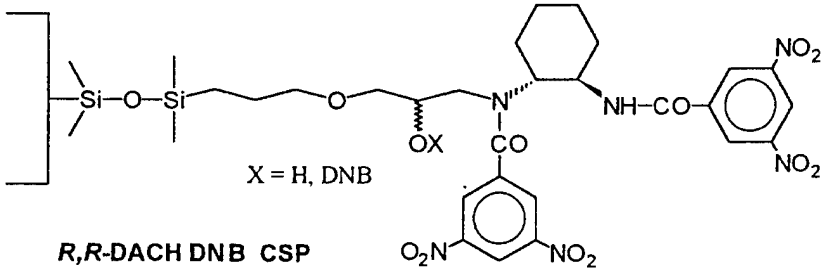
In a single case an asymmetric creation of the phosphorus stereogenic center within the phospholene framework by the action of a chiral base on an achiral phospholene epoxide has also been shown feasible.[9]



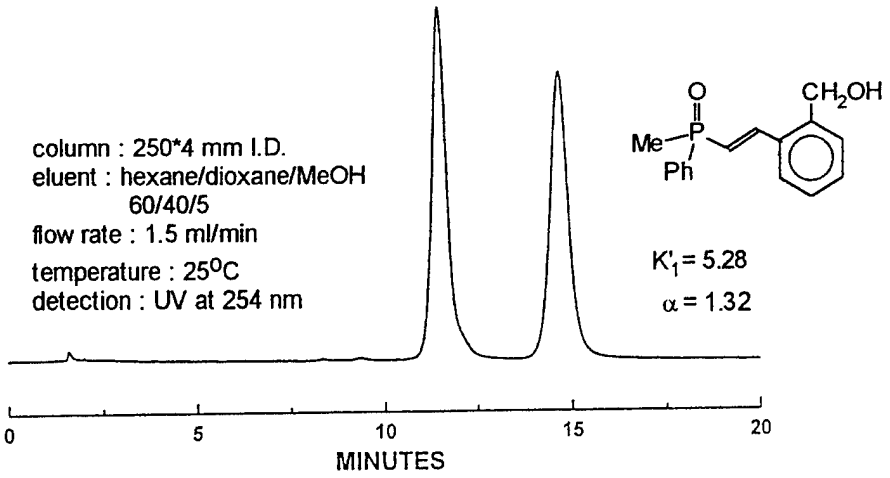
Finally, recent successful studies[11] on enzymatic resolutions of racemic P-chiral methyl phosphinoylacetates included among others also a P-vinyl model and provided access to still another acyclic unsaturated P-chiral system of virtually 100% enantiomeric purity.



Effective recognition of phosphorus chirality by various chemical and enzymatic systems mentioned above finds its close parallel in similarly efficient enantiomeric recognition in chromatography. A totally synthetic chiral stationary phase based on *trans*-1,2-diaminocyclohexane as selector (DACH-DNB CSP) developed by Gasparrini et al.[12] emerged recently as the CSP of choice for analytical and preparative resolutions



of P-chiral compounds. A wide range of P-chiral phosphinoylethenes including both unsubstituted and terminally substituted ones of either E or Z configuration, cyclic and acyclic, have been readily resolved by means of HPLC utilizing the DACH-DNB CSP.[13]



The DACH-DNB CSP is however best suited for the resolution of P-chiral secondary phosphine oxides which can now be promptly and completely resolved into enantiomers in a single preparative run on this phase.

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ACYLATION OF PHOSPHORUS SUBSTITUTED CH-ACIDS UNDER PHASE TRANSFER CATALYSIS CONDITIONS

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Abstract Acylation of phosphoryl- and thiophosphoryl acetonitriles under phase transfer catalysis (PTC) conditions leads in high yields to C-acylated products existing as Z-isomers of the corresponding enol forms. They are stabilized by strong intramolecular H-bonds. On the contrary, acylation of phosphorylacetone proceeds mainly at the oxygene atom and gives Z and E enolacetate. Phosphorus trichloride was used as an acylating agent under PTC conditions. S-Alkyldichlorophosphites were obtained by the reaction with mercaptanes. Alcohols react with PCl_3 in the presence of sodium carbonate to result in dialkylphosphites.

INTRODUCTION

PTC is known to be widely used in such reactions as the Wittig, Horner, Todd-Atherton, Michaelis-Becker, Pudovik reactions and others. However , acylation reactions of carbanions generated from phosphoryl substituted CH-acids, in particular, phosphoryl-acetonitriles, phosphorylacetones and some others appeared to be outside investigation .

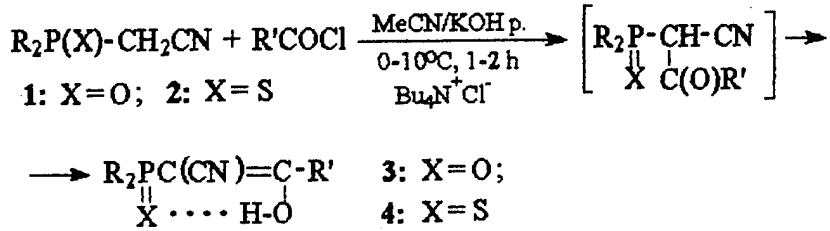
ACYLATION OF PHOSPHORYLACETONITRILES

Acylation of potassium salts of dialkoxyphosphorylacetonitriles is known. Kirilov and Petrov[1,2] carried it out under classic conditions carefully avoiding moisture traces. They have got acylation products in low yields, no more than 15-30% . The authors established that the C-acylated derivatives existing in equlibrium with their Z-enol forms were obtained.

The application of PTC called for the investigation of substrate CH-acidity . We have measured CH-acidity of phosphoryl- **1** and thiophosphorylacetonitriles **2** by the indicator transmetallation method in DMSO[3]. They proved to be CH-acids of a medium power with pKs equal to 15-20. Thus they are assigned to the CH-acids easily reacting under PTC

conditions. Thiophosphoryl compounds were on the average 0.9 pK unit stronger than phosphoryl analogues.

The action of acylchlorides on **1** under PTC conditions resulted in C-acylation with the complete transformation of acyl derivatives to Z-enols **3** [4]. Acyl derivatives were obtained in high yields, which were in direct relation with the CH-acidity of the initial phosphoryl compounds. So at pK about 17, the yields approached the quantitative ones, at pK about 19, they were 72-75%, and at pK near 20, they were about 30%. Steric hindrances to the intermediate generation also influenced the reaction.



$R_2P(X)\text{-}CH_2CN + R'COCl \xrightarrow[0\text{-}10^{\circ}C,\ 1\text{-}2\ h]{MeCN/KOH\ p.,\ Bu_4N^+Cl^-} \left[R_2P(X)\text{-}CH(C(O)R')\text{-}CN \right] \rightarrow$

1: X=O; **2**: X=S

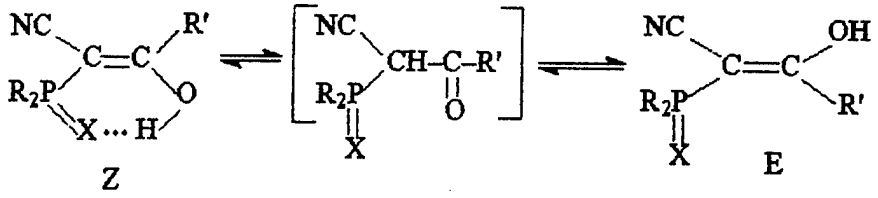
$\rightarrow R_2PC(CN)=C(R')\text{-}O\cdots H$ **3**: X=O; **4**: X=S

As for thioanalogues **2**, the yields of the acylation products were about 20% lower. In the presence of typical interphase catalyst, Bu_4NCl the yields increased by about 10-15%. It is no need in catalysts in the case of **1**. Probably the initial compounds **1** or the product of their acylation may play the role of the interphase catalysts.

Our acyl derivatives belong to triacylmethanes, the class of the extremely easy-to-enolize substances. As a rule they are completely enolized to give cis-enols stabilized by strong intramolecular hydrogen bonds. However, for dibenzoylmethane and tribenzoylmethane the existence of the triketo form in solutions or in the crystal state is typical.

That is why we thoroughly investigated the enolization of our compounds using NMR, IR and mass-spectra, bromometric titration and X-ray analysis. All the acylderivatives obtained were found to represent the pure enol forms. In none of the cases the presence of the keto forms were obsereved. In liquid or in the crystal state, enols have the Z configuration which is stabilized by strong intramolecular hydrogen bonds. In solutions of non-hydroxylic solvents, only one Z form is present. In hydroxylcontaining media it exists in equilibrium with the E-form. But the Z form with its own intramolecular hydrogen bond is still retained. The content of the Z and E forms in the equlibrium state depends on the nature of the substituents at the carbone atom.

We were interested in the problem of transformation of stereoisomers. Does it proceed through a keto form or via the mesomeric anion?



Z E

We studied the acidities of the substances obtained by the potentiometric method in 75% alkohol. They proved to be very strong acids with pK_s of 4.40-4.83. Thus in solutions of enol forms, mesomeric anions are always present at an appreciable concentration. That is why the Z=E transformation is rather likely to go without the keto form involvement.

We have also investigated the sterioisomer ratio of $[(EtO)_2P(O)C(CN)=C(R')O]^-M^+$, (M = K and Bu_4N) salts in MeCN and CD_3OD solutions by the NMR technique. The results obtained confirmed of Z=E transformation proceeding through the mesomeric anion.

Acyl derivatives of thiophosphorylacetonitriles proved also to be completely enolized. They form Z enols **4** with the intramolecular hydrogen bond P=S...H-O. It is known that the thiophosphoryl group is less capable of hydrogen bonding although H-bonds still occur and can be rather strong. In our case, all the data, namely PMR, IR and especially X-ray analysis, confirm the formation of the intramolecular H-bond with the P=S group. At the same time, its less strength endows some peculiarities to the enolized thioderivatives. Particularly it tells upon the ability of these derivatives to benzoylation of enol hydroxyle under PTC conditions.

$$\mathbf{2} + PhCOCl \longrightarrow \mathbf{4} + R_2P(S)C(CN)=C(Ph)OCOPh \quad (Z)$$

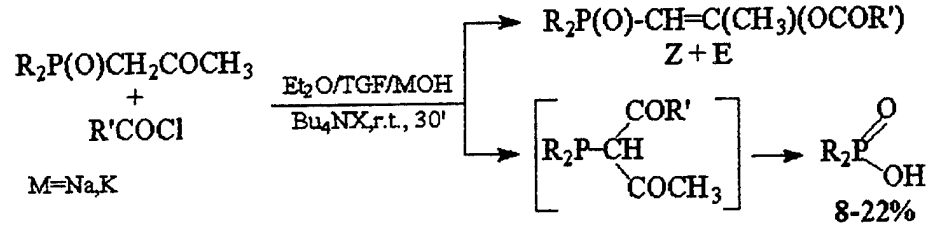
For phosphoryl derivatives we in no case observed benzoylation of the enol hydroxyl even if there was a great excess of benzoyl chloride.

ACYLATION OF PHOSPHORYLACETONES.

It is known from V.G.Sakhibullina's, N.A.Polezhaeva's and B.A.Arbuzov's works[5,6] that under classic conditions, the alkaline enolates of phosphorylacetone were acylated at the oxygen atom resulting in Z-acylenols. On acylation of the phosphorylacetone in the presence of triethylamine, a mixture of the Z and E isomers in the ratio of 2:1 was formed.

We have found that phosphorylacetone is readily acylated under PTC conditions in the system "diethyl ether or TGF/solid alkali" in the presence of tetrabutylammonium salts.

In this case too, the reaction occures mainly at the oxygen atom leading to the final product as a mixture of the Z and E isomers. The ratio of isomers is in close agreement with that obtained in performing this reaction in the presence of triethylamine.[6]



The corresponding phosphorus acids are formed as side products under PTC conditions in the yields from 8% to 22%. This suggests that C-acylation might take place simultaneously with O-acylation, but triacylmethanes obtained are easily cleaved at the P-C bond.

PHOSPHORUS TRICHLORIDE AS ACYLATING AGENT.

We undertook an effort to use PCl_3 under PTC conditions, in spite of it is hydrolyzed very easy. We hoped that PCl_3 being in the organc phase in the two phase system liquid/dry potassium carbonate may phosphorylate a substrate, which is also located in the organic phase, faster than it undergoes hydrolysis.We have used mercaptanes as substrates in this reaction and obtained thiodichlorophosphites in 75-85% yields . There were no need in catalysts.

$$RSH + PCl_3 \xrightarrow[TBA]{CH_2Cl_2/K_2CO_3} RSPCl_2 \qquad 75\text{-}85\%$$

Then we have carried out the reaction of alcohols with PCl_3 in the two phase system using dry Na_2CO_3 at room temperature and obtained $(RO)_2PHO$ in high yields and in the entirely pure state. This method is quite technological.

CONCLUSION

Our results show that PTC method harbours a lot of new and interesting things for organophosphorus chemistry especially with the use of easily hydrolized reagents.

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PHOSPHORINANE AND ENOL RINGS IN ONE MOLECULE. EVIDENCE FOR RECIPROCAL STABILIZATION OF HALF-CHAIR CONFORMATIONS

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Abstract.

The X-ray crystal structure of 2-(2′,4′-dioxo-3′-pentyl)-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane (**2**) reveals significant half-chair distortion of the axially oriented cis-enol ring. The molecule also undergoes in-plane deformations. R(O...O) = 2.410 Å in the enol moiety indicates a very strong hydrogen bonding. The enol content, δ_{OH} and thermodynamic parameters for the axial-equatorial conformational and keto-enol equilibriums were obtained from ^{1}H, ^{31}P NMR and IR measurements in comparison with the planar 4,6-dimethyl isomer (**1**) containing equatorially oriented enol ring. The X-ray single crystal structure of 5,5-dimethyl-2-(methoxycarbonyl-3′-oxo-2′-butyl)-2-oxo-1,3,2-dioxaphosphorinane (**3**) reveals the unusual half-chair conformation of the dioxaphosphorinane cycle disposed a trans-enol ring substituent. ^{1}H, ^{31}P NMR and IR solution data support the same structure displays a strong conformational preference while the minor forms are chair conformers with an axial or equatorial cis-enol ring.

Key Words: Conformational equilibrium; β-dicarbonyls; hydrogen bonding; keto-enol equilibrium; phosphorinane; tautomer.

Dicarbonyl compounds have been the subject of numerous studies.[1,2] The introduction of bulky alkyl substituent on the central carbon of the β-dicarbonyls depresses the enol content almost to zero, preventing a detailed analysis of enol form. Even in this case the enol ring was considered as planar, since downfield δ_{OH} shifts were observed in the ^{1}H NMR spectra. The conformational properties of β-dicarbonyl compounds received little attention.

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We have recently described, that the phosphorus-containing bulky substituents are most suitable for producing steric pressure on the β-substituents without decreasing enolization,[3] because of their electron-withdrawing properties. The introduction of the dioxaphosphorinane substituents provided a possibility to vary the direction of the steric pressure.

In the 4,6-dimethyl isomer (**1**) the equatorially oriented enol ring is in the plane of symmetry of the dioxaphosphorinane ring and undergoes only in-plane deformations.[3]

According to the crystal structure, **2** is in its enol form[4]. The P=O bond is perpendicular to the enol ring and equatorial to the chair dioxaphosphorinane ring. The most remarkable features of the enol ring are its deviation from planarity and the tilt of the methyls away from external oxygen atoms, the enol ring adopts a flattened *half-chair* conformation. To our knowledge we have found the first example of a nonplanar enol tautomer.

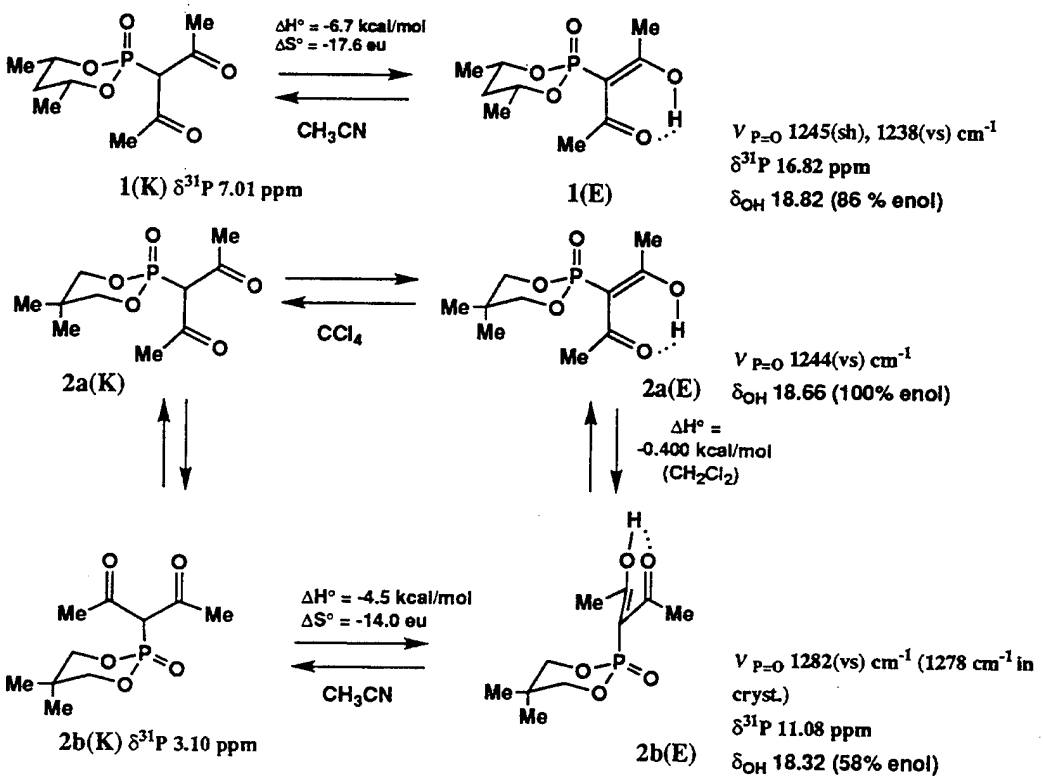
The molecule also undergoes in-plane deformations. The enol inner valence angles are enlarged (2-3°) compared to values for the 3-aryl derivatives of pentane 2,4-dione.[5] R(O...O) = 2.410 Å indicates a very strong hydrogen bonding. Judging from short van der Waals contacts of the enol methyl groups with phosphorinane oxygen atoms, the enol ring deformations and the strengthening of the hydrogen bonding in comparison with pentane-2,4-dione are due to the repulsive intramolecular interactions.

In terms of the two rapidly interconverting chair-ring conformations the less polar equatorial conformer **2a** is predominant in nonpolar solvent (CCl_4), whereas **2b** predominates in CH_3CN, as deduced from IR and ^{31}P NMR data (SCHEME I).[6]

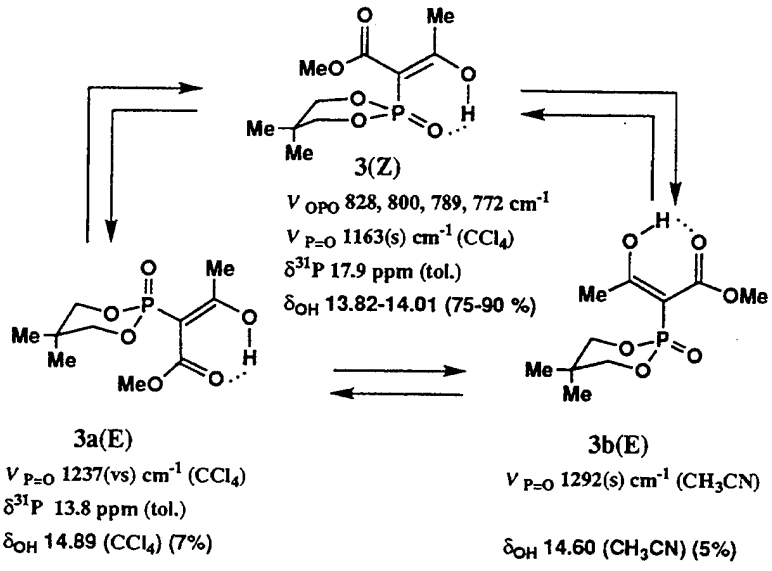
From variable temperature infrared spectra at 476 cm^{-1} **2a** and 488 cm^{-1} **2b** frequencies in CH_2Cl_2 the value of $\Delta H°$ was calculated to be -0.440 ± 0.100 kcal/mol (r=0.99) for the interconversion between **2a(E)** and **2b(E)**. Assuming the rotation isomer in **2b(E)** is the same in solution as in the crystalline phase, one would suppose similar distortions as those found by the X-ray diffraction study. In comparison with 2-methyl-2-oxo-1,3,2-dioxaphosphorinane[7] a smaller enthalpic stabilisation of the P=O equatorial conformer was observed and the difference (0.9 kcal/mol) could mainly be attributed to the energetically unfavourable nonplanar effects in the axially oriented enol ring.

^1H NMR experiments register the upfield shift of the δ_{OH} (0.50 ppm) from **1(E)** to **2b(E)** in CH_3CN (0.16 ppm in CCl_4) in which the dramatic difference in the conformational composition of these compounds have been found by IR. This indicates a relative weakening of the hydrogen bonding in **2b(E)**, compared with **2a(E)**.

The enol content of **2** is less than that in of **1**, which would be consistent with relative destability of the enol form in **2b** caused by the nonplanar effect. A smaller



SCHEME I



SCHEME II

enthalpy of enolization of the nonplanar enol **2b** in comparison with the planar **1** is observed (by 2.2 kcal/mol). As the intramolecular hydrogen bond of β-dicarbonyl compounds is the main reason for the stabilisation of the enol tautomers[1,2], a relative weakening of the hydrogen bonding because of deformation of the enol conjugated system is obvious and leads to this energy difference.

It was also of interest to reveal reverse influence of the enol conformation on the conformation of a substituent. It was known, that half-chair conformation is relatively rare for the phosphorinane ring, being obviously of very high energy.[8] We have synthesized β-keto-ester **3** and found that it is a mixture of trans and cis-enol forms.[9] The X-ray single crystal analysis shows that **3** exists in the trans-enol tautomeric form **3(Z)** (R(O...O) = 2.506 Å) and the conformation of the dioxaphosphorinane ring was *half-chair*. This is a first example of half-chair conformation of a phosphorinane cycle featuring hydrogen bond. NMR and IR solution data support the same structure displays a strong conformational preference while the minor forms are chair conformers with an axial and equatorial cis-enol ring (SCHEME II).

The deformation of the enol ring and the flattening of the phosphorinane ring are a result of severe steric hindrances in these molecules and can be conformationally dependent.

ACKNOWLEDGEMENTS

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THE SYNTHETIC POTENTIAL OF *C*-HALOPHOSPHAALKENES

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Abstract. Methodologies for the functionalization of phosphaalkenes Mes*P=$CHal_2$ were developed. Lithiation with *n*-butyllithium yielded carbenoids Mes*P=CLiHal which were reacted with various electrophiles such as acid chlorides, carbonyl compounds, and metal halides. The dihalophosphaalkenes were also converted to monohalophosphaalkenes; the latter proved to be suitable for Stille-type cross coupling reaction with Grignard reagents. New phosphaalkenes of the type *(E)*-Mes*P=C(H)Ar with a variety of functionalities were obtained in high yield and isomeric purity.

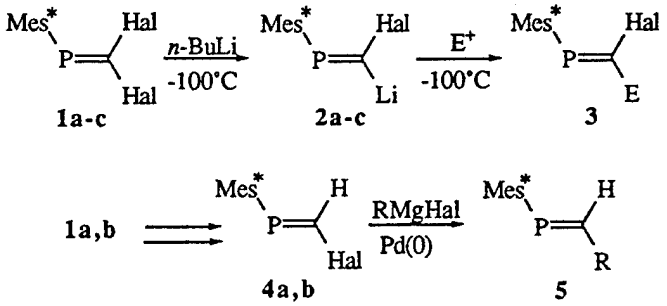
INTRODUCTION

Since 1981 halogen substituted phosphaalkenes have been reported.[1] Phosphaalkenes of the type Mes*P=$CHal_2$ (Mes* = 2,4,6-tri-*tert*-butylphenyl; **1a**: Hal = Cl; **1b**: Br; **1c**: I) can easily be converted to phosphavinylidene carbenoids of the type Mes*P=CLiHal by halogen-lithium exchange with *n*-butyllithium. Although these species should have a large synthetic potential, only few applications are known.[2,3] Challenged by the potentially rich chemistry of these carbenoids, we investigated their reactions with various electrophiles such as acid chlorides,[4] carbonyl compounds, and metal halides.

Recently, several groups have been reporting on the coordination of phosphaalkenes, incorporated in bidentate ligand systems. In order to develop a convenient method for the preparation of a variety of bidentate ligand systems, we investigated the reactivity of monohalophosphaalkenes with Grignard reagents in Stille-type cross coupling reactions. By this method (substituted) aryl groups were introduced.

SYNTHESIS

Halophosphaalkenes **1a-c** can easily be converted into *(Z)*-phospavinylidene carbenoids **2a-c** by low temperature halogen-lithium exchange (-100 to -130°C). Addition of an electrophile to a solution of the carbenoid results in the formation of *trans*-functionalized phosphaalkenes **3** with retention of configuration.[3] More interesting, e.g. for the synthesis of phosphaalkene based bidentate ligand systems, are *trans*-functionalized phosphaalkenes with aromatic substituents. However, these cannot be introduced via a Stille-type coupling reaction with the dihalophosphaalkenes **1a-c** or the carbenoids **2a-c**.[5] Therefore convenient new procedures for the synthesis of *(E)*-halophosphaalkenes **4a,b** were developed.[6] **4a,b** were subjected to a Pd(0) catalyzed cross coupling reaction with Grignard reagents furnishing **5** as shown in SCHEME 1.



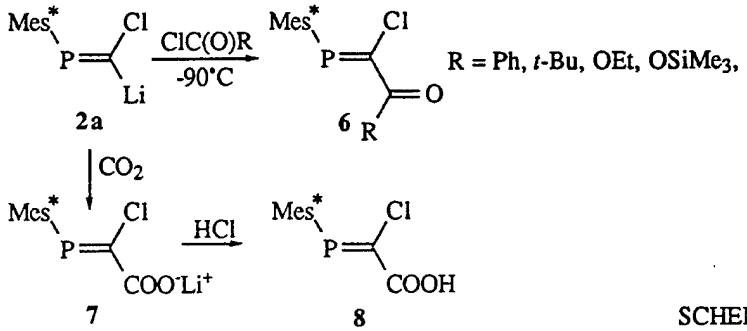
Hal = **a**: Cl, **b**: Br, **c**: I

SCHEME 1

REACTIONS

β-Phosphaenones

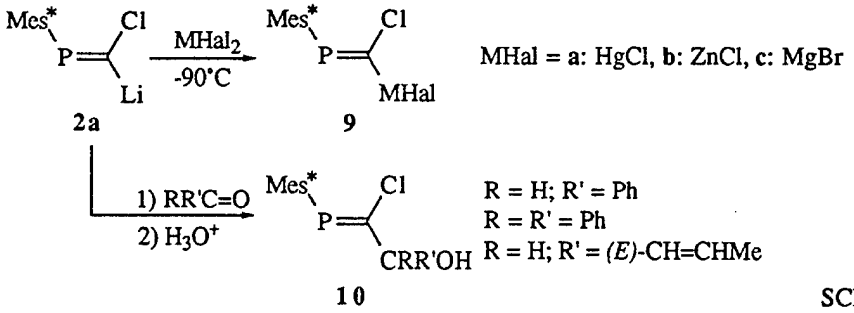
The chlorophosphavinylidene carbenoid **2a** was reacted at -100°C with acid chlorides furnishing β-phosphaenones **6** in high yield (SCHEME 2). Another method for the formation of β-phosphaenones is the reaction with CO_2 furnishing the unexpectedly stable carboxylate **7**. Acidification of **7** with hydrochloric acid furnished the first β-phosphaacrylic acid **8**. Because of the high stability of the products, the enones could be isolated, purified, and fully characterized by NMR, UV and IR spectroscopy.[4]



SCHEME 2

Transmetallation reactions

In general, the stability of carbenoids mainly depends on the halogen (Cl>Br>I) and the metal (Hg>Mg>Zn>Li).[7] Phosphavinylidene carbenoids decompose at temperatures below -50 °C. In order to determine their stability and reactivity with different metals, we transmetallated **2a** with $HgCl_2$, $MgBr_2$, and $ZnCl_2$. The mercury carbenoid **9a** was isolated as air stable crystals. The formation of the zinc (**9b**) and magnesium (**9c**) carbenoids could be proved indirectly by addition of D_2O at 15 °C and at RT, respectively. The deuterated product was isolated in high yield and isomeric purity in both cases, which demonstrates the thermal and configurational stability of these carbenoids. **9a** and **9b** were unreactive towards benzaldehyde. However, **2a** reacted with carbonyl compounds furnishing 3-phosphaallyllic alcohols **10** (SCHEME 3).

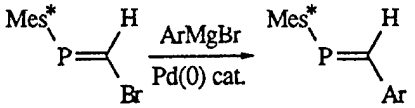


SCHEME 3

In spite of the increased stability of the **9c** (decomposition at 15°C), it did react with acetophenone to give 75% of the corresponding phosphaallyllic alcohol; in contrast, **2a** reacted exclusively by deprotonation.

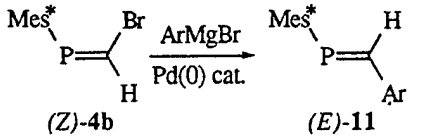
Coupling with Grignard reagents

The functionalization of phosphaalkenes via the carbenoid route is limited to nucleophillic reactions with reactive electrophiles. Recent developments in phosphaalkene chemistry show that there is interest in phosphaalkene based bidentate ligand systems.[8] For this reason, methodologies for the synthesis of *trans*-(aromatically)substituted phosphaalkenes were investigated. With dihalophosphaalkenes, Pd(0) catalyzed coupling with organometallic compounds could not be achieved.[5] Therefore, we developed new, convenient synthetic procedures for the preparation of *(E)*-halophosphaalkenes wherein the halogen is chlorine or bromine (**4a,b**; SCHEME 1).[6] *(E)*-Chlorophosphaalkene **4a** was reacted with Grignard reagents in the presence of a catalytic amount of $Pd(PPh_3)_4$ at room temperature. Only phenylmagesium chloride proved to be reactive under these conditions; the *trans*-phenylphosphaalkene **11** (Ar = Ph) was isolated in 76% yield. *(E)*-Bromophosphaalkene **4b** turned out to be much more reactive. A large variety of aromatic Grignard reagents could be coupled, furnishing the products **11** in high yield (80-90%), and isomeric purity (100% *(E)*-isomer) (SCHEME 4).

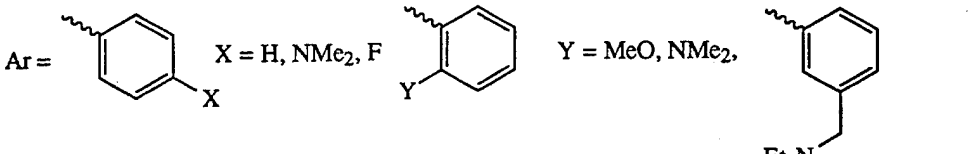


(E)-**4b** *(E)*-**11** SCHEME 4

In an attempt to synthesize the *(Z)*-isomers of **11**, we used *(Z)*-**4b** in analogous experiments. To our surprise, only the corresponding *(E)*-**11** were obtained in all cases (SCHEME 5). Apparently, a rapid rearrangement occurs after the oxidative addition of palladium(0) into the C-Br bond. The products were isolated in 80-90% yield, with 100% isomeric purity. In the case of *para*-substituted aromatics, the reaction takes 5 hours stirring at room temperarute. When the aryl-Grignard reagent contains an *ortho*-substituent, heating to 50 °C during 5 hours is needed, probably because of steric hindrance. Electron-withdrawing or electron-donating substituents on the aromatic ring seemed to have no effect on the rate of the reaction.



(Z)-**4b** *(E)*-**11**



SCHEME 5

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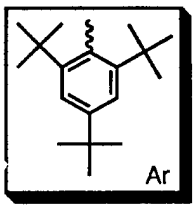
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CHEMISTRY OF STERICALLY PROTECTED BIS(PHOSPHINIDENE)-CYCLOBUTENES

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Abstract: Sterically protected low-coordinated phosphorus-containing cyclobutenes were prepared and characterized as well as [4]radialenes. The reactions were studied involving *E/Z* isomerization, transition-metal complex formation, and coupling reactions catalyzed by some palladium complex ligated with diphosphacyclobutenes.

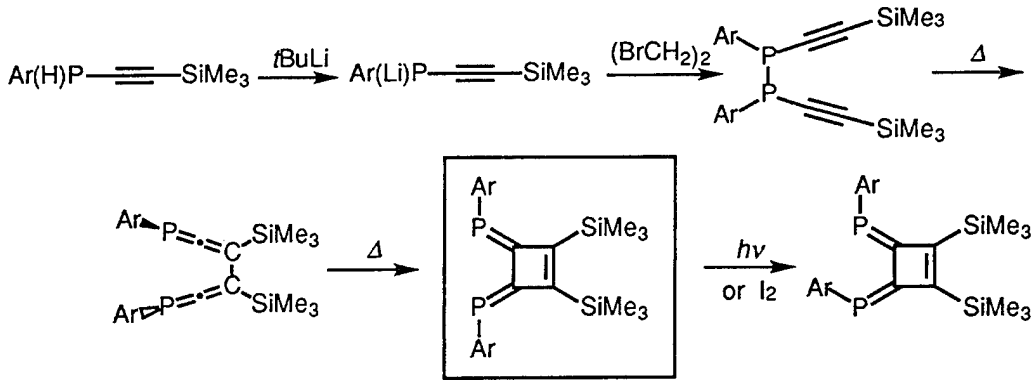
INTRODUCTION



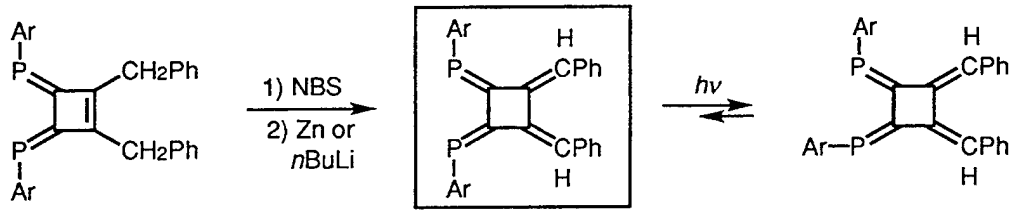
By utilizing a sterically bulky group such as the 2,4,6-tri-*t*-butylphenyl group (abbreviated to Ar), we have been successful in isolation and characterization of organophosphorus compounds in low-coordination states, including diphosphenes (–P=P–),[1a] diphosphaallenes (–P=C=P–),[1b] and phospha-alkynes (–C≡P).[1c,d] Here we report on the sterically protected cyclobutenes and the related low-coordinated phosphorus compounds.

RESULTS

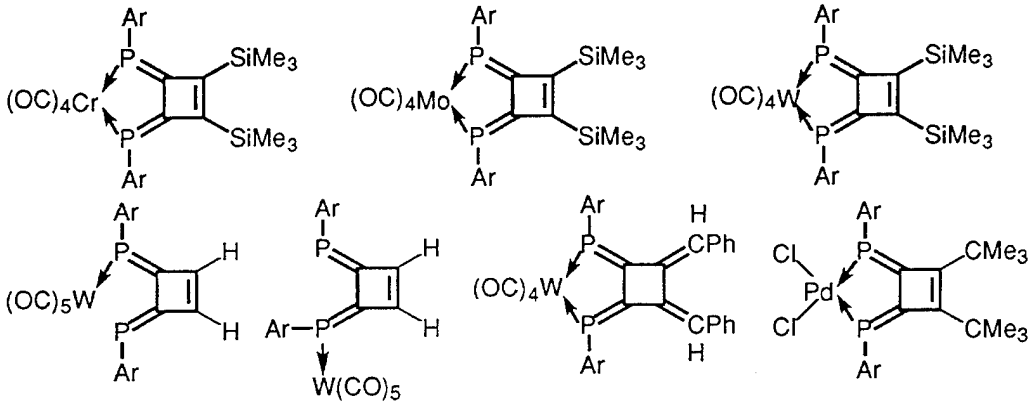
Starting from ArP(H)C≡CR, where R = H, Ph, CH_2Ph, *t*-Bu, Me, Tms, and CH_2Tms, 3,4-diphosphinidenecyclobutenes[2] were obtained by the phosphorus-Cope reactions via dialkynyldiphosphanes and bisphosphaallene compounds. A typical example is shown for R = Tms as follows.[2b] The system of diphosphinidenecyclobutene is of interest because it is a phosphorus analog of methylenecyclobutene involving either the 1,4-diphospha-1,3-butadiene or 1,6-diphospha-1,3,5-hexatriene system. Some of the crystal structures of diphosphinidenecyclobutenes were analyzed by X-ray crystallography indicating the planarity of the π-system.

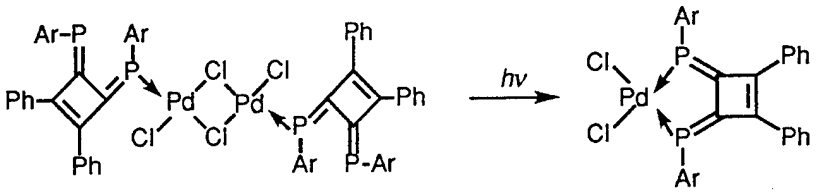


Very similarly, diphospha[4]radialenes were obtained using the benzyl derivative through bromination and debromination as shown below.[3] The *E/Z* isomerization was also accomplished with photoirradiation. The structure of the *E,E*-isomer was analyzed by X-ray crystallography, indicating that the [4]radialene system is almost planar with tilted Ar and Ph groups. UV-vis spectrum of the radialene indicated that the absorption shows a red shift compared to that of the phosphinidenecyclobutene indicating a very extended π-electron system of the radialene.

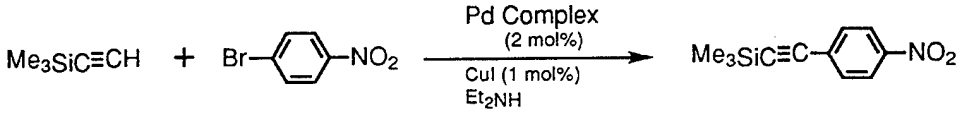


Several transition-metal end-on complexes including Cr(0), Mo(0), W(0), and Pd(II), having such cyclobutene ligands, were prepared as depicted below and some of those were analyzed by X-ray crystallography.[2f]

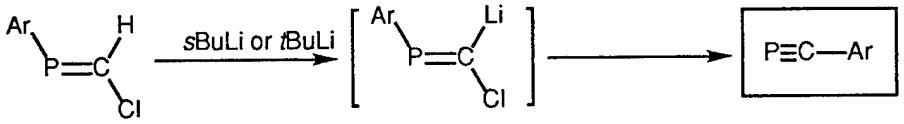




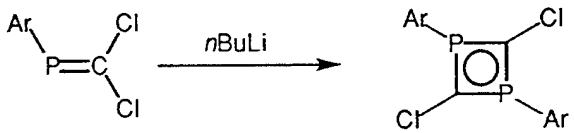
Among those transition-metal complexes, palladium(II) complexes thus obtained worked as efficient catalysts (2 mol%) for some of the coupling reactions of aromatic halides with acetylenes in diethylamine in the presence of copper(I) iodide as shown below.[2e]

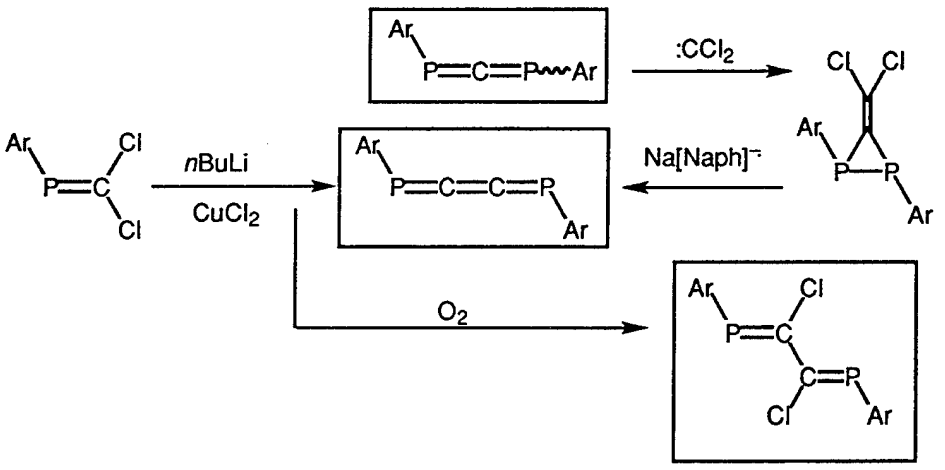


We have found a phosphorus version of the Fritsch-Buttenberg-Wiechel reaction as follows to give phosphaalkynes starting from *E*-2-chloro-1-phosphaethenes.[1d] The reaction might involve a carbene or carbenoid intermediate. On the other hand, the reaction from the corresponding *Z*-derivative did not take place, while the reaction either from *E*- or *Z*-phosphaethene in the presence of copper salts gave a phosphaalkyne.



Furthermore, the corresponding dichlorophosphaethene in the presence of a copper salt gave 1,4-diphosphabuta-1,2,3-triene,[4] which we had prepared from a methylenediphosphirane and a SET reagent.[4b] It should be noted that the reaction gave 1,4-diphospha-1,3-butadiene when oxygen gas was bubbled through a reaction mixture at low temperature.[5] The structure of (*Z*,*Z*)-2,3-dichloro-1,4-diphospha-1,3-butadiene was confirmed by X-ray crystallography. Although the reaction mechanism for giving either butatriene or butadiene depending upon the introduction of oxygen, our results are of interestt in contrast to the recent results reported by Niecke et al.[5b] on the formation and structural determination of diphosphacyclobutanediyl which was obtained under very similar reaction conditions without any copper salts.





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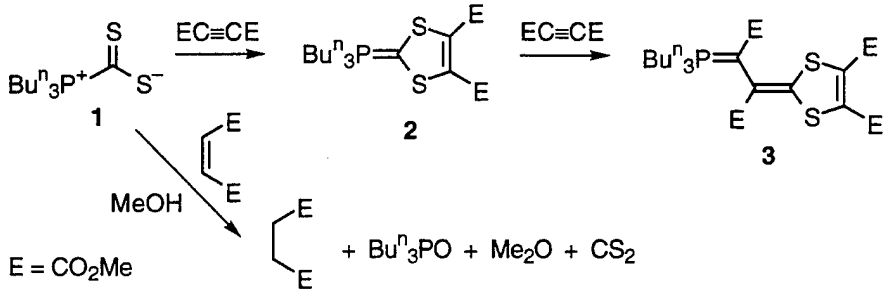
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CONSTRUCTION OF EXTENDED AND POLYMERIC 1,3-DITHIOLANE AND TETRATHIAFULVALENE DERIVATIVES USING CYCLOADDITION OF $Bu^n_3P{\bullet}CS_2$

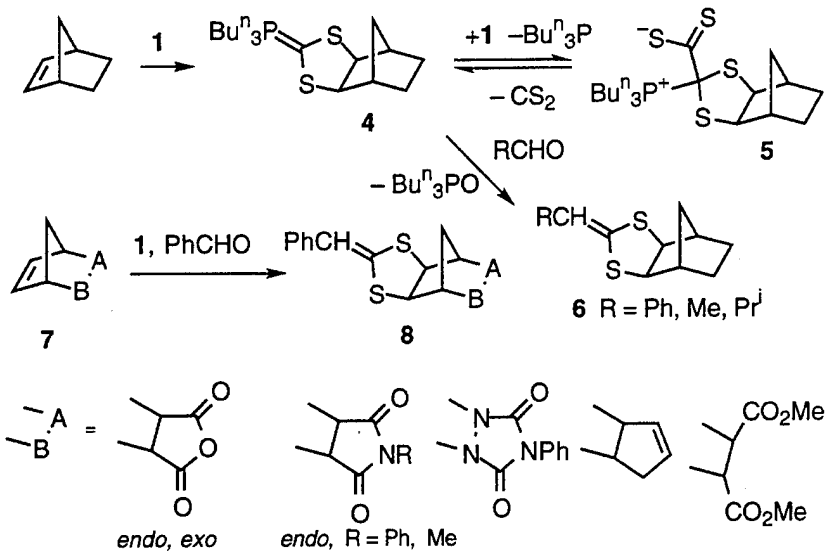
R. ALAN AITKEN*, LAWRENCE HILL and TRACY MASSIL
School of Chemistry, University of St. Andrews, North Haugh, St. Andrews, Fife, KY16 9ST, U. K.

Abstract Cycloaddition of the adduct between Bu^n_3P and CS_2 to strained double bonds such as in norbornene gives novel zwitterionic products such as **5**. This dissociates to the ylide **4** so that carrying out the reaction in the presence of an aldehyde leads to a Wittig reaction to give 2-alkylidene-1,3-dithiolanes. The compound **5** reacts with acetylenic dipolarophiles by cycloaddition accompanied by loss of Bu^n_3P to give dihydro-TTF derivatives. Both these reaction types also occur for norbornadiene and by using this together with dialdehydes or diacetylenes a range of new sulfur-rich extended and polymeric structures have been obtained.

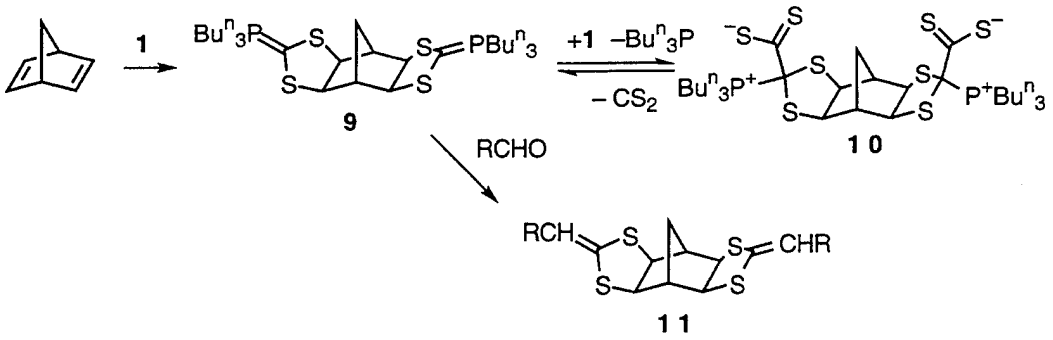
The red crystalline adduct **1** between Bu^n_3P and CS_2 was prepared at an early stage,[1] but it is only recently that its cycloaddition chemistry has been examined. With activated alkynes it adds through the two sulfur atoms to give the ylides **2** but in the absence of any trap these react further to give the 1 : 2 adducts **3**.[2] The only previous report of reaction of **1** with a double bond was the reaction with dimethyl maleate to give dimethyl fumarate as shown but this is unlikely to involve a cycloaddition reaction.[3] Recently we described the reaction of **1** with norbornene to give the stable zwitterionic structure **5** as a



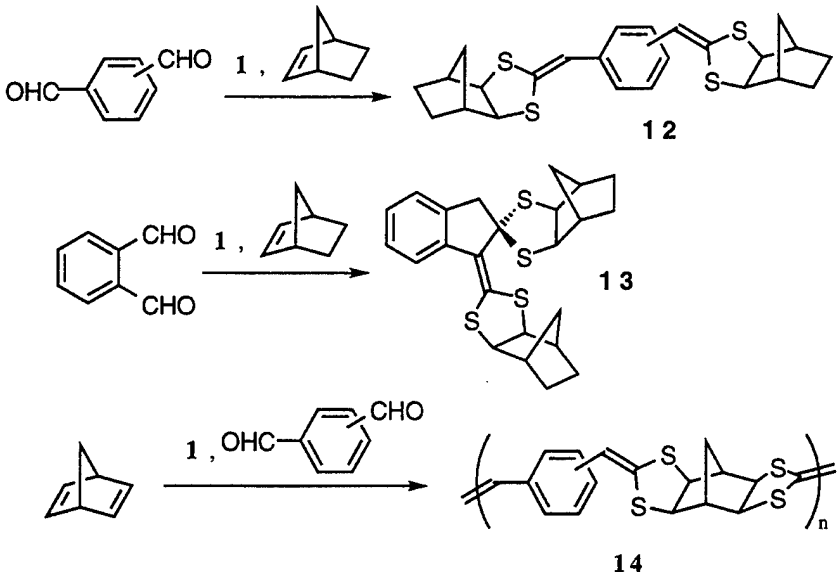
pink solid.[4] In CH_2Cl_2 this dissociates significantly to the ylide **4** which can be trapped by a Wittig reaction with added aldehydes to give the tricyclic alkylidenedithiolanes **6**. The same reaction can be applied to a range of strained double bond compounds **7** readily available from Diels-Alder reactions of cyclopentadiene to give the products **8**.[4]



The reaction of **1** with norbornadiene gives an insoluble pink adduct of uncertain structure but this behaves as though it were **10**. As for norbornene, performing the reaction in the presence of an aldehyde leads to trapping of the ylide form in a Wittig reaction to give a mixture of *E* and *Z* isomers of **11**.

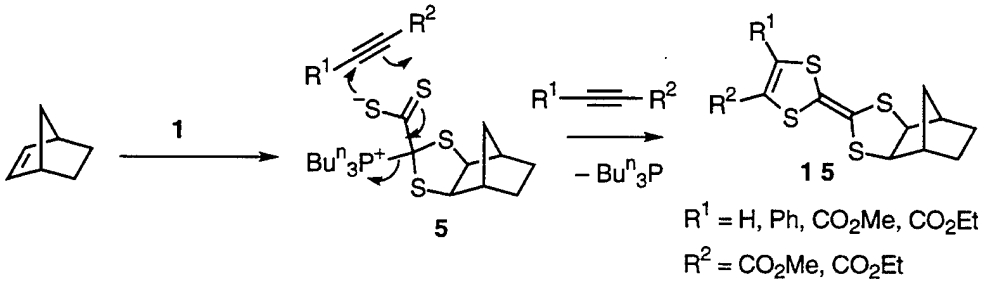


Reaction of the isomeric benzene dialdehydes with **1** and norbornene gives the expected bis-dithiolanes **12** for terephthalaldehyde and isophthalaldehyde but for phthalaldehyde the unexpected rearrangement product **13** is formed and its structure has been confirmed by X-ray methods.

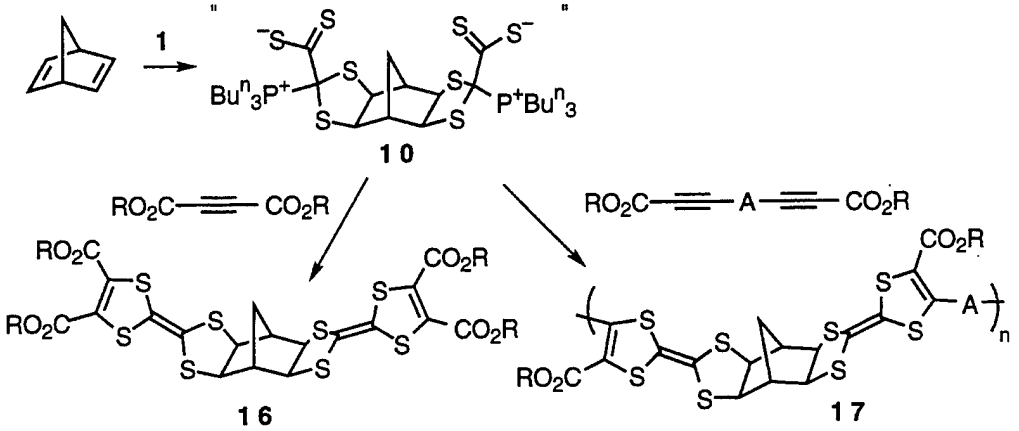


When the *m* and *p* dialdehydes are reacted with **1** and norbornadiene the novel sulfur-rich polymers **14** are produced although due to their insolubility the molecular weight of these could not be determined.

An important recent discovery is that **5** reacts with acetylenic dipolarophiles in a completely different way as shown below, by cycloaddition and loss of the phosphine to form the dihydrotetrathiafulvalene derivatives **15**.[5] These are readily obtained in pure form by chromatography, albeit only in moderate yield and this represents an exceptionally direct route to such compounds. The corresponding reaction of the



norbornadiene adduct **10** leads to the bridged bis-dihydro-TTF compounds **16**. The X-ray structure of the compound **16** (R = Me) has been obtained and shows that all the sulfurs lie essentially in a plane. The electrical properties of these molecules are currently under investigation and they are expected to be of considerable interest in this connection. Once again this process can be adapted to polymer formation and preliminary studies on reaction of **10** with diacetylenes suggest that the polymeric structures **17** should be accessible.



Acknowledgement We thank the Engineering and Physical Sciences Research Council for financial support of this work (GR/J 38895).

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ADVANCES IN TRIFLUOROMETHYLATING PHOSPHORUS COMPOUNDS

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Abstract The System CF_3I/Me_3P is re-investigated and Me_2PCF_3, $Me_4P^+I^-$, $(CF_3)_2PMe_3$, Me_3PI_2, $[Me_3(CF_3)P]^+I^-$ are found as products. Using $CF_3Br/P(NEt_2)_3$ the phosphines $R^1{}_2PCF_3$ and $R^1P(CF_3)_2$ (e.g. R^1 = Me, *i*Pr, NEt_2) can be obtained which are precursors either for phosphoranes (e.g. $1,2\lambda^5\sigma^5$-oxaphosphetanes) or phosphonium salts (e.g. $[R^1{}_2(Me)PCF_3]^+X^-$ or $[R^1(Me)P(CF_3)_2X^-]$. The latter are deprotonated to furnish methylene phosphoranes $R^1{}_2(CH_2{=})PCF_3$ or $R^1(CH_2{=})P(CF_3)_2$, reactive synthons. From $CF_3Br/P(NEt_2)_3/P(OPh)_3$ the phosphine $P(CF_3)_3$ is available, which turned out to be a potent electrophile. Amido phospites $ROP(NEt_2)_2$ and halides R^2X (R^2= CCl_2CF_3, X= Cl; R^2= $CF{=}CFCF_3$, X= F; R^2= C_6F_5, X= Br, I; R^2= $C(CF_3)_3$, X= Br; R^2= SCF_3, X= CF_3) undergo an ARBUZOV reaction.

Keywords: Trifluoromethylated phosphines, P-trifluoromethylated phosphonium salts and ylides, oxaphosphetanes, phosphoranides, ARBUZOV reaction.

INTRODUCTION

Trifluoroiodomethane, CF_3I and PMe_3 react to give[1] $Me_4P^+I^-$ and CF_3PMe_2, which adds $(CF_3)_2CO$ or MeI to furnish an oxaphosphetane or the phosphonium salt $[Me_3PCF_3]^+I^-$, respectively[2]. The latter is easily fluorinated yielding the phosphorane $Me_3(F)PCF_3$. With $P(NR_2)_3$ (R=Me, Et) the compounds $CF_3P(NR_2)_2$, $(R_2N)_4P^+I^-$ or $[CF_3P(NR_2)_3]^+I^-$ and $[(R_2N)_3PI]^+I^-$ are observed depending on temperature and solvent[3,4]. The system $CF_3Br/P(NEt_2)_3/PCl_3$ is found to yield $CF_3P(NEt_2)_2$ and the phosphonium salt, $[CF_3P(NEt_2)_3]^+Br^-$, as a by-product, which was investigated regarding its structure and reactivity[5,6]. The amidophosphites $ROP(NEt_2)_2$ (R=CH_2Ph, CH_2CO_2Et, CHMeCOOEt) and CF_3SSCF_3 react to give[7] $(Et_2N)_2P(O)SCF_3$ and $RSCF_3$.

RESULTS AND DISCUSSION

The re-investigation of the system CF_3I/ PMe_3 without a solvent showed that not only CF_3PMe_2 and $PMe_4^+I^-$, but also $[CF_3PMe_3]^+I^-$, $(CF_3)_2PMe_3$[8] (Fig.1) and Me_3PI_2[9] are being formed probably via a radical mechanism.

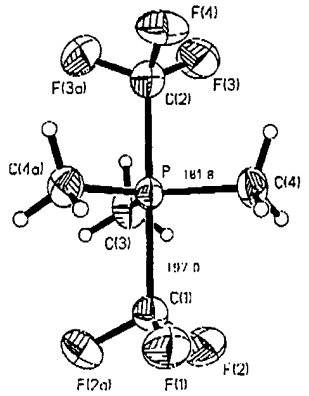


FIGURE 1 Molecular structure of $(CF_3)_2PMe_3$

The straightforward fluorination of $[CF_3PMe_3]^+I^-$ using the covalent $F_2P(NEt_2)_3$ (Fig. 2) give $CF_3(F)PMe_3$ and $[FP(NEt_2)_3]^+$(Fig.3).

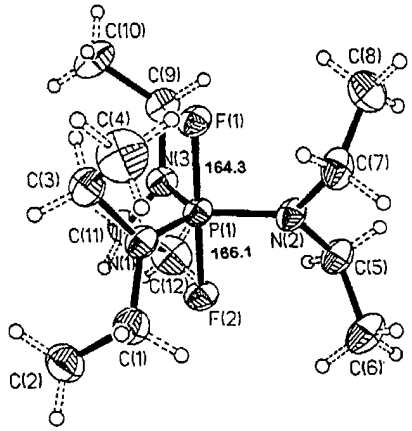


FIGURE 2 Molecular structure of $F_2P(NEt_2)_3$

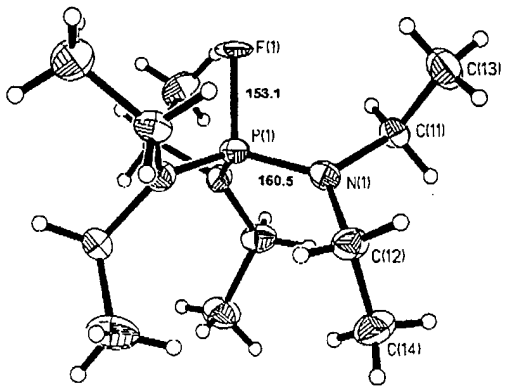
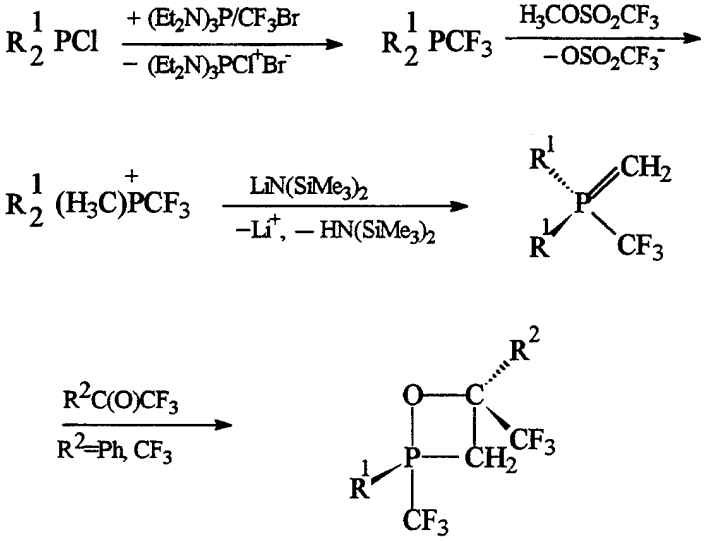
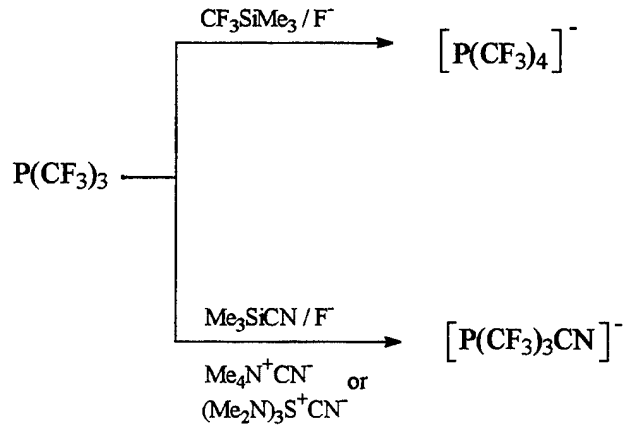


FIGURE 3 Molecular structure of $[FP(NEt_2)_3]^+$

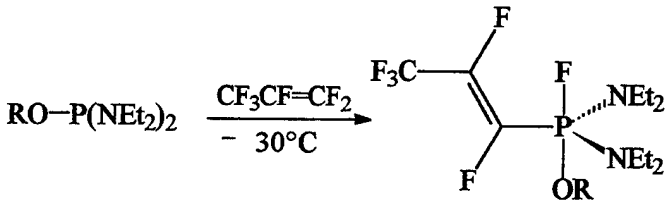
The chlorophosphines $R^1{}_2PCl$ and R^1PCl_2 (R^1=Me, *i*Pr, NEt_2) are trifluoromethylated using the RUPPERT reagent to yield $R^1{}_2PCF_3$ and $R_1P(CF_3)_2$. Both types of phosphines are methylated and the resulting phosphonium salts deprotonated to give methylene phosphoranes which can be stabilized adding activated ketones to furnish oxaphosphetanes.

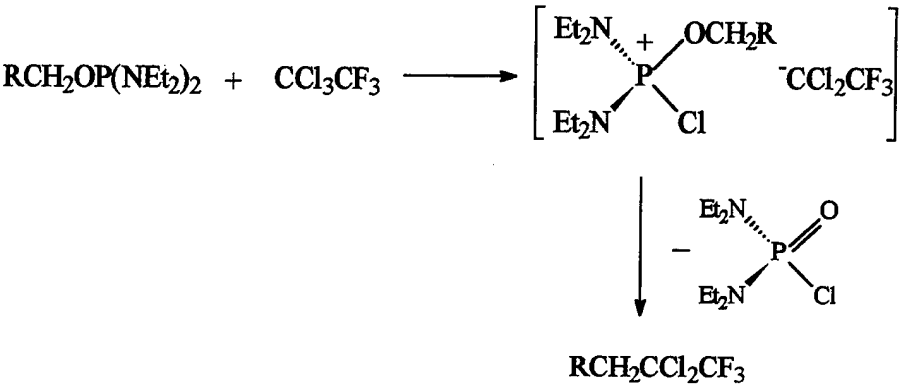


From $CF_3Br/P(NEt_2)_3/P(OPh)_3$ the tertiary phosphine $P(CF_3)_3$ is prepared in very good yield. Addition of F^-, CN^-, $[CF_3^-]$ leads to phosphoranides $[FP(CF_3)_3]^-$, $[NCP(CF_3)_3]^-$ and $[P(CF_3)_4]^-$.



Amidophosphites $ROP(NEt_2)_2$(R= CH_2Ph, CH_2CF_3, $CH(CF_3)_2$) and hexafluoropropene form monofluorophosphoranes which decompose in the case of R= CH_2Ph, CH_2CF_3 under formation of FR and an amidophosphonate. The ARBUZOV reaction with CCl_3CF_3 results in the formation of $(Et_2N)_2P(O)Cl$ and $RCH_2CCl_2CF_3$. The latter compound is dehydrochlorinated to yield $RC{\equiv}CCF_3$, (R=Ph, CF_3) using $(Et_2N)_3P{=}NMe$.





A similar transfer of a benzyl group is observed in the case of $PhCH_2OP(NEt_2)_2$ and $XC(CF_3)_3$ and XC_6F_5 (X=Br, I)

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GENERATION OF PHOSPHIDE ANIONS FROM PHOSPHORUS RED AND PHOSPHINE IN STRONGLY BASIC SYSTEMS TO FORM ORGANYLPHOSPHINES AND -OXIDES

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Abstract Generation of phosphide anions from phosphorus red or phosphine under the action of strong bases followed by their reactions with organyl halides, electrophilic alkenes and alkynes proves to be the most straightforward and well-controlled route to mono-, di- or triorganylphosphines or phosphine oxides of diverse structure.

Key words: phosphorus, phosphine, electrophiles, super bases.

INTRODUCTION

Simple phosphorus-centred nucleophiles like phosphide and phosphinite anions generated from elemental phosphorus or phosphine under the action of strong bases are valuable intermediates for the synthesis of various organyl phosphines and -phosphine oxides, although until recently this opportunity to easily create carbon-phosphorus bond remained almost neglected.

A decade ago we started a systematical study of the red phosphorus P-P bond cleavage in super base media, which has led to a series of facile methods for the preparation of diverse organic phosphines and phosphine oxides [1, 2].

Here we present new data and overview the results together with rationalizations basically dealing with the formation of the P-C bond from elemental phosphorus and/or phosphine in super base media.

Systems P(red)/KOH/Polar Nonhydroxylic Solvent

The essence of the reactions proceeding in the super base systems of type P(red)/KOH/polar nonhydroxylic solvent (DMSO or HMPA)/electrophile is a competition between the hydroxide anion and phosphorus nucleophiles for the electrophile. Therefore, the key question is, how well do the phosphorus nucleophiles match the electrophile in a sense of the frontier orbitals interaction or the HSAB concept?

In fact, in the system P(red)/KOH/DMSO/H_2O, benzyl chloride reacts mostly with the phosphorus nucleophiles to afford tribenzylphosphine oxide in 65% yield [2], whereas the phenyl bromide and iodide as well as allyl chloride give no expected phosphine oxides at all. But, with acetals of bromoacetaldehyde, in the same system, they again are formed in 11-18% yield.

Unexpectedly, an excellent electrophile - nucleophile correspondence was discovered for phosphorus nucleophiles generated from red phosphorus in the above systems and weakly electrophilic olefines like styrene and vinylpyridines. The 40-60% yield of substituted triethylphosphine oxides has been achieved in the DMSO - tailored systems with styrene [2], 4-vinyl- and 2-methyl-5-vinylpyridines [3] at 80-110°C.

$$\text{P/KOH/DMSO} \xrightarrow{\text{RCH=CH}_2} (\text{RCH}_2\text{CH}_2)_3\text{P=O}$$

R = Ph, 4-pyridyl , 2-methyl-5-pyridyl

The steric requirements prove to be important in this reaction as it is demonstrated with α-methylstyrene. No tri(2-phenylpropyl)phosphine oxide at all has been detected in this case.

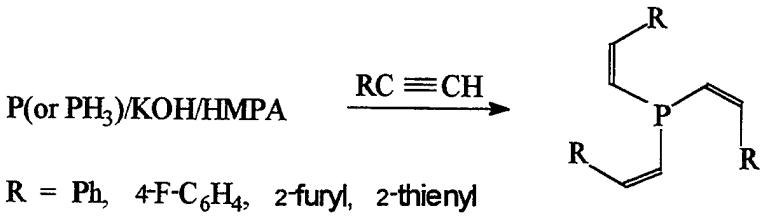
Vinylarenes and vinylhetarenes proved to be also the active traps of the phosphide anions, generated from phosphine in the KOH/DMSO system. We have succeeded in finding the conditions (60-65°C, atmospheric pressure) allowing selective synthesis of secondary phosphines in 60-80% yields [4]. Phosphine was obtained from phosphorus red and potassium hydroxide in water-dioxane media.

$$\text{PH}_3 + \text{R(R')C=CH}_2 \xrightarrow{\text{KOH/DMSO}} [\text{R(R')CHCH}_2]_2\text{PH}$$

R = H, R' = Ph, 4-F-C_6H_4, 2-furyl, 4-pyridyl, 2-thienyl; R = Me, R' = Ph

Arylacetylenes are another group of electrophiles for which the phosphorus nucleophiles generated from phosphorus red or phosphine in KOH/HMPA suspension proved to be capable of winning the competition over hydroxide ion to give chemo-,

regio- and stereoselectively Z,Z,Z-isomers of substituted trivinylphosphines in a yield up to 80% [2, 5, 6].



Phase-transfer Conditions

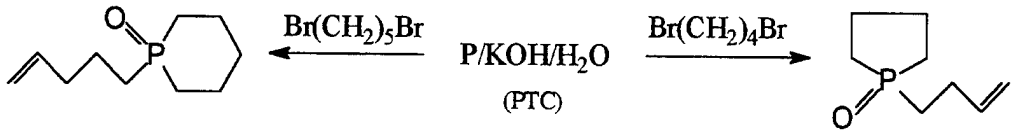
The phase-transfer catalysis with strongly basic aqueous solutions is commonly considered as producing super bases [7]. We have found that under phase-transfer conditions (PTC), the suspensions consisting of red phosphorus, KOH, dioxane, water, and phase-transfer catalyst (benzyl triethyl ammonium chloride) react readily with organyl halides to form tri(organyl)phosphine oxides [1, 2]:

$$R_3P{=}O,\ R = n\text{-Alk}\ (60\text{-}65\%),\ Bz\ (75\%),\ EtSCH_2\ (10\%).$$

Under similar conditions allyl halides are also capable of phosphorylating to afford tri(allyl)phosphine oxide and its isomer, tri(E-1-propenyl)phosphine oxide [2]:

$$(CH_2{=}CHCH_2)_3P{=}O\ (30\%),\quad (E\text{-}CH_3CH{=}CH)_3P{=}O\ (35\%).$$

1,4- And 1,5-Dibromoalkanes react with phosphorus nucleophiles produced in the above-mentioned phase-transfer system to furnish alkenyl phospholane- and phoshorinane oxides in moderate yield (12 and 25%, respectively) due to side elimination processes manifested themselves by the presence of alkenyl group at the phosphorus atom.



The feasibility of the ring closure falls from the six- to five-membered ring with the four membered ring being not capable to form at all. Instead, in the case of 1,3-dibromopropane, a mixture of tri(allyl)- and tri(E-1-propenyl)phosphine oxides has been isolated.

Systems P/Li/NH_3/*t*-AlkOH

Petrov *et al.* reported on the reaction of red phosphorus with sodium in liquid ammonia and subsequent alkylation, affording tetraalkyldiphosphines, dialkylphosphines and tri-alkylphosphines (isolated as phosphine sulfides) in 17-34% yields [8].

We have developed a new method of selective generation of mono- or diphosphide anions from red phosphorus by the system Li/NH_3 liq in the presence of *t*-BuOH which as a mild proton donor drastically assists the fission of P-P bonds in the phosphorus molecule. As a result of alkylation the primary or secondary phosphines have been prepared in 65-85% yield [9, 10].

$$P + 3Li + 2t\text{-BuOH} \xrightarrow{NH_3\ liq} LiPH_2/2t\text{-BuOLi} \xrightarrow{RX} RPH_2$$

$$P + 3Li + t\text{-BuOH} \xrightarrow{NH_3\ liq} Li_2PH/t\text{-BuOLi} \xrightarrow{2RX} R_2PH$$

R = alkyl, cycloalkyl, benzyl; X = Cl, Br

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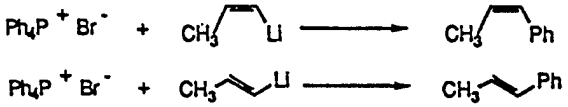
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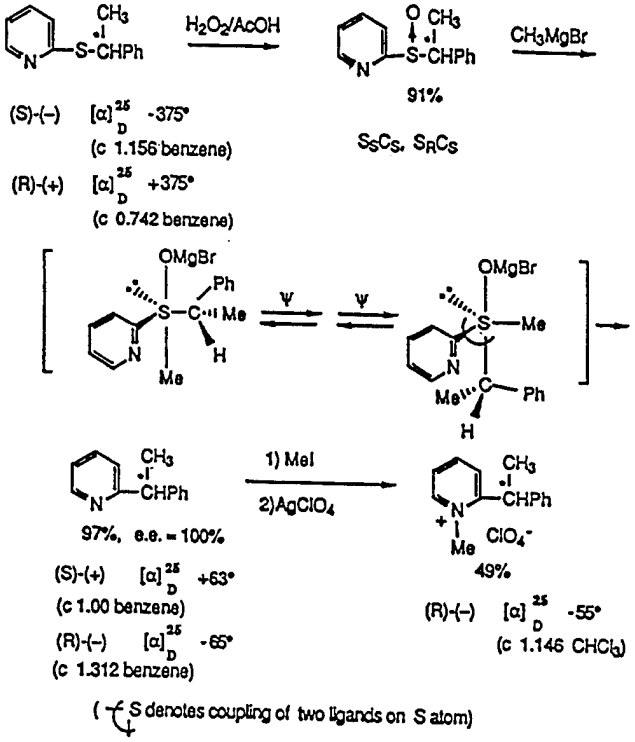
ELECTROPHILIC SUBSTITUTIONS ON TRIS(PYRIDYL)PHOSPHINE

Yuzuru Uchida, Department of Applied Chemistry, Osaka Institute of Technology, Osaka 535 and
Shigeru Oae, Institute of Heteroatom Chemistry, 2509 Hirao Minami- kawachi-gun, Osaka-fu 587 Japan.

Eversince Seyferth ran the very odd reaction which he dit not add any word, this has remained as the first example of stereochemistry of phosphorus atom centered ligand coupling reaction in the hypervalent species and the reaction is the following.(1)



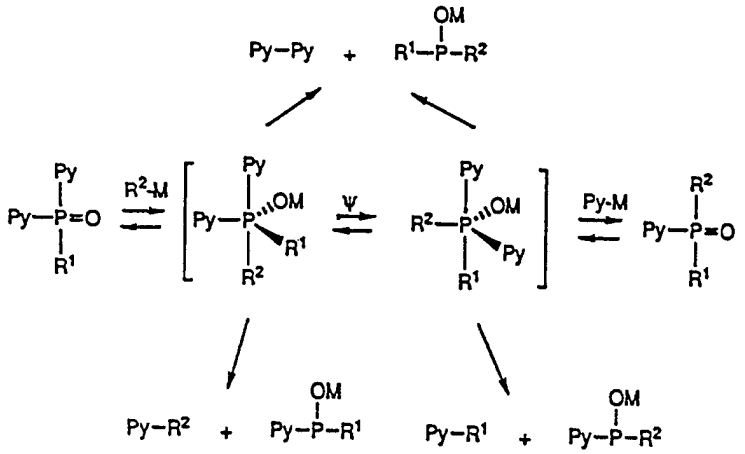
The yield of the reactions are good while the stereochemistry in both cases are nearly 100 %. This means that the coupling between an apical and an eqatorial ligands is both intramolecular and concerted, as in the case of the sulfur species which we have shown earlier.(2)



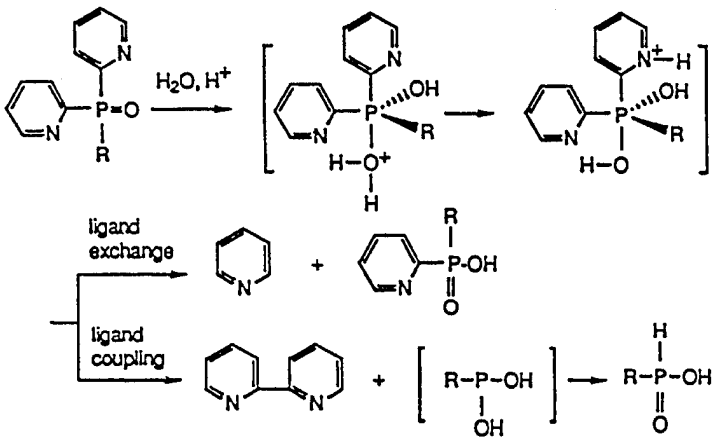
In the meantime, the M. O. calculation, performed on hypervalent chalcogen species has shown that there are certain amounts of interactions between the apical and the equatorial ligands.(3)

The early work of Hey and Ingold,(4) who claimed to have obtained hydrocarbons by coupling of alkyl groups by the treatment of quaternary phosphonium

salts with alkoxides was recently found to be wrong.(5) We have shown many examples of ligand coupling involving 2-pyridyl groups as shown below. (6, 7, 8, 9)

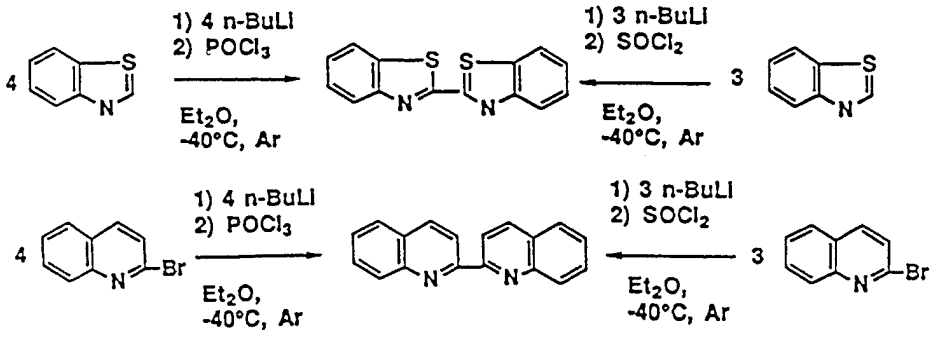


[a] Py = 2-pyridyl; R^1 = 2-pyridyl, Ph; R^2 = Me, Ph, $PhCH_2$, 4-$MeC_6H_4CH_2$; M = Li, MgX.

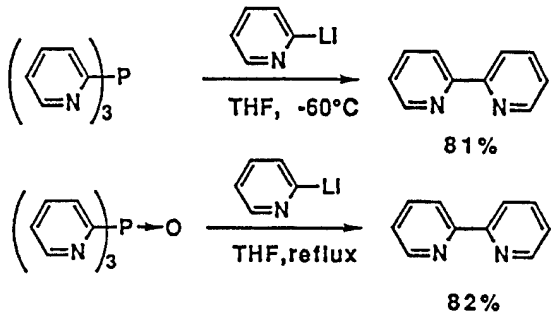


All these reactions are ligand couplings forming pentacoordinated phosphorus intermediates and do not require any alkaline condition(10) nor quaternay phosphorus compounds.

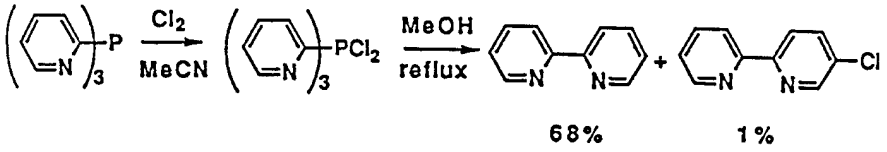
The uses of phosphorus trichloride, phosphorus oxychloride and thionyl chloride were found to undergo coupling reaction with the following heterocycles.(11)



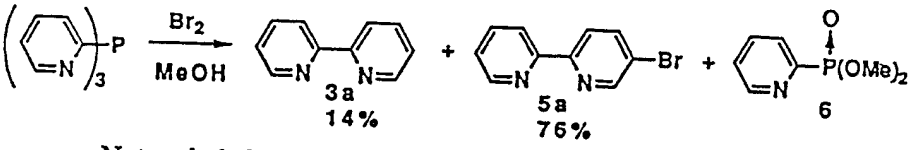
2-Pyridyllithium is known to react with either tris(2-pyridyl)phosphine or its oxide in the following manner.(12)



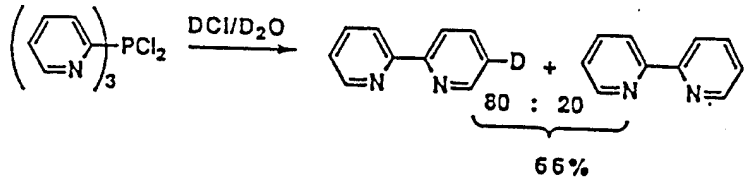
In the meantime, the following electrophic substution by chlorine was found to take place.(13)

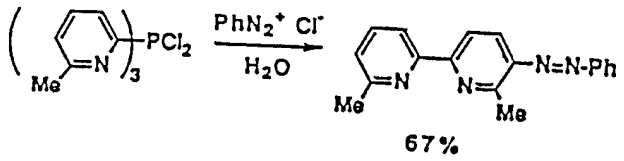


The use of methanol was found to be much more effctive and even bromine in methanol was quite effective in the electrophilic substitution. The normal ligand coupling was also observed to some extent.

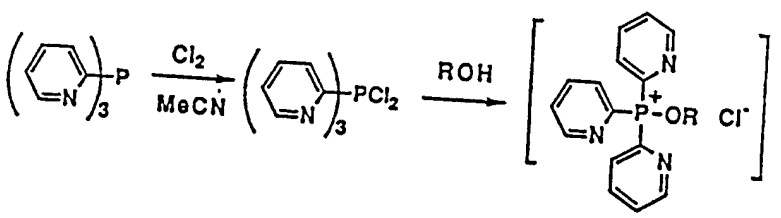


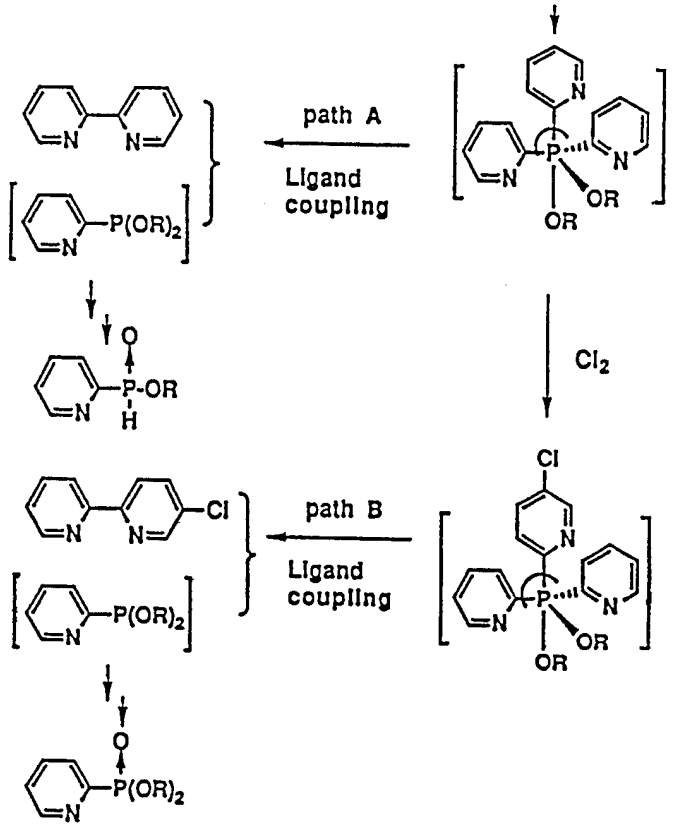
Not only halogenations, but also the deuteration and diazo-coupling reaction took place, as shown below.





The following is our tentative scheme of the path. In other words, the phosphorus atom in the hypervalent species is prone to an electrophilic substitution.





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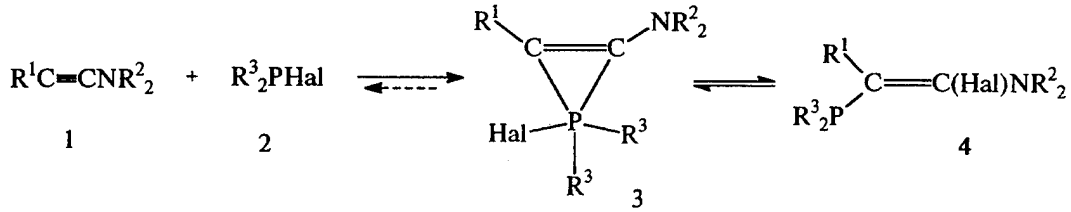
COMPETITIVE ADDITION AND CYCLOADDITION OF LOW COORDINATED ORGANOPHOSPHORUS COMPOUNDS TO ALKOXY- AND AMINOALKYNES.

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MARINA A. KAZANKOVA, IRINA P. BELETSKAYA.
Department of Chemistry, Moscow State Lomonosov University, 119899, Moscow

Abstract Reactions of two- and three coordinated organophosphorus compounds with nucleophilic alkynes can proceed as competitive addition, [2+1]-, and [2+2]- cycloaddition reactions. Ring-chain tautomerism for phosphirenes and isomeric alkenylphosphines has been observed.

Recently the investigations carried out in our laboratory have shown that the addition of phosphorus halides to triple bond of ynethers leads to the formation of β-halogeno-β-alkoxyalkenylphosphines, phosphirenes, phosphorus(III) substituted ketenes and other compounds. Here we report on the reactions of phosphorus(II) and (III) halides and other phosphorus (II) compounds with nucleophilic alkynes which proceed as competitive addition, cycloaddition and insertion processes.

The reaction of halogenophosphines **1** and ynamines **2** leads to phosphirenes **3**, halogenoalkenylphosphines **4** or their mixtures depending on the nature of reagents and solvents used. The reaction of iodo- or bromodiisopropylphosphines with ethyldiethylaminoacetylene or the reaction of chlorodiisopropylphosphine with ynamines with R^1 or R^2 = i-Pr forms exclusively **3**. In the case when only one of R^3 substituents in starting **2** is electron-withdrawing group (R^3=Cl, Ph) the sole isomer of alkenylphosphine **4** is formed. However in most cases we have observed competitive formation of **3** and **4**.



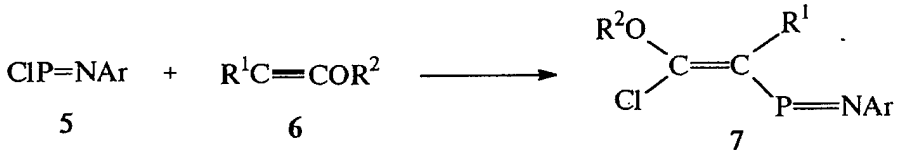
We have shown that ring-chain tautomerism for **3** and **4** takes place. For example, for **3** and **4** (where R^1=R^2=Et, R^3=i-Pr, Hal=Cl) the mixture contains 10% of **3** in pentane, 50% of **3** in benzene and 100% of **3** in dichloromethane. The equilibrium depends on the nature of halogen atom, electron and steric properties of substituents at

triple bond and phosphorus atom and on solvents used. The content of **3** increases in following sequences : R^1=Me<Et<i-Pr; R^2=Et<i-Pr; R^3=Et<c-C_6H_{11}=i-Pr<(i-Pr,t-Bu); Hal=Cl<Br=I. Thus the increase of steric hindrances and electron-donating properties of substituents leads to the increase of stability of **3**.

Solvation of **3** is very important for the position of equilibrium between **3** and **4**. Obviously P-Hal bond in **3** is partly ionic and the extent of ionization increases both in polar solvents and in the sequence Hal=Cl<Br<I. A strong upfield shift of ^{31}P resonance signal of chlorophosphirenes in pentane or benzene (*ca* 17-25 ppm) as compared to dichloromethane and upfield shift of ^{31}P resonance signal of chlorophosphirenes (*ca* 9-26 ppm) as compared to bromo- and iododerivatives confirm the decrease in P-Hal bond ionization and the increase in phosphorane character of **3** in the sequence I<Br<Cl. Thus easier ionization of P-Hal bond in **3** results in the increase of stability of phosphirenes.

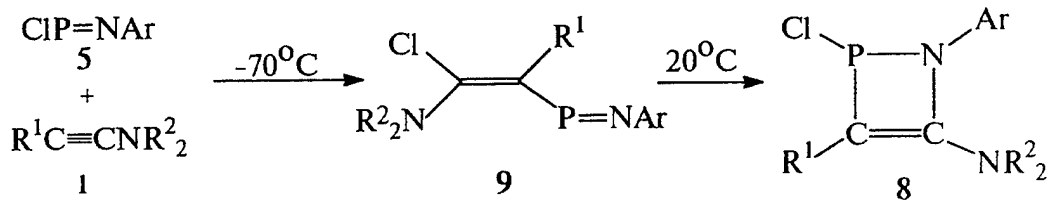
NMR ^{13}C data of **3** show that these molecules exist in the state of distorted bipyramid at phosphorus atom with apical P-Cl and P-C(NR_2) bonds. NMR ^{13}C data for **4** show that one isomer is formed in most cases. However thermodynamically controlled mixture of 70-80% major and 30-20% minor isomers was observed for several compounds due to easy cis-trans isomerization of α–chloroenamines. One of us thoroughly elaborated the method of establishing the configuration of the double bond in P(III)-substituted alkenylalkyl ethers. This method is based on the difference in the values of $^2J(PC)$ of olefin carbon atom for different isomers. Later this method proved to be applicable also for P(III)-substituted enamines. We assume that this method can be applied to compounds of type **4**, and the major isomer of **4** has E-configuration of the double bond.

The reaction of P-chloroiminophosphine **5** with 1-alkoxyalkynes **6** leads to 1,2-addition to triple bond with the retention of two-coordinated phosphorus, and previously unknown 1-aza-2-phosphabutadienes-1,3 **7** are formed in quantitative yields.

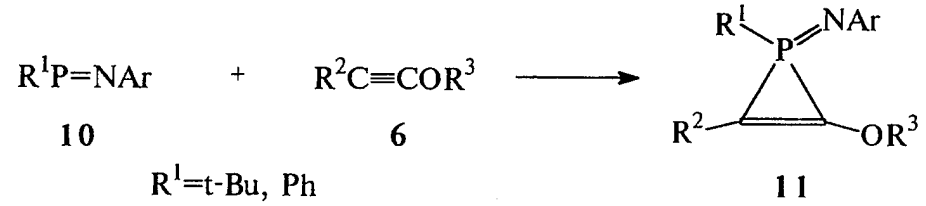


Ar=2,4,6-tri-tert.-butylphenyl

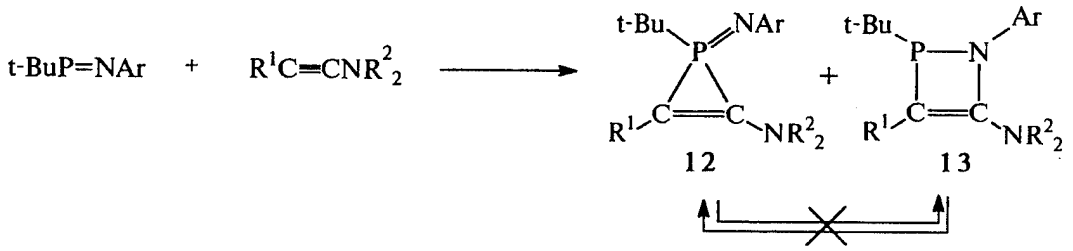
In most cases 1-aza-2-phosphabutadienes **7** are formed as pure Z-isomers. The reaction of P-chloroiminophosphine **5** with 1-aminoalkynes **1** leads to 1,2-azaphosphetines **8** in high yields, and 1,2-addition to triple bond with formation of **9** takes place here as an intermediate process.



According to calculations made by Schoeller and Niecke iminophosphines can react with unsaturated compounds either as carbene analogs or as alkene analogs which makes possible [2+1]- and [2+2]-cycloaddition reactions to proceed. We have investigated the reactions of iminophosphines **10** with non-terminal 1-alkoxyalkynes and demonstrated the formation of [2+1]-cycloaddition products **11**.

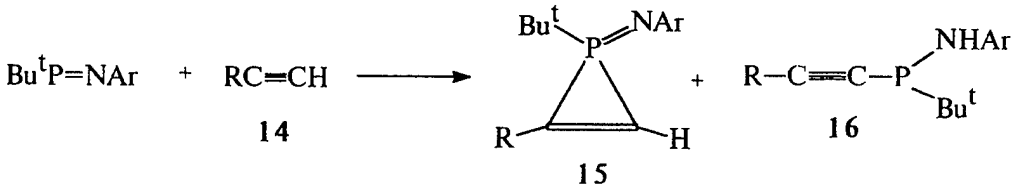


Nevertheless the reaction of P-tert.-butyliminophosphine with 1-aminoalkynes generally produces the mixture of phosphirene **12** with azaphosphetine **13**.



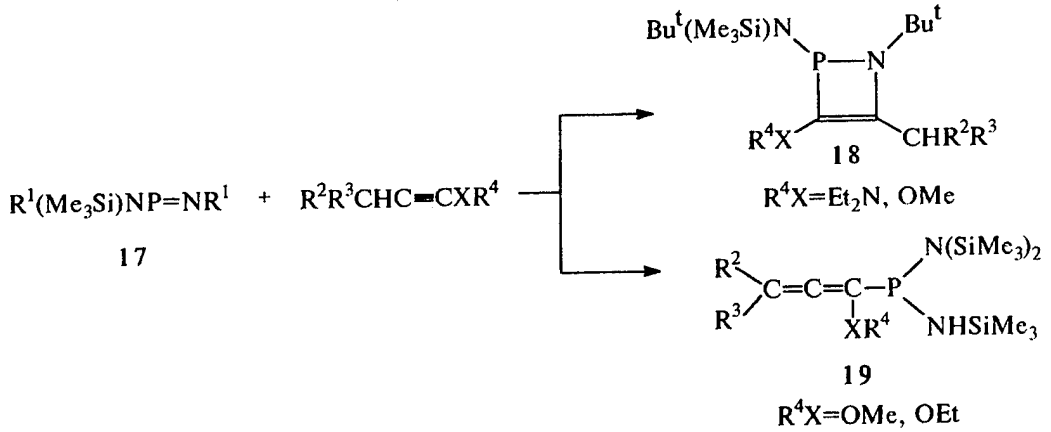
The formation of these products is a result of competitive [2+1]- and [2+2]-cycloaddition reactions. The increase of spatial hindrances of R^1 group as well as the use of polar solvents results in preferable formation of azaphosphetine **13**, the increase of steric hindrances at nitrogen atom of amino group results in exclusive formation of phosphirene **12**.

The reaction of P-tert.-butyliminophosphine with terminal non-activated alkynes **14** produces not only expected phosphirenes **15** but also less or more amount of acyclic P(III)-substituted alkynes **16** due to competitive reactions of [2+1]-cycloaddition and addition of C-H bond of alkyne to P=N bond.

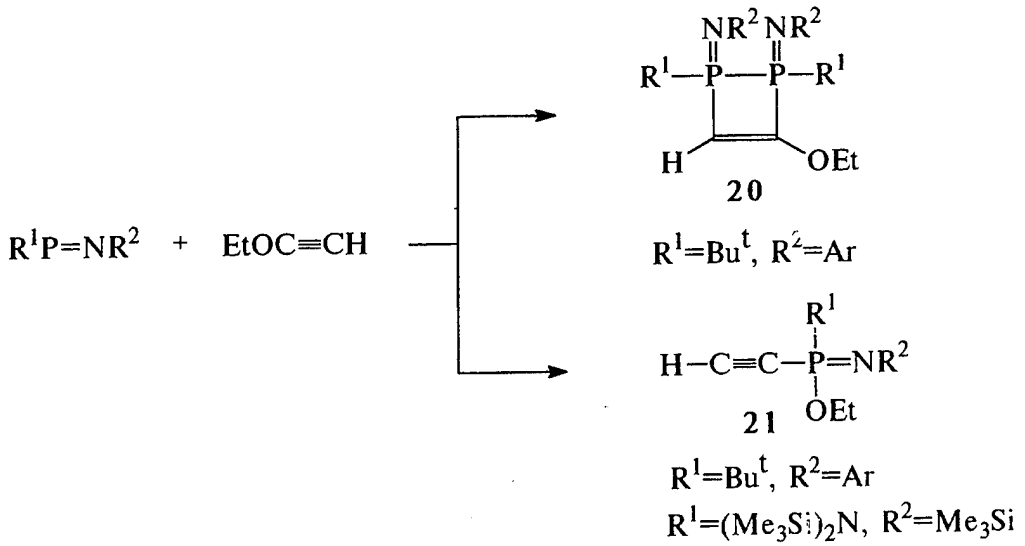


Amidoiminophosphenites **17** react with 1-aminoalkynes to form 1,2-azaphosphetines **18**. The reaction is regioselective and in this case regioselectivity is opposite to that in the

addition of P-tert.-butyliminophosphine to 1-aminoalkynes. The reaction of amidoiminophosphenites **17** with 1-alkoxyalkynes gives rise to new interesting products - azaphosphetines **18** or allenes **19**.



Unexpected results have been obtained when terminal ethoxyacetylene was used in the reactions with iminophosphines. P-tert.-butyliminophosphine and ethoxyacetylene in pentane solution furnished 1,2-diphosphetene **20** whereas in polar acetonitrile substituted acetylene **21** was found to be the major product. This unusual formation of acetylene *via* formal cleavage of C(sp)-O bond has been also observed in the reaction of amidoiminophosphenite with ethoxyacetylene.



Some of presented results were published by us in *Mendeleev Commun.* 1993. N2. P. 68-70, *Tetrahedron Lett.*, 1993, Vol.34, N8, pp. 1331-1334,.and in six articles in *J. of Organic Chemistry (Russia)* in 1994-1995.

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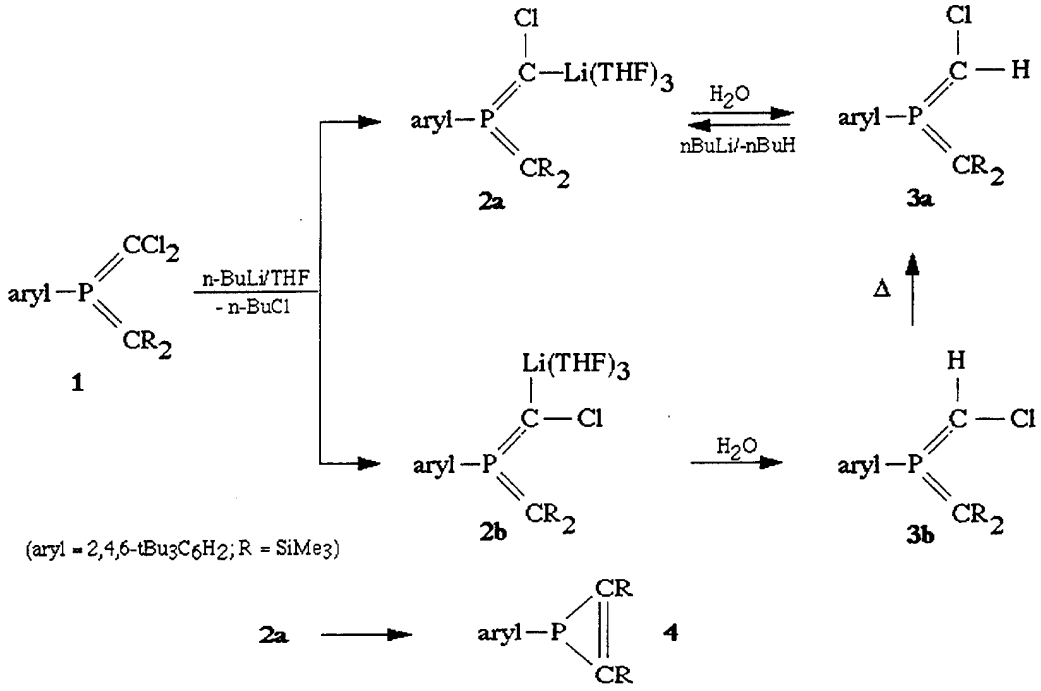
NOVEL ASPECTS IN THE SYNTHESIS OF CARBENOIDS CONTAINING P/C-pπ-BONDS

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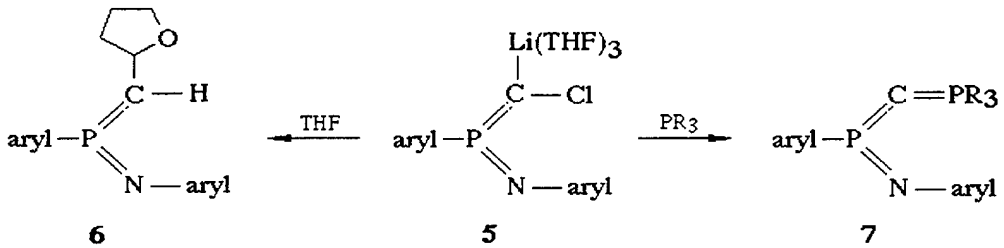
Abstract The synthesis and x-ray structure analysis of a novel type of carbenoids, aryl-P(=E)=C(Cl)Li(thf)$_3$ (E=N-aryl, C(SiMe$_3$)$_2$), as well as the first example of a 1,3-diphosphetane-2,4-diyl, (aryl-PCCl)$_2$, is reported and on the basis of quantum chemical calculations its bonding situation is discussed. Furthermore, selected examples for the varying reaction behavior of both types of compounds are presented.

Carbenoids with a carbenoid center incorporated in a π-system have been attributed a great deal of interest. With respect to the existence of a heteroatom substituted species of this type , a phosphanyl carbenoid has been detected recently by nmr spectroscopy and its chemistry has been exploited in some detail[1].

Now we found that the bis(methylene)phosphorane **1**, acts as a suitable starting compound to a novel type of carbenoids , which upon reaction with *n*-butyl lithium afforded the two isomers **2a,b**; their constitution has been proven by NMR spectroscopy. Quenching the reaction with water results in the hydrogen substituted bis(methylene)phosphoranes **3a,b**, of which **3a** could be isolated in pure form. Hydrogen/lithium exchange with this isomer (**3a**) led selectively to the carbenoid **2a** and the structures of **2a** and **3a** were subjected to X-ray crystallographic studies[2]. Quantum chemical calculations on the model compounds, HP(=CH$_2$)=CClLi, HP(=CH$_2$)=CClLi(H$_2$O)$_3$, HP(=CH$_2$)CCl$^-$, indicate the importance of the donor solvent for the stabilization of the carbenoid and reveal a formal relationship between the solvated carbenoid with the free carbanion. LiCl elimination of **2a** occured at -10°C and resulted in the formation of the phosphirene, **4**.



By analogy, starting from the imino(methylene)phosphorane, aryl-P(=Naryl)=CCl_2, the corresponding iminophosphoranylidene carbenoid **5** was obtained. The constitution of **5** was proven by NMR spectroscopy and suitable trapping experiments. On heating to -10°C **5** reacted by elimination of LiCl with addition of the solvent (thf) to **6**, while in the presence of phosphanes (Ph_3P, $(Me_2N)_3P$) a novel type of carbodiphosphoranes, **7** was obtained[3]. The X-ray structure analysis of **7a,b** indicated a high degree of P/C-multiple bonding (PC 158.8 [159.2 pm], ∢ PCP 149.3 [157.5°]), as summarized in the following canonical valence bond formula **A** and **B**[4].



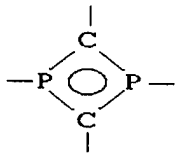


Surprisingly, starting from the methylenephosphane, aryl-P=CCl_2, reaction with *n*-butyl-lithium in the molar ratio of 2:1 afforded a novel type of PC-heterocycles **8**[5].

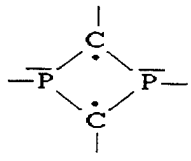


8

According to the x-ray analysis **8** forms a planar $(PC)_2$-skeleton with the substituents at the carbon and the phosphorus atoms suited in a *trans* configuration (PC 175.0°; CPC 87.8°; PCP 92.2°; Σ ∢ P 337°; Σ ∢ C 347°). Ab initio calculations (at MCSCF level) reveal for the parent structure, $(HPCH)_2$, a singlett ground state with C_i-symmetry, with a small singlet triplet energy separation (with MRCI correction). The configuration interaction procedure results in two dominant contributions. The first one accounts for delocalization within the ring system (as is found in S_2N_2) while the mixing in of the second contribution introduces biradical character within the ring system. Both contributions can be summarized by the two resonance structures **C** and **D**.

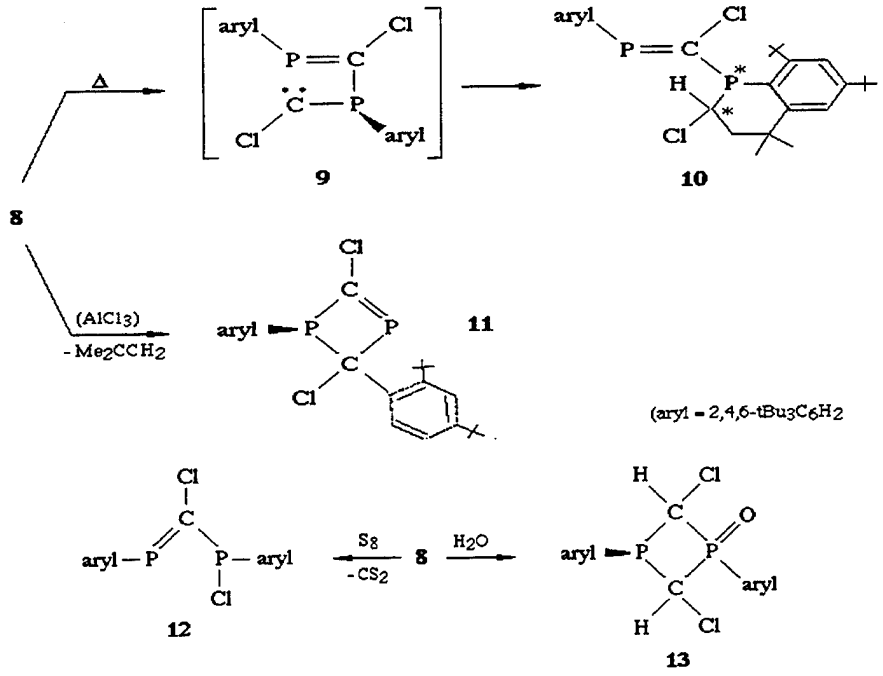


C



D

On heating the heterocycle **8** in toluene isomerized under cleavage of one PC-bond affording to two stereoisomeric diphosphapropene-derivatives **10**. The constitution of the main product was confirmed by x-ray structure analysis. As an intermediate the phosphinocarbene **9**, was assumed which stabilizes by CH-activation involving one of the *o*-tert.-butyl group of the aryl substituent. However, in the presence of a Lewis acid ($AlCl_3$), a 1,3-diphosphetene **11** was formed; by aryl shift from the phosphorus to the carbon atom and loss of Me_2CCH_2. Reaction of the heterocycle **8** with sulfur or water produced the 1,3-diphosphapropene **12** (via shift of the chlorine from the carbon to the phosphorus atom and loss of CS_2) and the 1,3-diphosphetane **13**. The latter was structurally confirmed by X-ray analysis (PC 184.5, 189.0, 187.9; CPC 82.3°, 84.5°; PCP 94.8°, 94.3°).



Furthermore, ab initio calculations on the different isomers of parent 1,3-diphosphetane-2,4-diyl yield the following relative energies: HP=CH-P(H)-C(H): (+14); HP-CH-CH-PH (-37); HP=CH-CH=PH(-49); HP-CH=CH-PH(-52); P=CH-P(H)-CH_2 (-54 kcal/mole).

Acknowledgement

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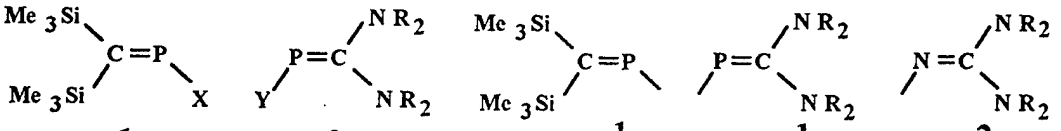
FEATURES OF PHOSPHABUTADIENES STRUCTURE: NMR SPECTROSCOPY AND X-RAY INVESTIGATION

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VITALII V. POLOVINKO, ALEXANDER N. CHERNEGA
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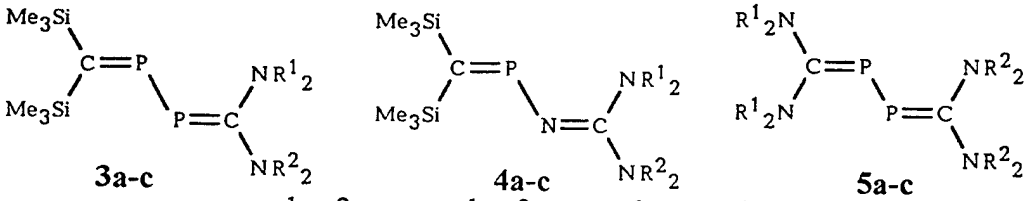
Abstract Conjugation effects in various phosphabutadienes are considered.

INTRODUCTION

There has been revealed an essential contribution of the n,π-conjugation effect to thermodynamical stabilization of phosphaalkenes **1** and **2**. It should be expected that having combined the moieties which characterized by π-donating ($\mathbf{D^1}$ and $\mathbf{D^2}$) and π-withdrawing ($\mathbf{A^1}$) properties into the diene systems **3a-c** and **4a-c** one could reveal conjugation effects of the π-type bonds with low-coordinate phosphorus involved.



1 **2** $\mathbf{A^1}$ $\mathbf{D^1}$ $\mathbf{D^2}$



3a-c **4a-c** **5a-c**

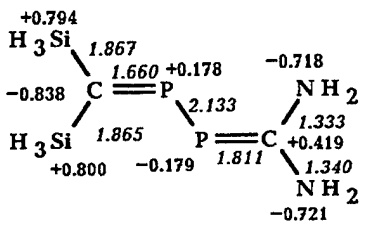
a R^1=R^2=Me; b R^1=R^2=Et; c R^1=Me, R^2=Et

RESULTS AND DISCUSSION

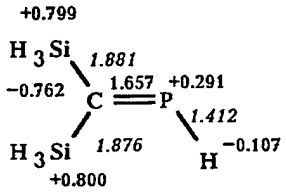
The X-ray investigation of structure of phosphadiene **3b** shows neither essential P-P bond shortening (2.155 Å) nor Si_2P=C and P=CN_2 bonds lengthening (1.683 and 1.777 Å). The comparison of the NMR chemical shifts in **3a** with those in compounds **6** and **7** indicates charge alternation in phosphabutadienes **3**.

$(Me_3Si)_2C=P-P(Bu^t)_2$	$(Me_3Si)_2C^1=P^1-P^2=C^2(NMe_2)_2$		$(But)2P^2-P^1=C(NMe_2)_2$
6	**3a**		**7**
δP^1=450 ppm.	δP^1=454 ppm.	δP^2=99 ppm.	δP^1=-11 ppm.
δC=228 ppm.	δC^1=172 ppm.	δC^2=201 ppm.	δC=201 ppm.
$^1J_{PP}$=245 Hz	$^1J_{PP}$=396 Hz	$^1J_{PP}$=396 Hz	$^1J_{PP}$=256 Hz
$^1J_{CP}1$=98 Hz	$^1J_{C1P1}$=88 Hz	$^1J_{C2P2}$=87 Hz	$^1J_{CP}1$=83 Hz

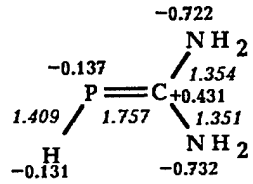
The *ab initio* (6-31G**/3-21G*) calculations of the model compounds **8-10** lead to the planar structures and enable one to suggest the π,π-interaction between the $(H_3Si)_2C=P-$ and the $-P=C(NH_2)_2$ moieties.



8



9



10

In symmetric phosphabutadienes **5** both moieties are characterized by π-donating properties, and, as judged from the NMR data for **5a** [δP= 34 ppm, δC= 197 ppm, $^1J_{CP}$= 32 Hz, $^1J_{PP}$= 289 Hz (for **5c**)] the conjugation between the moieties is absent.

In the context of the problem considered, of interest is the possibility of the P=C bond conjugation with a classical π-system, i.e. the -N=C bond (dienes **4a-c**).

Analysing the NMR data for **4a** and **6,11,12** one can note the significant π-donating influence of the $-N=C(NMe_2)_2$ moiety.

$(Me_3Si)_2C=P-NMe_2$	$(Me_3Si)_2C^1=P-N^1=C^2(NMe_2)_2$		$Ph-N^1=C(NMe_2)_2$
11	**4a**		**12**
δP=330 ppm.	δP=338 ppm.	δN^1= -151 ppm.	δN^1=-173 ppm.
δC=125.4 ppm.	δC^1=144.4 ppm.	δC^2= 161.4 ppm.	δC=159.1 ppm.
$^1J_{CP}$ = 77 Hz	$^1J_{C1P}$=71 Hz	$^1J_{PN}$=81 Hz	$^1J_{CP}1$=83 Hz

Successive replacement of the dimethylamino groups in **4a** with less donating phenyl substituents (transition to dienes **4d** and then to **4e**) is accompanied by appreciable deshielding of carbon C^1.

$(Me_3Si)_2C^1=P-N=C^2(NMe)Ph$		$(Me_3Si)_2C^1=P-N=C^2Ph_2$	
4d		**4e**	
δP=357 ppm.	δC^2= 165.7 ppm.	δP=323 ppm.	δC^2= 170.5 ppm.
δC^1=161.5 ppm.	$^1J_{C1P}$= 72 Hz	δC^1=159.5 ppm.	$^1J_{C1P}$= 74 Hz

The X-ray structure analysis of the compound **4d** shows no shortening of the P-N bond (1.683 Å). This seems to result from both mutual repulsing of sterically bulky substituents in the compound **4d** and the P-N bond twist (the torsional angle

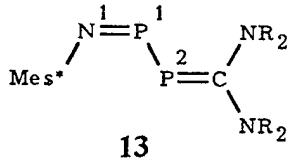
C^1PNC^2=155.3°). A value for the C =P bond length experimentally obtained (1.668 Å) is within the limits of the values typical of phosphaalkenes (**1**) (1.64-1.67 Å). But the analysis of *ab initio* calculation data for some model compounds makes it possible to conclude that along with the bond lengthening (weakening) by means of the conjugation effects, its shortening (strengthening) occurs due to inductive withdrawing properties and the group electronegativity of π-donating substituents, in particular.

This conclusion is also confirmed by the data on the barrier of hindered rotation around the multiple C=P and C=N bonds in dienes **3,4** and **5**. One can observe free rotation of this moiety (Si_2C=P) around the P=C bond in the NMR time scale in diene **4b** only; whereas for other compounds the barrier values exceed 113 KJ/mole. Our research shows the π-donating ability of the substituents $\mathbf{D^1}$ and $\mathbf{D^2}$ to be considerably lower than that of dialkylamino groups and, at the same time, they are also characterized by σ-withdrawing properties, which, on the contrary, favor the bond shortening.

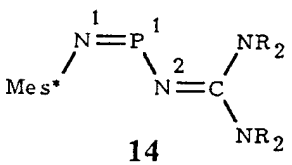
Table 1. Barriers of Hindered Rotation Around P=C and N=C Bonds ($\Delta G^{\neq}_{303K}$) in Compounds of Interest, kJ/mol.

Compo-und	Chemical formula	$(Me3Si)_2C$=P- (A^1)	$P=C(NR_2)_2$ (D^1)	$N=C(NR_2)_2$ (D^2)
3a	$(Me_3Si)_2C$=P-P=$C(NMe_2)_2$	>113	<40	-
4a	$(Me_3Si)_2C$=P-N=$C(NMe_2)_2$	>113	-	<40
4b	$(Me_3Si)_2C$=P-N=$C(NEt_2)_2$	112	-	<40
5a	$(Me_2N)_2C$=P-P=$C(NMe_2)_2$	-	68	-

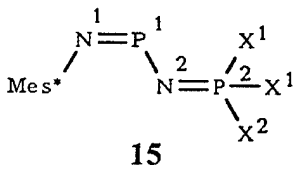
It was of interest to study the possibility of realization of the π,π-conjugation in the diene systems **(13-15)**.



13



14



15

13,14 a R^1=R^2=Me; b R^1=R^2=Et; c R^1=Me, R^2=Et; **15** a X^1=X^2=NMe2; b X^1=X^2=Ph; c X^1= Bu^t, X^2=Ph

A characteristic feature of phosphabutadienes **13** is a large P-P coupling value (Jpp=472 Hz for **13a**), which exceeds even the values of 396-403 Hz obtained for compounds **3a-c** and is close to the values typical of diphosphenes (550-650 Hz). This can be explained by the higher polarity of the P-P bond, which is confirmed by the results of *ab initio* calculations performed for the model compounds. The X-ray analysis data showed that the P-P bond in compound **13a** (2.133 Å) is even shorter than in

phosphabutadiene **3b** (2.155 Å) that is likely due to its larger polarity. The Mes* moiety is turned out relative to the plane of the P=N π-system by the angle 89.1°. Both Me_2N-C bonds are shortened (1.340 and 1.347 Å) and the P=C bond is lengthened (1.809 Å). Some P-P bond twisting (torsional angle NPPC=176.7°) does not exclude the conjugation between the N=P and P =C π-systems.

The replacement of the phosphorus atom with nitrogen going to dienes **14a**, is accompanied by the shielding of the ^{31}P (δP=204 ppm) and $^{15}N^1$ (δN= -102 ppm)] nuclei. These chemical shift values obtained can be attributed to those in compound Mes*-N=P-$N(Me)_2$ **(16)** wherein the n,π-conjugation between a lone electron pair of the nitrogen atom and the N=P-system is observed. Thus, the π-systems in dienes **13,14** are also capable of conjugation provided the molecule is coplanar enough.

16	**15a**		**17**
δP^1= 203 ppm.	δP^1= 141 ppm.	δP^2= 16 ppm.	δP= 40 ppm.
δN^1= -119 ppm.	δN^1= -90 ppm.	δN^2= -224 ppm.	δN^2= -348 ppm.
$^1J_{PN}{}^1$=91 Hz	$^1J_{P^1N^1}$= 108 Hz	$^1J_{P^2N^2}$= 8 Hz	$^1J_{PN^2}$= 30 Hz
δN^2= -257 ppm	$^1J_{P^1N^2}$= 98 Hz		
$^1J_{PN^2}$= 103 Hz			

As follows from the X-ray structure analysis of the compound **15b** containing both the three- and penta-valent phosphorus atoms, the central $CN^1P^1N^2P^2$ group is practically planar. The P-N bond (1.597 Å) is shortened, as compared to the interval (1.65-1.70 Å), typical of the single phosphorus-nitrogen bond. The double P =N bond is essentially lengthened. An unusual increase in the valence angle $P^1N^2P^2$ (159.7°) seems to be due to the fact that the molecule **15b** is sterically crowded. Analysis of the ^{15}N and ^{31}P NMR data obtained shows an essential π-donating effect of -N=$P(NMe_2)_3$ substituent. Taking into account a semipolar character of the N^2=P^2 bond, as well as the absence of the appreciable changes in the shielding of the P^2 nuclei, one could assume that such a drastical change in δN on going from HN=$P(NMe_2)_3$ **(17)** to phosphabutadiene **15a** is due to the conjugation of the electron pair, which forms the π-bond and is mainly localized along the p_z-orbital of the nitrogen atom, with the N=P bond. On its action the above conjugation is similar to the n,π-conjugation of a lone electron pair of the nitrogen atom of the dimethylamino group in the compound **16**.

Thus, the NMR spectroscopy and quantum chemistry investigation of phosphabutadienes (**3,4,5,13,14**, and **15**) containing the two-coordinate phosphorus atom, prove the significant role of the conjugation effects in their stabilization.

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PHOSPHOCYANINE DYES

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Abstract

The conjugated organic polymethine salts (cyanine dyes) are widely used in industry. Numerous applications in chemistry (dyes, photochemical sensitizers for photographic emulsions...) and physics (in optical devices, non linear optics and erasable laser disks) have been developed.
We present here a synthetic pathway towards previously unknown phosphocyanine dyes by condensation of N-silylated phosphinimines on carboxonium salts. As the synthesis of these dyes results in the enhancement of the conjugation path, new physical properties are expected. Furthermore their aza-Wittig reactivity allows the obtention of new series, i.e. the reaction with isocyanides lead to original α-aminopyridines.

Key Words : Phosphocyanine dyes, phosphaimines, aza-Wittig reactivity, isocyanides, substituted α-aminopyridines synthesis.

INTRODUCTION

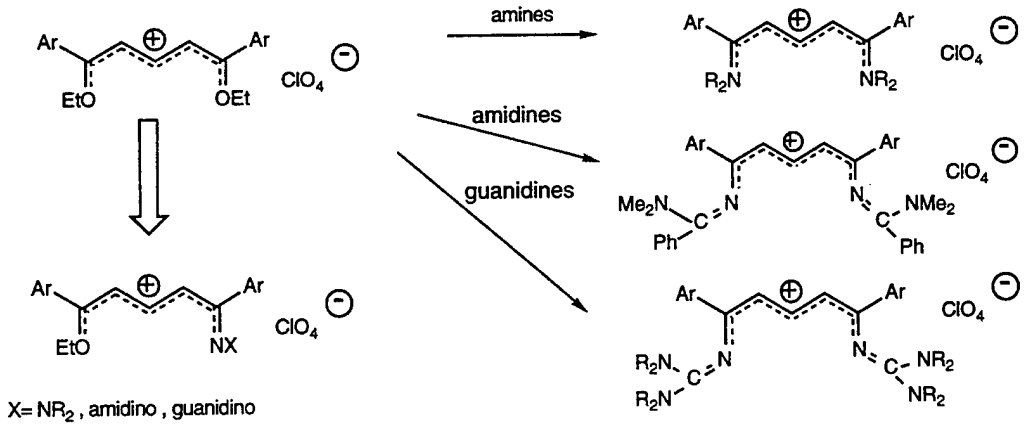
The search of new synthetic methods leading to charged polyenic systems is currently developed in our laboratory. Our actual results are based on two different methods. First, the reaction of *tris*dialkylaminoarsanes or stibanes on pyrylium salts afford highly substituted and symmetrically aminated pentadienylium salts [1]. The second, the most general one, utilizes the selective reactivity of carboxonium salts, isolable cationic intermediates in the synthesis of pyrylium salts [2].

Owing to the large application pattern of the polyenylium salts in chemistry (dyes, sensitizers for color photography...), biology (fluorescence assays, DNA intercalation...), physics (non linear optics, optical data storage...) it seemed interesting to obtain new types of salts whith enhanced conjugation pathway either by delocalization beyond the nitrogen atoms (with imino nitrogen groups in amidino or

guanidino environment) or by synthesis of polypentadienylium systems with active conjugated spacers. Other salts with passive or neutral spacers confering more degrees of freedom to the structure can be easily obtained. Furthermore, we try to replace the amino nitrogen terminal groups by other group 15 heteroelements.

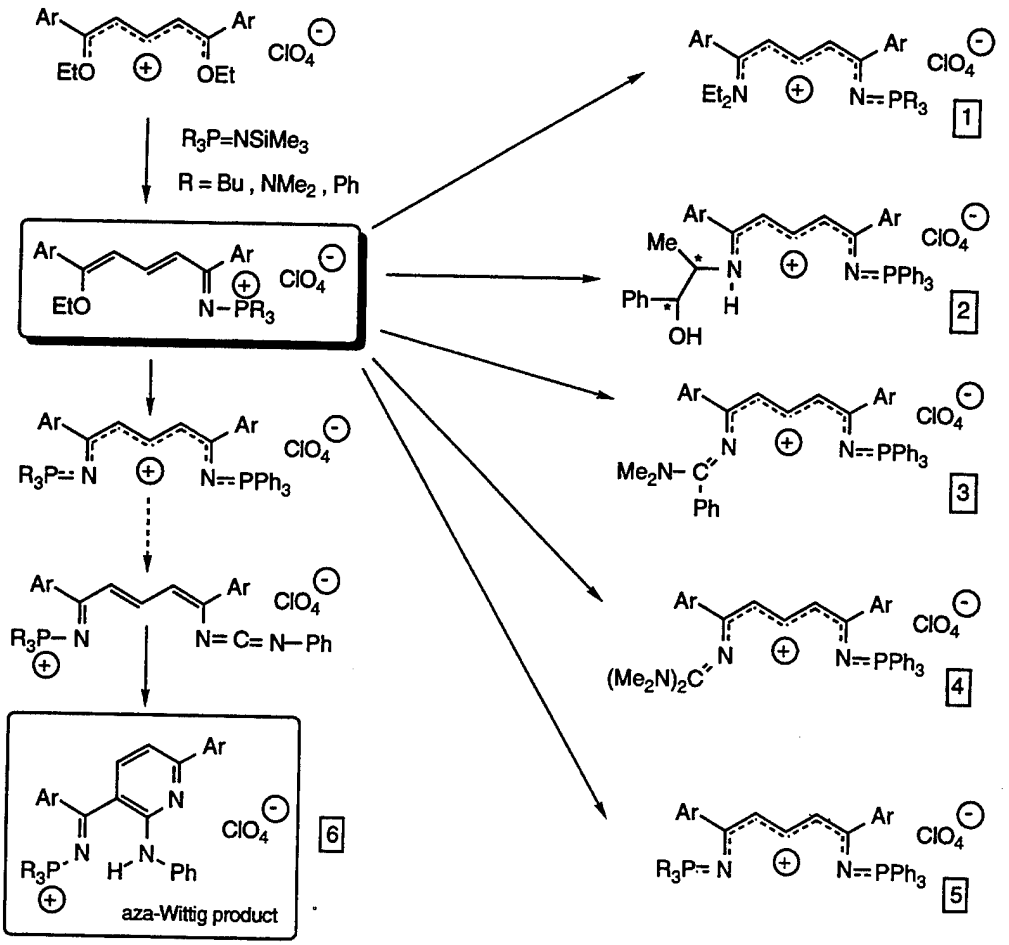
RESULTS AND DISCUSSION

The following scheme summarizes the general reactivity of carboxonium salts with amino and imino reactants; the possibility to obtain hemicarboxonium salts is to be emphasized for it opens the way to homo and hetero reactions leading to symmetrical and non-symmetrical compounds respectively [3].



The same reaction pathway was attempted with an other group 15 element, the phosphorus. Thus secondary phosphanes afford only traces of the expected products, the main part beeing formed of the ketodienether obtained by dealkylation of the carboxonium salt and formation of the phosphonium perchlorate. This was confirmed by the quantitative synthesis of the dealkylated product in presence of tertiary phosphanes. Nevertheless we decided to introduce the phosphorus heteroelement by the way of the reactivity of silaphosphaimines which revealed to be an important and extensive reaction.

Like in the reaction of amino and imino compounds, the formation of the monosubstituted phosphorus synthon has an outstanding importance for the obtention of a great variety of new non symmetrical pentadienylium salts [4]. The following scheme summarizes the main possibilities.



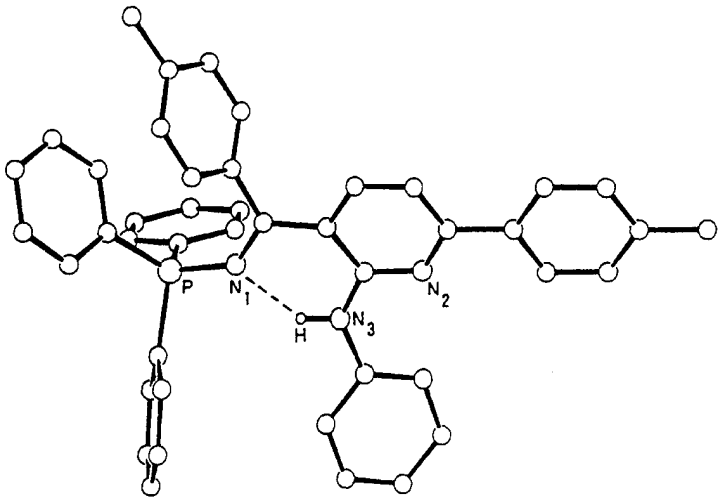
Compounds [1] and [2] are obtained by the action of amines with our "magical" building block. In the case of an optically active aminoalcohol like the (-)norephedrin,{α_D = -40} a striking change in rotatory power is observed (i.e. α = - 248 with Ar = $pMeOC_6H_4$ and R = Ph). Even larger effects on the optical rotation of cyanine dyes were recently described [5].

For examples [3] and [4] the amidino and guanidino groups permit the extension of the conjugation pathway over the nitrogen atom leading to a bathochromic and an hypochromic effect as compared to products of type [1] . Thus if Ar = $pMeOC_6H_4$ and R = Ph, we observed a red shift of 62 nm [475 ([1]) versus 537 (for [3] and [4])] whereas the molar extinction coefficients falls from 75000 to 54000 and 41000 for [3] and [4] respectively.The diphosphazenyl compounds like [5] (R = NMe_2; $\delta\,^{31}P$ = 28.9 and 13.5 ppm or R = Ph; $\delta\,^{31}P$ = 13) offered the possibility of an azaWittig like reactivity [6] as it is demonstrated by the isolation of an aminopyridine phosphonium salt, cyclized end product of the reaction with phenylisocyanate. Moreover we obtained the solid state structure of [6] with Ar = $pMeC_6H_4$ and R = Ph.

crystal data

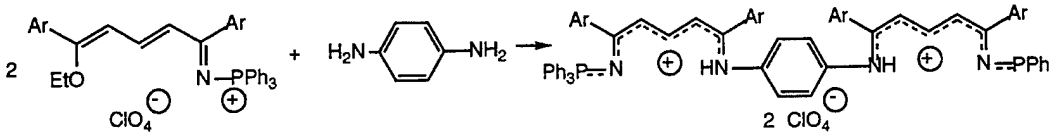
$C_{44}H_{38}ClN_3O_4P$, M = 739.2, monoclinic, a = 11.660(9) b = 20.388(7), c = 16.161(6) Å, V = 3771.9 $Å^3$, Z = 4, d_c = 1.30 g cm^{-3} , space group $P2_1/c$, F(000) = 1548.

Selected distances (Å)
P-N_1 = 1.634(4)
N_1...H = 1.91(4)
H-N_3 = 0.89(4)
N_1 N_3 = 2.660(4)
and angle (°)
N_1...H-N_3 = 141(3)



CONCLUSION

The introduction of the phosphazenyl group at the end of charged polyenic system opens the way to an unlimited amont of new cyanine dyes. The new physical properties thus induced (i.e. solvatochromism) or their enhanced reaction pattern are currently studied. One example of these features is given hereafter with the synthesis of a dicationic entity with an active spacer. For Ar = $pMeC_6H_4$ we observed a large solvatochromic shift of $\Delta\lambda$ = 54 nm going from CH_3CN (λ = 503 nm) to toluene (λ = 557 nm).



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OXIDATIVE-REARRANGEMENT REACTIONS OF σ^3, λ^3 DIALKYL(SILYLAMINO)PHOSPHINES WITH CHLOROPHOSPHINES; FORMATION OF A P–P BOND VIA A NEW ROAD TO PHOSPHINOPHOSPHORANIMINES

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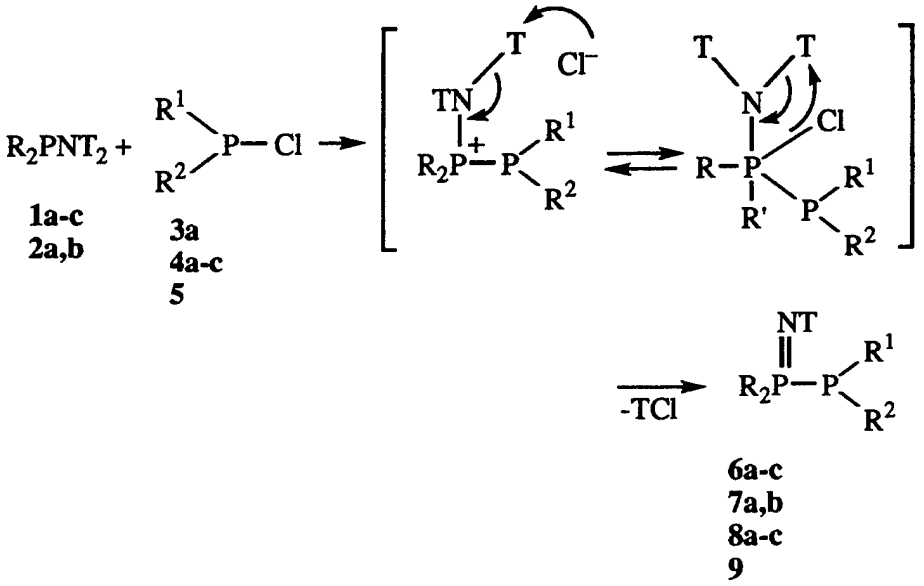
Abstract: Chlorophosphines react with trivalent (silylamino)phosphines *via* a direct oxidative addition process with elimination of trimethyl silyl chloride to produce phosphino-phosphoranimines with concomitant formation of a P-P bond. Oxidation of the phosphine center with sulfur and an exchange transformation of the phosphine are discussed.

INTRODUCTION

There are many bis-phosphorus compounds containing a P-P bond wherein both P-atoms are found in the same oxidation and coordination state. Methods of synthesis have been reviewed.[1] Bis-phosphorus compounds containing two phosphorus in different oxidation states (e. g. $P^{III}P^{V}$) are not so readily formed. The most inaccessible of this type of compounds are the phosphino-phosphoranimines ($\rangle P-\underset{|}{\overset{|}{P}}=N-$) which have been previously prepared by various means: reactions of $LiNT_2$ (T= $SiMe_3$) and chlorophosphines,[2] from the reactions of chlorophosphines with substituted amides abstracting HX with base,[3] as products in the reactions of amines with dicoordinate phosphines, T_2N-PET (E=CH, N)[4] and it has long been known that attempts to synthesise $N(PR_2)_3$ types of compounds lead in general to the isomeric form $R_2PP(R)_2=NPR_2$.[5] Our recent studies of the reactivity of (silylamino)phosphines (R_2PNT_2) with variety of organic compounds show that these reagents are good synthons for preparation of bifunctional compounds[6] yielding a variety of pentavalent phosphorus imines. The reaction route depends on the structure of the phosphine and on the nature of the halide.[7] We have recently found that when

the halogen is bound to an electron acceptor group such as $PhCH_2$, CH_2CN, CO, CH_2CO, etc. the reaction always proceeds with elimination of Me_3SiCl to form σ^4, λ^5 phosphoranimines.[6] We describe herein extension of this reaction to a selection of chlorophosphines which proceed directly to phosphino-phosphoranimines products.

Reactions of dialkyl **1a-c** and dialkoxy **2a,b** (silylamino)phosphines with chlorophosphines **3a**, **4a-d** and **5** were carried out by combining the reagents initially at 0°C in dichloromethane. The mixture was then allowed to warm to room temperature overnight yielding the iminophosphorano-phosphines **6-9** (Table).



6a-c
7a,b
8a-c
9

TABLE

Compound	R	R^1	R^2	$^1J_{PP}$ (Hz)
6a	Me	Ph	Ph	218
6b	Et	Ph	Ph	217
6c	^nPr	Ph	Ph	217
7a	C_2H_5O	Ph	Ph	156
7b	^iPrO	Ph	Ph	146
8a	Me	Me	NT_2	270
8b	Me	Et	NT_2	268
8c	Me	^iPr	NT_2	275
8d	Me	Ph	NT_2	307
9	Me	OEt	OEt	160

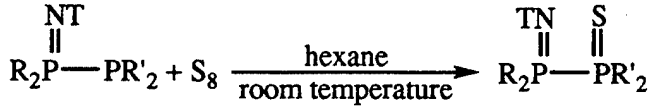
The phosphino-phosphoranimines **6**, **7** and **8** were isolated as air sensitive colorless liquids by vacuum distillation. The compounds, which are stable at ordinary

temperatures in an argon atmosphere, were characterized by ^{1}H, ^{13}C and ^{31}P NMR spectra and elemental analysis. The phosphorus NMR spectra showed the characteristic two equal intensity doublets with P^{V} to high field and P^{III} to low field with a large one bond coupling (145-306 Hz) in each region. [2, 4] In the ^{13}C NMR spectra of **6a-c, 7a-b** methyl and methylene C-atoms on P^{V} appeared as doublet of doublets in the ^{13}C NMR spectra due to both one bond coupling with P^{V} and two bond coupling with P^{III}. The same type of C-atoms bonded to P^{III} showed only a doublet structure due to the one bond coupling. Two bond coupling of the carbon on P^{III} to P^{V} was not observed.

The success of the reaction depends on the substituents on the chlorophosphine reagents. For example, chlorodiphenyl and chlorodiethoxyphosphines reacted smoothly with the full series of (silylamino)phosphines. However under the same conditions, dimethyl, diethyl and dipropyl chlorophosphines were without reaction even after several days at room temperature. Replacing one of the alkyl groups of the chlorophosphine with a bis-trimethylsilylamino group provided more reactive chlorophosphines and again phosphino-phosphoranimines were produced. We attribute these variances to the electrophilic character of the chlorophosphine center which is enhanced by the large -I substituents such as phenyl and bis(trimethylsilyl)amino. The first step of the reaction appears to be the nucleophilic addition of the chlorophosphine phosphorus with the formation of a phosphonium salt (or possibly a phosphorane intermediate). An oxidative elimination rearrangement follows in which Me_3SiCl is eliminated and the phosphoranimine center is developed.

The strength of the approach lies in the fact that there is little isomerization and/or rearrangement in the reactions. None of the products encountered herein exhibited isomerism or equilibria between different forms. A large variety of chlorophosphines can be used and the product is predictable. The generality of the route remains to be established.

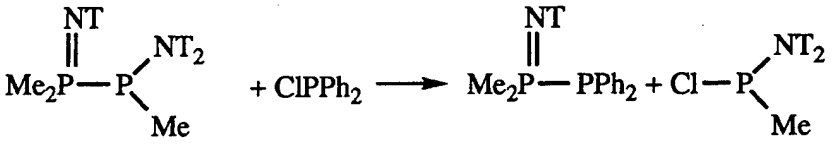
The phosphino-phosphoranimines can be further oxidized. Thus, treatment with sulfur in hexane at room temperature gave the phosphinesulfide-phosphoranimines as viscous light yellow liquids:



	R	R'
10a	Me	Ph
10b	Me	OEt
10c	EtO	Ph

The structures of **10a-c** were obtained by NMR studies and elemental analysis. The ^{31}P NMR spectra show doublets of doublets with smaller $^{1}J_{PP}$ values appropriate to coupling between two pentavalent phosphorus centers. The reaction of the phosphino-phosphoranimines with MeI or EtI resulted in cleavage of P-P bond to give a mixture of monophosphorus compounds. No products were isolated from this reaction mixture.

The phosphino-phosphoranimine **8a** reacts with diphenylchlorophosphine in CH_2Cl_2 again with cleavage of the P-P bond in the starting bis-phosphorus compound however a new P-P bond is formed. This is in contrast to the behaviour of differently substituted phosphino-phosphinimines which reacted with chlorophosphines to give R_2PPR_2 and $R_2PCl{=}NY$ products.[3]



8a **6a**

CONCLUSION

We show that (silylamino)phosphines react readily with chlorophosphines to provide a facile method of synthesis of phosphino-phosphoranimines. Development of this reaction will provide a route to a variety of potential bis-phosphorus ligands.

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OXIDATIVE ADDITION OF HEXAFLUOROACETONE, PERFLUORINATED 1,2-DIKETONES AND TETRACHLORO-o-BENZOQUINONE TO COMPOUNDS OF LOW-VALENT PHOSPHORUS - NEW MODES OF ADDITION AND UNUSUAL PRODUCTS

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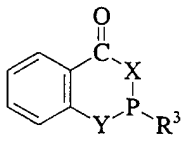
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Abstract The reaction of hexafluoroacetone (HFA) with the benzoxazaphosphorinone **1** leads to the λ^5-oxazaphosphepinone **2**. In several cases unusual products, **3**, **8 - 14**, **16**, and **17**, were isolated in the reactions of **1**, **4 - 7**, and **15** with HFA, tetrachloroorthobenzoquinone (TOB) and perfluorinated 1,2-diketones. X-Ray crystal structure analyses were carried out for the derivatives **2**, **3**, and **8 - 10**.

Key Words: Oxidative Addition; N-Alkylation; Phosphoranes, bicyclic; Phosphoranes, tricyclic; Single Crystal X-Ray Structure Determination.

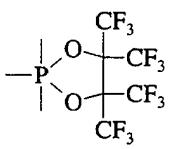
INTRODUCTION

Benzoxaza- and diazaphosphorinones of type **A** are known to react with nucleophiles either with displacement of the P-bonded substituents (usually chlorine) or with cleavage of the phosphorinone ring [1-8]. Many phosphorus(III) compounds have been reported to undergo oxidative addition reactions with HFA with formation of phosphoranes involving the structural element **B** [9,10].

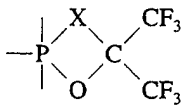


X = O Y = NR^1
X = O Y = O
X = NR^2 Y = O
X = NR^2 Y = NR^1
R^1 = Me R^2 = Alkyl, Aryl
R^3 = Hal, Amino, Alkoxy

A



B



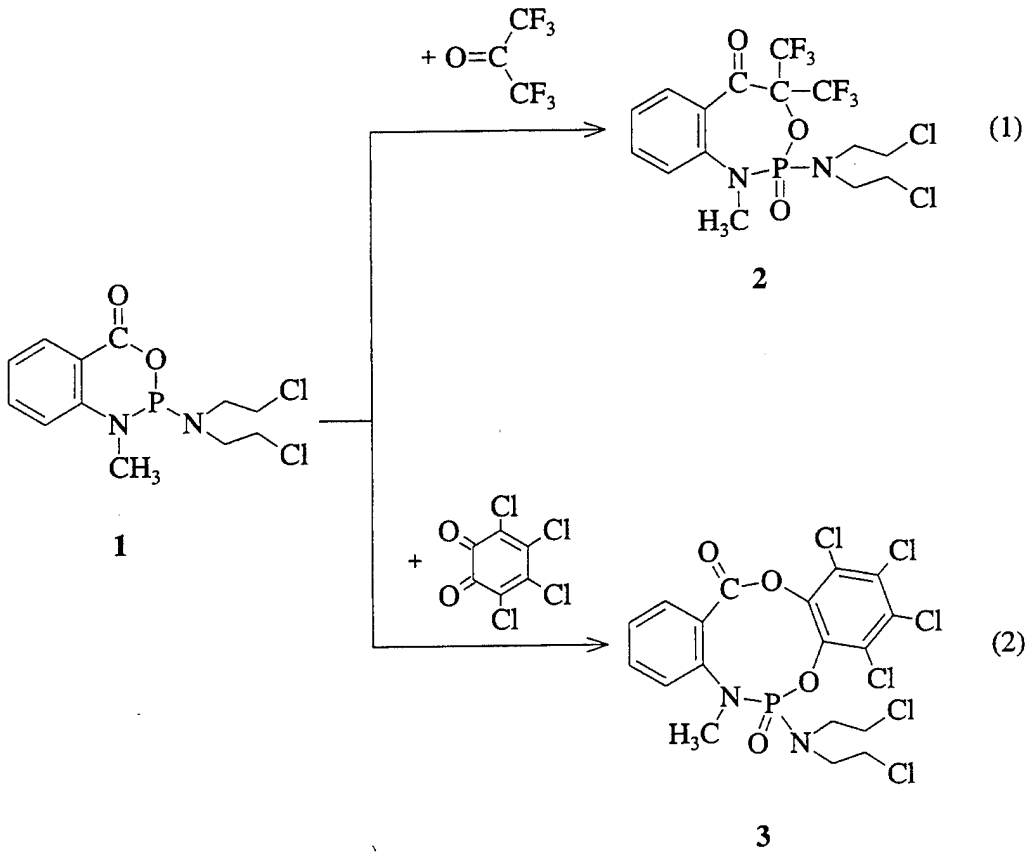
X = CH_2, CHCl, NR^1
R^1 = Alkyl, Aryl

C

The reaction of phosphorus(III) compounds with HFA was found to lead to λ^5-oxaphosphetane derivatives of structure **C** when CH_3, CH_2Cl, or NHR substituents were bonded to P(III) [10-12].

RESULTS AND DISCUSSION

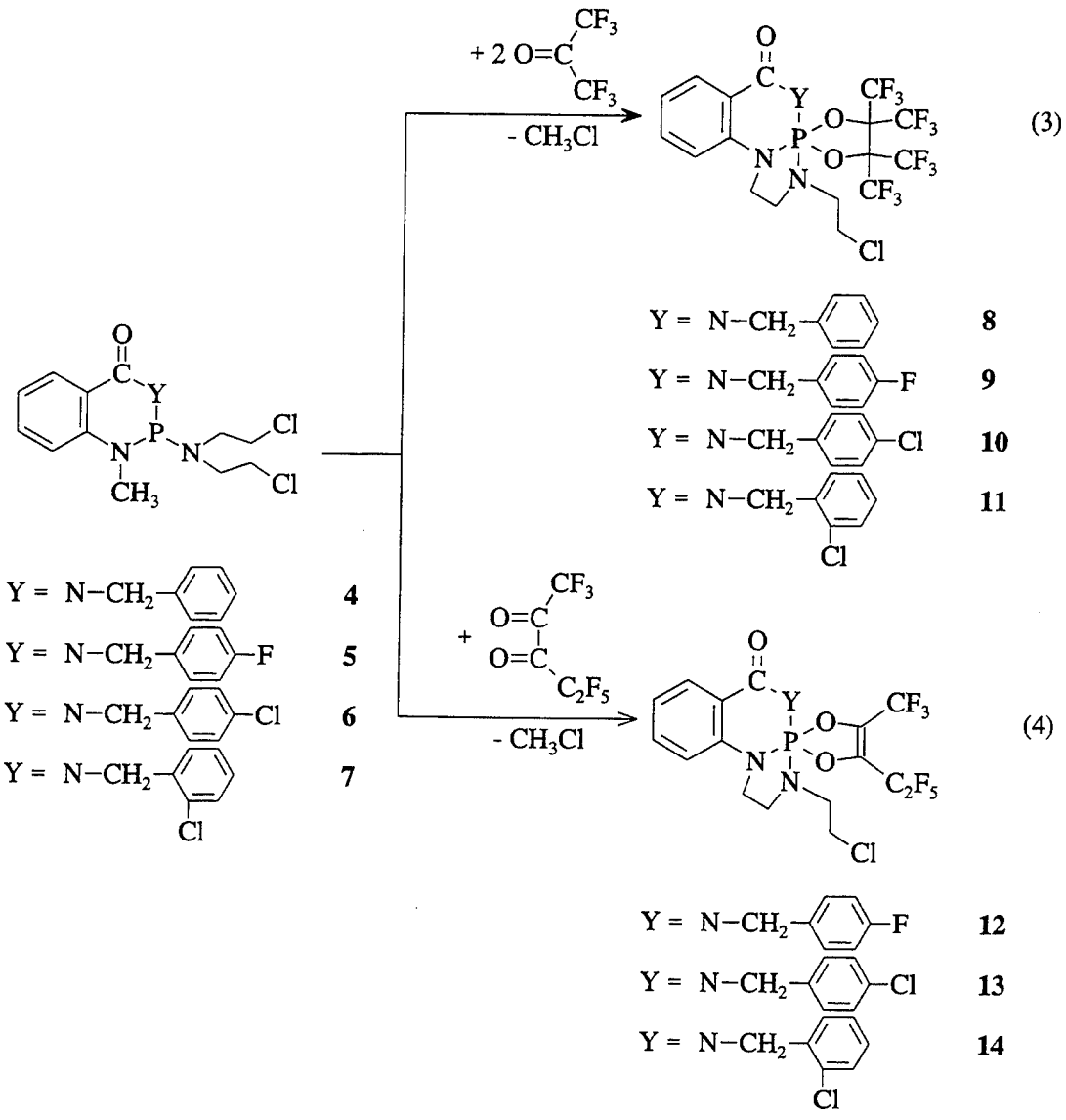
The reaction of the bis(2-chloroethyl)amino-1,3,2-oxazaphosphorinone derivative **1** with HFA and TOB did not lead to the expected spirocyclic products by oxidative addition of HFA or the quinone system to the λ^3-P-atom. Instead, cleavage and expansion of the heterocyclic ring system with formation of the oxazaphosphepinone **2** and the tricyclic derivative **3** was found to occur (Eq. (1) and (2)).



1 **2** **3**

The structures of **2** and **3** were confirmed by single crystal X-ray structure determination [5,11]. The derivatives **4** - **7** reacted with HFA and trifluoromethyl-pentafluoroethyl-1,2-diketone (TMPE) in an unexpected fashion. The oxidative addition of HFA and TMPE to the P(III) compounds was invariably accompanied by an unusual N-alkylation reaction, involving one of the two CH_2CH_2Cl-groups bonded via nitrogen to the

phosphorus atom. The alkylation reaction leads to ring closure and formation of the tricyclic phosphorane ring systems **8 - 11** and **12 - 14** (Eq. (3) and (4)).

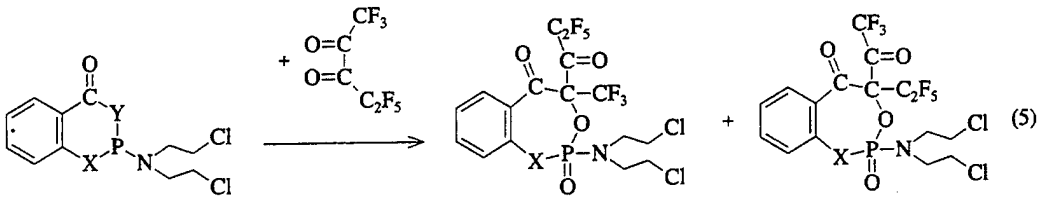


(3)

(4)

The structures of the tricyclic n-benzyl-, p-fluorobenzyl-, and p-chlorobenzyl-phosphorane derivatives **8 - 10**, involving the phosphorus atom as a spiro center, linking one six-membered and two five-membered rings together, were confirmed by single crystal X-ray structure determinations [13].

In the reaction of **1** and **15** with TMPE, insertion of the diketones into the heterocycle of **1** and **15** with formation of **16** and **17**, involving dioxa- and oxazaphosphepine ring systems, was found to take place. Compounds **16** and **17** were obtained as mixtures of the isomers **16a** and **16b**, and **17a** and **17b** (Eq.(5)).



(5)

X = Y = O **1**

X = NCH_3, Y = O **15**

16a X = NCH_3 **16b**

17a X = O **17b**

ACKNOWLEDGEMENT

We thank Dr. A. A. Kadyrov for the synthesis of the oxazaphosphepinones **16** and **17** and Dipl.-Chemiker R. Sonnenburg for drawing the formulae.

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