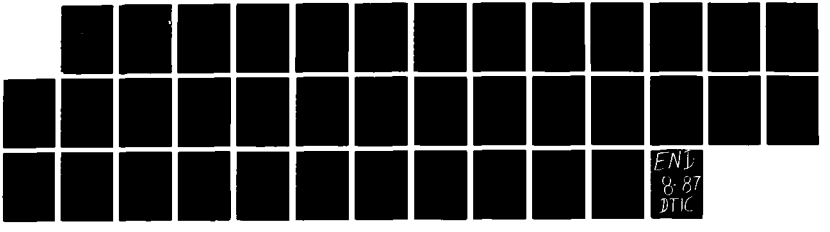
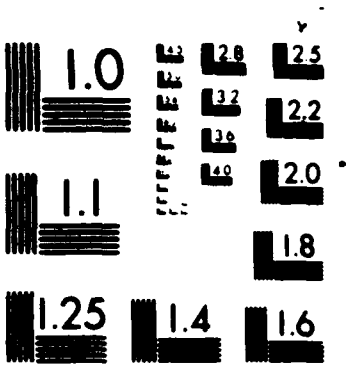
AD-A182 674 A CRITICAL EVALUATION OF STUDIES EMPLOYING ALKENYL HALIDE 'MECHANISTIC PR.. (U) TEXAS A AND M UNIV COLLEGE STATION DEPT OF CHEMISTRY M NEWCOMB ET AL. 07 JUL 87 1/1

UNCLASSIFIED TR-9 N00014-79-C-0584 F/G 7/4 NL





Unclassified

SECURITY CLASSIFICATION OF

TION PAGE

RICTIVE MARKINGS

AD-A182 674

1a REPORT SECURITY CLASSIFIC
Unclassified

2a SECURITY CLASSIFICATION AUTHORITY

3 DISTRIBUTION / AVAILABILITY OF REPORT
Approved for Public Release
Distribution Unlimited

2b DECLASSIFICATION / DOWNGRADING SCHEDULE

4 PERFORMING ORGANIZATION REPORT NUMBER(S)

5. MONITORING ORGANIZATION REPORT NUMBER(S)

DTIC ELECTE JUL 15 1987 S D

6a NAME OF PERFORMING ORGANIZATION	6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION
Texas A&M University		Office of Naval Research

6c. ADDRESS (City, State, and ZIP Code)	7b. ADDRESS (City, State, and ZIP Code)
Department of Chemistry College Station, TX 77843	Department of the Navy Arlington, VA 22217

8a. NAME OF FUNDING / SPONSORING ORGANIZATION	8b. OFFICE SYMBOL (If applicable)	9 PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
		N00014-79-C-0584

8c. ADDRESS (City, State, and ZIP Code)	10 SOURCE OF FUNDING NUMBERS			
	PROGRAM ELEMENT NO	PROJECT NO.	TASK NO.	WORK UNIT ACCESSION NO
			NR053-714	

11 TITLE (Include Security Classification) (Unclassified)
A Critical Evaluation of Studies Employing Alkenyl Halide "Mechanistic Probe" as Indicators of Single Electron Transfer Processes.

12 PERSONAL AUTHOR(S)
Martin Newcomb, Dennis P. Curran

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Technical Report	FROM _____ TO _____	1987, July 7	34

16 SUPPLEMENTARY NOTATION

17 COSATI CODES		
FIELD	GROUP	SUB-GROUP

18 SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
electron transfer, mechanistic probes, free radicals, kinetics

19 ABSTRACT (Continue on reverse if necessary and identify by block number)

Recently it has been suggested that many reaction traditionally classed in polar terms may proceed via single electron transfer (SET) processes. The results of experiments with rearrangeable alkenyl halide "probes" have often been cited as evidence to support the conclusion that an SET mechanism is operative. Serious complications in this analysis have surfaced. This Account critically evaluates the utility of these alkenyl halide probes as mechanistic probes for SET. Reactions which interfere with the standard analysis include the rearrangement of non-radical intermediates and the isomerization of the starting probe halide by a halogen atom transfer mechanism. Guidelines are presented which are useful in evaluating the accuracy of past conclusions drawn from alkenyl halide probe experiments and in designing future experiments which are free from complication.

(Keywords:)

20 DISTRIBUTION / AVAILABILITY OF ABSTRACT	21 ABSTRACT SECURITY CLASSIFICATION
☒ UNCLASSIFIED/UNLIMITED ☒ SAME AS RPT ☐ DTIC USERS	Unclassified

22a NAME OF RESPONSIBLE INDIVIDUAL	22b TELEPHONE (Include Area Code)	22c OFFICE SYMBOL

DD FORM 1473, 84 MAR 83 APR edition may be used until exhausted
All other editions are obsolete

SECURITY CLASSIFICATION OF THIS PAGE
Unclassified

OFFICE OF NAVAL RESEARCH

Contract N00014-79-C-0584

Task No. NR 053-714

TECHNICAL REPORT NO. 9

A Critical Evaluation of Studies Employing Alkenyl Halide "Mechanistic Probes" as Indicators of Single Electron Transfer Processes

by

Martin Newcomb, Dennis P. Curran

Prepared for Publication in

Accounts of Chemical Research

Texas A&M University
Department of Chemistry
College Station, TX 77843

July 7, 1987

A Critical Evaluation of Studies Employing Alkenyl Halide "Mechanistic Probes" as Indicators of Single Electron Transfer Processes.

Martin Newcomb*
Department of Chemistry
Texas A&M University
College Station, TX 77843

and

Dennis P. Curran*
Department of Chemistry
University of Pittsburgh
Pittsburgh, PA 15260

Abstract: Recently it has been suggested that many reaction traditionally classed in polar terms may proceed via single electron transfer (SET) processes. The results of experiments with rearrangeable alkenyl halide "probes" have often been cited as evidence to support the conclusion that an SET mechanism is operative. Serious complications in this analysis have surfaced. This Account critically evaluates the utility of these alkenyl halide probes as mechanistic probes for SET. Reactions which interfere with the standard analysis include the rearrangement of non-radical intermediates and the isomerization of the starting probe halide by a halogen atom transfer mechanism. Guidelines are presented which are useful in evaluating the accuracy of past conclusions drawn from alkenyl halide probe experiments and in designing future experiments which are free from complication.

A Critical Evaluation of Studies Employing Alkenyl Halide "Mechanistic Probes" as Indicators of Single Electron Transfer Processes.

Martin Newcomb*
Department of Chemistry
Texas A&M University
College Station, TX 77843

and

Dennis P. Curran*
Department of Chemistry
University of Pittsburgh
Pittsburgh, PA 15260

Introduction: Chemical reactions come about through the reorganization of valence electrons. The notion that organic reactions proceed via either polar or single electron transfer (SET) processes is widespread in organic chemistry. At a glance, the two pathways might seem quite different. However, more careful analysis reveals the similarity between the polar and SET pathways,[1] which might be viewed as limits in a continuum of electronic reorganizations. Nonetheless, the polar/SET classification is useful, and demonstrable differences exist between the two pathways. In particular, a single electron transfer mechanism can clearly be confirmed if the existence of an odd electron intermediate can be demonstrated *and* a correlation between the intermediate and the final product can be established. Good evidence exists that a variety of important organic reactions proceed via single electron transfer mechanisms.[2]

Recently, it has been suggested that many organic reactions classed traditionally in polar terms may proceed via single electron transfer mechanisms. Such reactions include nucleophilic additions[3] and substitutions[4], hydride reductions[5], and halogen-metal exchange reactions.[6] Evidence for these conclusions has been based on the detection of radical intermediates in a reaction or on the isolation of products derived from radicals. Commonly, the presence of free radical intermediates has been inferred from the well known intramolecular rearrangement of a variety of unsaturated radical clocks[7] generated from alkenyl halides: so-called "mechanistic (or

cyclizable) probes".[8] It has usually been *assumed* that these intermediates are on the *direct* pathway between starting materials and products.

This Account will critically evaluate the utility of these "mechanistic probes" in the detection of single electron transfer processes. Several interfering reactions can compromise the use of alkenyl halide mechanistic probes. The possibility of rearrangement of the probe via a non-radical pathway has been recognized. With appropriate control experiments, this alternative can be investigated. A more insidious problem has surfaced recently. This Account will demonstrate that, while alkenyl halide cyclizable probes may indeed rearrange through radical intermediates, these intermediates may not always be on the direct pathway between reactants and products. As such, the observation of rearranged products in a cyclizable probe experiment does not provide *de facto* evidence for a single electron transfer pathway in the reaction under study. Quantitative evidence which supports this conclusion will be presented and past interpretations (not results) of cyclizable probe studies will be reevaluated in light of these considerations. It will be concluded that alkenyl halide "mechanistic probes" should be used only with great care as evidence for the occurrence of single electron transfer processes. Guidelines for the use and interpretation of these experiments will be provided.

Anionic Cyclizations: The halogen-metal exchange reaction between alkyl halides and alkyllithium reagents (Eq. 1) has been the subject of numerous mechanistic investigations.[9] On the basis of cyclizable probe studies, it has been proposed that the reaction of alkyl iodides and bromides with t-butyllithium can proceed via radical intermediates.[6] A mechanism often invoked[6] is outlined in Eq. 2. Single electron transfer (SET) from t-butyllithium to an alkyl halide produces a transient radical anion **1** which rapidly loses the halide to give radical **2**. Single electron transfer from another molecule of t-butyllithium provides the alkyllithium product. This mechanism accounts for the formation of the alkyllithium, but a full balanced equation is not usually presented. It also requires the use of two equivalents of t-butyllithium for the exchange reaction. In addition to the alkyllithium product and lithium halide, two equivalents of t-butyl radical are generated. The fate the (presumed?) t-butyl radical intermediate is not often discussed.[10]

$$R\text{-}X + R'\text{-}Li \rightleftharpoons R\text{-}Li + R'\text{-}X$$

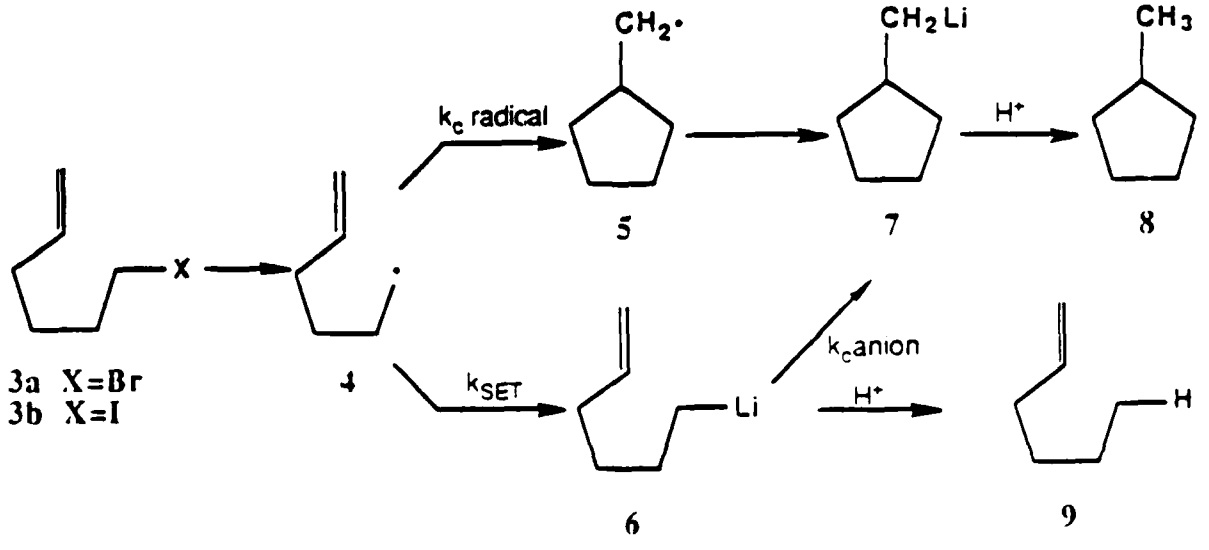
$$R\text{-}X \xrightarrow{t\text{-}BuLi} R\text{-}X^{\bullet -} \xrightarrow{fast} R\bullet + X^{-} \xrightarrow{t\text{-}BuLi} R\text{-}Li \qquad \text{Eq. 2}$$

1 2

According to the (somewhat ill-defined) mechanism proposed in Eq. 2,[6] the hexenyl radical 4, generated as an intermediate (Eq. 3), could partition between cyclization ($k_c$radical) to give the cyclopentylmethyl radical 5, and single electron transfer (k_{SET}) to give hexenyllithium 6. Single electron transfer to 5 gives cyclopentylmethyllithium 7. After protonation, the ratio of methyl cyclopentane (8) to 1-hexene (9) is presumed to reflect the relative rates of the two competing reactions of intermediate radical 4.

This analysis is valid only if the rate of cyclization of the hexenyl anion 6 ($k_c$anion) to cyclopentylmethyllithium 7 is negligible under the conditions of the experiment. That anion cyclizations could be competitive reactions in such experiments has been recognized by Bailey and Garst.[11] The occurrence of anionic cyclizations can be probed by independent control experiments and by stereochemical studies involving methyl-substituted alkenyl halides. Indeed, the cyclization of alkenyl- and alkynyllithium reagents is beginning to emerge as a useful synthetic method.[12]

Eq. 3



Past results of studies in this area have been recently re-evaluated in light of more critical experiments.[13] It is now agreed by both Bailey[13a] and Ashby[6c] that the halogen-metal exchange

reaction between 6-iodo-1-hexene (**3b**) and t-butyllithium in THF at -78 °C produces only hexenyllithium **6**. This is indicated by the production of **9** in virtually quantitative yield after methanolysis. This evidence strongly supports a polar mechanism.[14] However, both groups[6c,13b] have proposed that alkyl bromides have a significant SET component in their reaction with t-butyllithium. A detailed picture of the halogen-metal exchange reaction between alkyllithium reagents and alkyl halides is far from secure and further experimentation is required. For cyclizable probe experiments to provide useful evidence for an SET mechanism, it must be demonstrated that the cyclic products arise only from a radical process and not from the cyclization of an organometallic intermediate. We suggest that future mechanistic discussions in this area provide balanced equations to indicate the proposed fate of all the reactive intermediates formed in a mechanism under consideration.

Reaction of Organic Halides with Nucleophiles: The belief that reactions of 1°- and 2°-alkyl halides with most nucleophiles and reducing agents proceed by a polar (S_N2) pathway is supported by kinetic and stereochemical evidence. However, many reactions once classed as polar processes have now been reformulated as single electron transfer (SET) reactions. Such reactions include the reduction of primary and secondary alkyl halides[5] with lithium aluminum hydride, aluminum hydride and lithium triethyl borohydride, and the displacement of such halides with metal enolates[4a,b], alkoxides[4i], alkali stannanes[4d-h] and organocopper species.[4c]

The single electron transfer mechanisms often proposed are outlined in Scheme I. Reaction of a 1°- or 2°-organic halide (RX) with a nucleophile (Nu- or NuM) can result in electron transfer [step (1)] to give the halide radical anion and the corresponding radical of the nucleophile (Nu• or [NuM]+•). Rapid fragmentation of the halide radical anion to R• and X- then ensues [step (2)]. It has been assumed[4,5] that the organic radicals (R•) would be transformed in subsequent steps to the formal products of substitution (RNu). Two paths which can lead to net substitution are radical-radical coupling [step (3)] or radical-nucleophile coupling followed by electron transfer of the resulting complex to the starting halide [steps (4) and (5)]. The former pathway is a non-chain process. Since the direct coupling of free radicals is unlikely to account for

much product. cage processes have been proposed for step (3). The latter pathway is a chain process (S_{RN}) in which step (1) is an initiation step and steps (4) and (5) comprise the propagation sequence.

Scheme 1

$$R\text{-}X + Nu^{-} \longrightarrow R\text{-}X^{\bullet -} + Nu\bullet \quad (1)$$

$$R\text{-}X^{\bullet -} \longrightarrow R\bullet + X^{-} \quad (2)$$

$$R\bullet + Nu\bullet \longrightarrow R\text{-}Nu \quad (3)$$

$$R\bullet + Nu^{-} \longrightarrow (R\text{-}Nu)^{\bullet -} \quad (4)$$

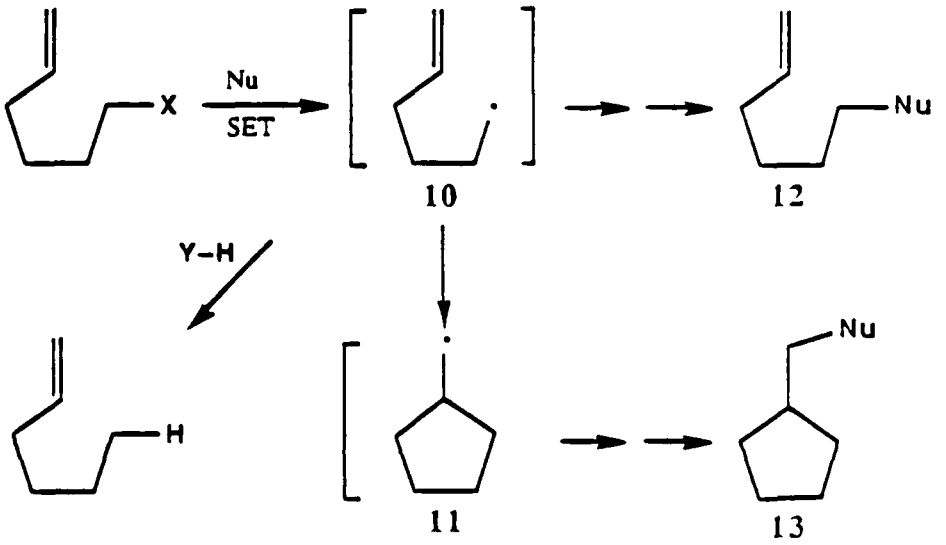
$$(R\text{-}Nu)^{\bullet -} + R\text{-}X \longrightarrow R\text{-}Nu + R\text{-}X^{\bullet -} \quad (5)$$

The results of alkenyl halide cyclizable probe studies have been widely cited in support of mechanisms of the general type outlined in Scheme 1.[4,5] An example of this analysis is outlined in Eq. 4. A hexenyl halide "cyclizable probe" (**3a**, **3b** or a related molecule) is permitted to react with a nucleophile or reducing agent. The ratio of acyclic product **12** to cyclic product **13** is determined. It has been assumed that the observation of cyclic products in such an experiment provides *prima facie* evidence for the operation of an SET mechanism since the cyclic product **13** must result from the intermediate radical **11**. Furthermore, it is often assumed that the yield of **13** provides a direct measure of the ***minimum*** SET component in the reaction. Such a qualitative analysis is correct only if the intermediate radicals **10** and **11** are on the *direct* reaction path to the substitution products **12** and **13**.

Similarly, the qualitative application of probe halides in the detection of SET processes would be fruitless if radical--molecule/ion reactions (cf. [step 4]) were fast relative to the rate of radical rearrangements. In such a case, large numbers of radicals could be formed but only small amounts of rearrangement products would be detected. Speculating that radical--molecule reactions are fast, the authors of some probe studies have concluded that electron transfer reactions

between a nucleophile and a class of alkyl halides was the major reaction pathway even when rearranged products were not observed in high yields.

In addition to the observation of cyclic products, reactions conducted in the presence of hydrogen atom donors (YH), have been cited as evidence for the intermediacy of radicals related to **10** and **11**, and by implication, evidence for the SET path. Here, it is assumed that the interception of unrearranged radicals by the H-atom donor is rapid relative to rearrangement.



Eq. 4

Whether the assumptions cited above, or the other steps demanded by the mechanisms outlined in Scheme 1, are reasonable has not been carefully examined. In some cases, direct evidence to the contrary exists. Their is now good reason to believe that free radical intermediates may be formed which are not on the direct pathway between reactants and products, that the reaction of certain hydride reducing agents with organic radicals [step (4), Scheme 1] is not a facile reaction, and that certain widely employed hydrogen donors do not react sufficiently rapidly to quantitatively intercept even relatively slow alkenyl probe radicals before rearrangement.

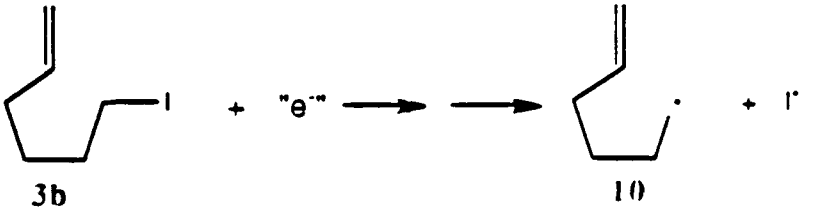
Qualitative Considerations

An alternative to the Eq. 4 mechanism for the formation of cyclic products is presented for hexenyl iodide (**3b**) in Scheme 2. Radical **10** can be generated from **3b** [step (1)] by an electron transfer step, followed by loss of iodide, as outlined in Eq. 4. Hexenyl radical cyclization

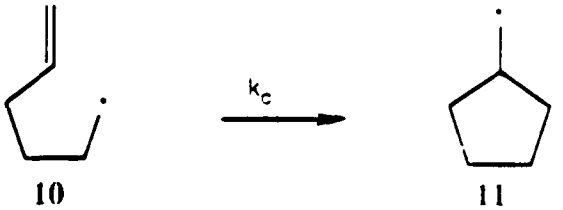
[step(2)] generates **11**. Now, radical **11** can abstract an iodine atom from *any* alkyl iodide present in the reaction mixture. The S_H2 iodine atom transfer from **3b** to **11**, shown in step (3), is a productive event which transfers the chain, providing the cyclic iodide **14** and the starting radical **10**. Iodine atom transfer must be reversible since the C–I bond strengths and the stabilities of the radicals involved are essentially equal. Assuming that k_I is sufficiently rapid, so that all the alkyl iodides in the reaction are in equilibrium, the result is isomerization of **3b** to **14** by a chain process in which step (1) is only an initiation step. In a slower step (4), the cyclic iodide **14** may then react with the reagent under study by a polar process to provide the cyclic product **13**.

While the cyclic product is formed via the intermediacy of a radical, a single electron transfer mechanism for the formation of **13** is not demanded. Since the electron transfer reaction [step (1)] is only an initiation step in the chain, a few initiation events will suffice to provide a large amount of cyclic product. In this scenario, the yield of cyclic products may be only remotely related to the "SET component" of the reaction because the result of each single electron transfer step is multiplied many times by the ensuing propagation sequence [steps (2) and (3)]. While the initiation may result from SET from the reagent under study, the amount of initiator required could be so limited that trace contaminants of the reaction mixture might be responsible for the initiation step.[15]

Scheme 2

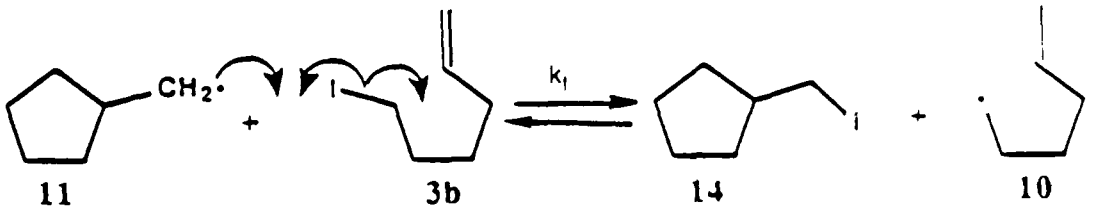


(1)

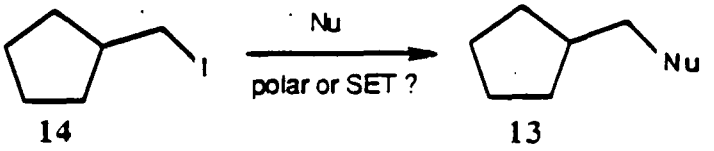


(2)

Scheme 2, cont.



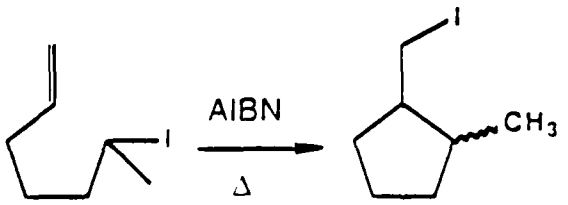
(3)



(4)

For the proposal outlined in Scheme 2 to be operative, the rate of the isomerization of **3b** to **14** must be greater than the direct reaction of the nucleophile with the organic halide. While the rates of propagation steps in a radical sequence can usually be defined with reasonable accuracy, determination of the overall rate of a radical process requires a knowledge of the number and nature of initiation and termination events. Quantitative discussions which support the postulate put forth in Scheme 2 are reserved for the next section. Qualitative indications that the proposed chain reaction is indeed rapid were reported more than twenty years ago.

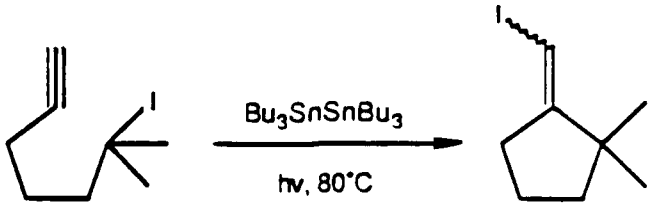
In 1966, during an investigation of the mechanism of polymerization of 1,6-heptadiene, Brace studied the isomerization of 2-iodo-1-heptene (**15**) to (iodomethyl)cyclopentane **16** (Eq. 5). He reported that simple heating of **15** with a catalytic amount of AIBN resulted in the formation of **16** in 75 % yield.[16] The success of this reaction implies that a facile equilibrium between alkyl radicals and alkyl iodides must exist through the intermediacy of iodine atom transfer. Elegant experiments by Hiatt and Benson,[17] and later Castelhano and Griller,[18] relied on the equilibrium of alkyl radicals in the presence of alkyl iodides by means of a rapid iodine atom transfer.[19]



Eq. 5

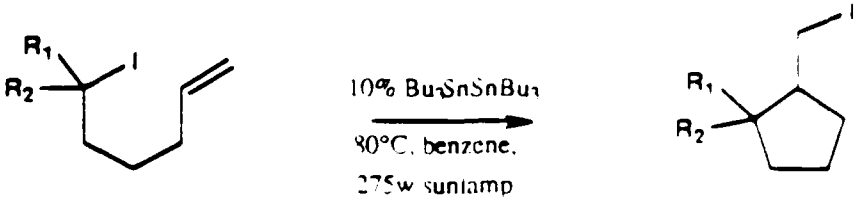
15 16

In 1986, Curran, Kim and Chen reported that the isomerization of alkynyl iodides to (iodomethylene)cyclopentanes in the presence of a catalytic amount of a hexaalkylditin was a facile and synthetically useful process (Eq. 6).[20] The rate constant for the key iodine atom transfer from the alkyl iodide to the vinyl radical was found to approach the diffusion controlled limit. The importance of the donor capability of the alkyl iodides was apparent since the corresponding bromides failed to undergo the isomerization reaction. This is because the halogen atom transfer step is retarded by the strength of the carbon-bromine bond.



Eq. 6

The success of this reaction prompted the investigation of the isomerization of the related alkenyl iodides (Eq. 7).[21] While heating hexenyl iodide **3b** with AIBN according to the report of Brace resulted in the formation of only trace amounts of (iodomethyl)cyclopentane, irradiation of a solution of **3b** and 10% hexabutylditin resulted in the formation of significant amounts **14**. At 90% conversion, the GC yield of **14** reached a maximum of 72% before beginning to decline as the reaction neared completion. In addition, a 1.5% yield of cyclohexyl iodide was also indicated by GC. This is identical to the known 50/1 partitioning of the 5-hexenyl radical between 5-exo and 6-endo modes of cyclization. Similar results were obtained for the isomerization of the 3°-iodide **17** and a 75% maximum GC yield of **18** was indicated, again at about 90% conversion. In a preparative experiment, **18** was isolated in 45% yield.



Eq. 7

3b	$R_1=R_2=H$	**14**	
15	$R_1=CH_3$, $R_2=H$	**16**	
17	$R_1=R_2=CH_3$	**18**	

That these reactions succeed indicates that the alkyl iodide pool is continually equilibrated via iodine atom exchange between radicals and alkyl iodides as indicated by the mechanism outlined in Scheme 2. The abstraction of iodine atoms from alkyl iodides by alkyl radicals is a facile process which must be more rapid than other reactions such as hydrogen atom abstraction from the solvent (benzene) or the reactants, or addition to the solvent. Considering the rate of a typical S_N2 reaction and the rates of the propagation steps in Scheme 2, it can be estimated that a few initiation events could cause substantial isomerization of an alkenyl iodide to a cyclic iodide in a typical cyclizable probe study.

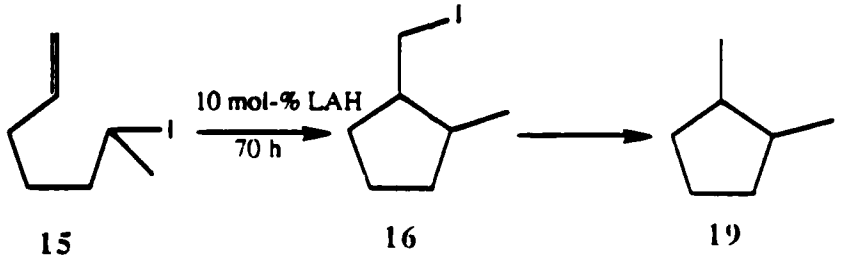
Common observations of the cyclizable probe experiments are readily interpreted by this atom transfer mechanism. For example, maximum amounts of cyclic products are always formed with alkyl iodide probes. On occasion, alkyl bromides provide trace amounts of cyclic products but alkyl chlorides or alkane sulfonates never provide cyclic products. In the past, these observations have been interpreted in terms of reduction potentials. However, the controlling factor in the formation of cyclic products in SCheme 2 is the halogen atom donor capability of the starting halide. Only alkyl iodides donate halogen rapidly enough to propagate the chain. In addition, it is not uncommon to see contrasting results reported from apparently similar experiments. This may be attributed to the importance of the initiation step in the sequence. Small variations in purity of reagents or reaction conditions could affect the number of initiation events which will then be multiplied by the chain length when translated to the final ratio of acyclic to cyclic products.

The mechanism for formation of cyclic products outlined in Scheme 2 permits clear-cut and testable predictions. It demands the accumulation of the cyclic iodide **14** in the reaction medium, provided that the starting iodide and the cyclic iodide are of comparable polar reactivity with the reagent under study.[22] This observation has already been reported by Ashby on several occasions (Eq. 8). For example, treatment of iodide **15** with 10 mol-% LAH for 70 h resulted in conversion to (iodomethyl)cyclopentane (**16**) in 70% yield.[4b] The similarity of this result to the Bruce report is striking. LAH (or a contaminant) simply initiates the isomerization of **15** to **16**. In a slower

reaction, the cyclic iodide **16** can be reduced to 1,2-dimethylcyclopentane (**19**) if sufficient reducing agent is present. Clearly then, most of the final reduced product is produced via the intermediacy of **16**. Related observations have been made with cyclooctenyl iodide **20** which was obseved to isomerize to **21**.[4c,d]

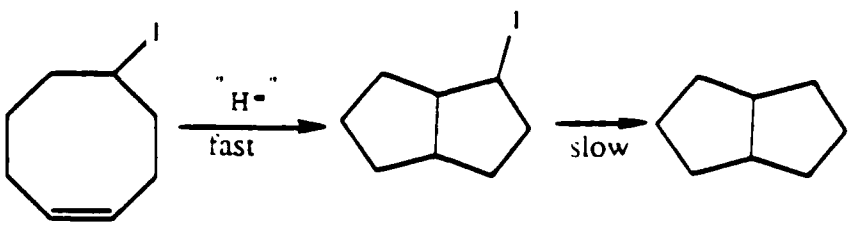
Ashby and co-workers recognized that the intermediacy of products related to **16** compromised the conclusion that the reactions proceeded by SET, and they postulated the correct mechanism for formation of **16**.[4b-d] However, it was still concluded that an SET mechanism was operative in the conversion of **16** to **19**, based in part upon experiments conducted in the presence of hydrogen atom donors. The details of the conversion of **16** to **19** aside, it is now clear that the "cyclizable probe" is not really probing for an SET mechanism. While the heptenyl radical is undoubtedly involved in the conversion of **15** to **16**, it is not on the direct pathway to **19**, but is merely an intermediate in the "pre-equilibration" of the alkyl iodide pool.

We emphasize that *the ineffectiveness of a "cyclizable probe" in providing evidence for an SET mechanism is in no way proof that a polar mechanism is operating*. Whether, the conversion of **16** to **19** occurs by a polar or SET process is an open question. We argue that the use of precursors such as **15** in these experiments provides quite limited information.[23] It actually complicates the interpretation of the experimental data.



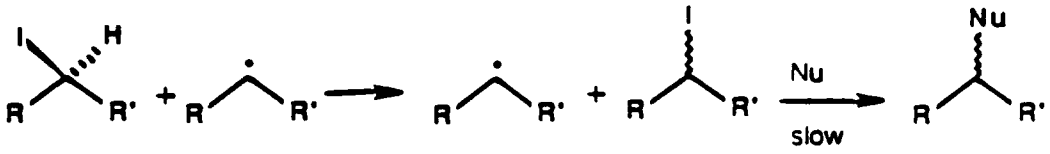
15 **16** **19**

Eq. 8



20 **21**

Other conclusions can be drawn from the mechanism in Scheme 2. Since the generation of trace amounts of alkyl radicals should effect the equilibration of all alkyl iodides in the reaction (both cyclic and acyclic), the mechanism demands racemization of an optically active 2°-iodide prior to nucleophilic substitution (Eq. 9). Thus, the use of optically active alkyl iodides as stereochemical probes should be avoided unless it can be demonstrated that the reaction under study is more rapid than the radical chain equilibration.

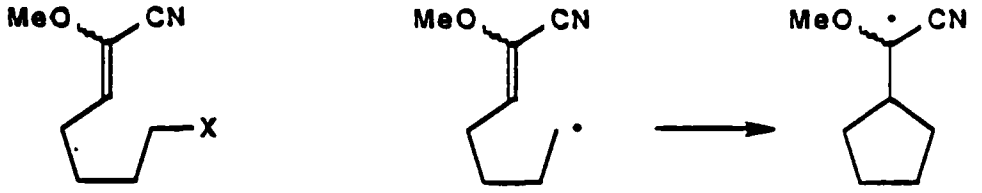


Eq. 9

Finally, the facility of the atom transfer step will be dramatically effected by the relative stability of the starting versus cyclic radicals. Thus, the atom transfer step can be accelerated by designing systems in which the product radical is *less* stable than the starting radical. Iodine atom transfer will be significantly exothermic and useful preparative procedures can result.[20] In the systems studied previously as SET probes, iodine atom transfer is (nearly) thermoneutral. Alternatively, if the product radical is *more* stable than the starting radical, iodine atom transfer will be endothermic and should be retarded.

Thus, if the mechanism outlined in Scheme 2 is correct, the incorporation of radical stabilizing groups into the "cyclizable probe" should actually reduce the amount of cyclic products formed (even if they accelerate the cyclization!) by not permitting the chain propagation by iodine atom transfer,. This prediction has recently been confirmed by Newcomb, Chung and Park[24] in the reaction of various hydride reducing agents with halides 22. Radical 23 cyclizes to 24 at a rate >100 times that of the parent 5-hexenyl radical.[25] Any radical 23 formed in the reduction of 22 should rapidly cyclize to 24. However, since 24 is a capto-dative radical, it would not be expected to abstract a halogen atom from 22. This effectively subverts the chain reaction of Scheme 2 for formation of cyclic product. Indeed, the reaction of 22 with various hydride reducing agents gave acyclic dehalogenated products but gave no products derived from 24. It can

be concluded that SET from the hydride reagents to form intermediate free radical 23 must occur in less than 0.1% of the reactions.



Eq. 10

22 X = I, Br 23 24

Kinetics of Radical Reactions

Despite the quantitative information inherently available from well-calibrated radical clocks, many mechanistic probe studies have employed these tools only in a qualitative sense. That is, the object of the studies was to observe products arising after radical rearrangements. Often this approach was justified because, although the rate constants for the radical rearrangement may have been known, the rate constants for a variety of radical-molecule reactions were not available. However, as we have noted, the qualitative application of probe halides can result in confusing results when radical chain reactions compete. If kinetic results had been available, such speculation would not have been necessary, and qualitative conclusions concerning the extent of electron transfer might have been made.

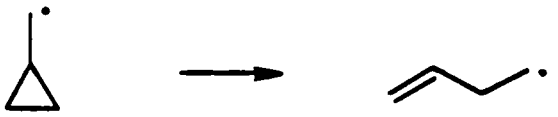
Over the past few years, several studies have provided kinetic information that is important in understanding the details of reactions occurring in radical probe experiments. In this section we have collected representative rate constants for several types of radical reactions. With these rate constants, one can determine whether mechanistic probe studies of potential SET reactions or other reactions involving radical intermediates would give meaningful results.

Radical Rearrangements: Among the reactions of interest for this Account, the radical rearrangements are the best studied. Compilations of radical rearrangement rate constants are available.[7] Representative rate constants are given in Table I. A widely used radical rearrangement

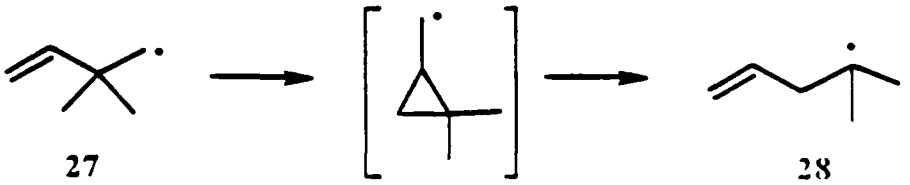
probe has been the 5-hexenyl cyclization: this reaction is also among the slowest radical rearrangements employed in probe studies.

-INSERT TABLE I- (contains references 26, 27, 28, 29, 30)

Another common probe reaction has been the cyclopropylcarbinyl ring opening. Despite the fact that this reaction is among the fastest known radical skeletal rearrangements, cyclopropylcarbinyl halides probably should not be employed as qualitative mechanistic probes. These halides rearrange to butenyl products via processes that involve cationic,[31] anionic,[32] and radical intermediates. They can even give butenyl products via processes in which no free intermediates are formed.[33] Given the multitude of pathways available for conversion of a cyclopropylcarbinyl probe to a butenyl product, one should employ the radical ring opening only as a "clock"[8] in reactions known to proceed via radical intermediates.

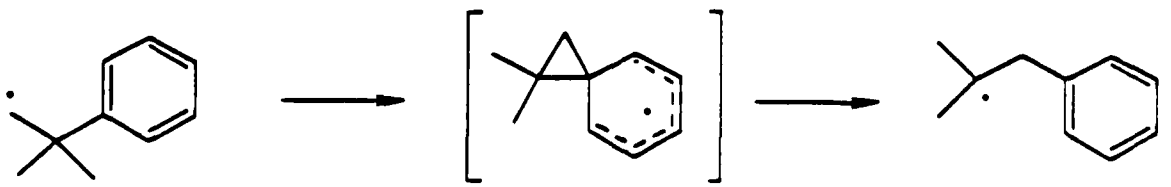


25 26



27 28

10 11



29 30

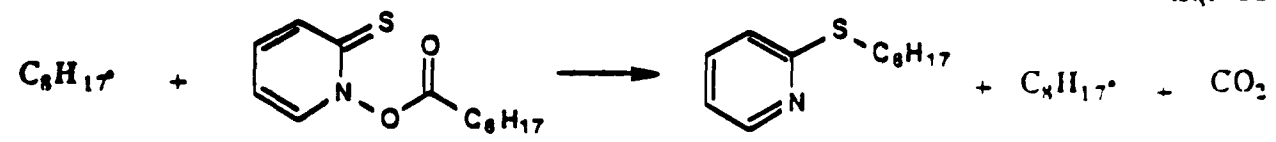
Rate Constants for Halogen Atom Transfer: As noted, qualitative evidence that iodine atom transfer from an alkyl iodide to an alkyl radical is a fast reaction was available in the literature.[16-19] Rate constants for reactions of phenyl radicals with alkyl iodides and bromides have been reported to be quite fast (see Table II), and generally phenyl radicals react only about three order of magnitude faster than alkyl radicals with a variety of substrates.[34] Newcomb *et. al.*[35] have recently studied the rates of reaction of octyl radicals with various alkyl halides at 50 °C. The results of these studies are also collected in Table II. The order of reactivities found was predictable; the alkyl halides reacted in the order RI > RBr > RCl and 3° > 2° > 1°.

-INSERT TABLE II- (contains references 36, 37)

Rate Constants for S_H2 Hydrogen Atom Transfer: If alkyl radicals are formed as intermediates via SET reactions, then they could be reduced to alkanes by abstracting hydrogen atoms from solvent. Most "probe" studies of reactions of nucleophiles with an alkyl halide have been conducted in ethereal solvents such as THF. Since α-alkoxy radicals formed from ethers are relatively stable, it has been assumed that hydrogen atom abstraction from ethers was an important reaction in these studies. Alkyl radicals could also be reduced by hydrogen atom donation from a trapping agent intended to intercept these intermediates; dicyclohexylphosphine (DCPH)[38] and 1,4-cyclohexadiene (CHD) have been used.

Despite the stability of the radicals formed by hydrogen abstraction from ethers or trapping agents, little was known about the kinetics of these reactions. In an attempt to provide quantitative information about these rate constants, Newcomb and Park measured the rates of reactions of two alkyl radicals, 5-hexenyl (**10**) and 2,2-dimethyl-3-butenyl (**27**), with various hydrogen atom donors using the radical clock method.[39] Some results are given in Table III. The rate constants for reactions of radicals with THF (pseudo first order in solvent THF) were estimated by competition between reduction of the radical by THF and addition of the radical to its precursor *N*-hydroxypyridine-2-thione ester; the rate constant for reaction of octyl radical with its parent ester **31** has recently been reported by Newcomb and Kaplan (Eq. 11).[40]

Eq. 11



31

-INSERT TABLE III- (contains references 41, 42)

The results in Table III demonstrate that, regardless of the stability of the product radical, hydrogen atom abstraction reactions are sluggish. THF reacts so slowly with alkyl radicals that essentially all radical rearrangements used as probes to date are unaffected by THF. Thus, if a significant yield of reduced-unrearranged products is formed from the reaction of a probe alkyl halide with a nucleophile in an ethereal solvent, these products did not arise from the reaction of radical intermediates with solvent.

From the rate constants for reactions of the trapping agents DCPH and CHD one sees that these reagents donate hydrogen too slowly to prevent substantial skeletal rearrangements of probe radicals. When the probe rearrangement is the (relatively) slow cyclization of 5-hexenyl, DCPH at 1.0 M concentration is required to trap 50-60% of the radicals before rearrangement. DCPH reacts with a primary radical with about the same rate constant as does an alkyl iodide, and, at appropriately high concentrations, DCPH can intercept an alkyl radical and may effectively derail Scheme 2. However, we do not know the fate of the phosphorus centered radical thus formed; Ashby has suggested that this radical can react with another alkyl halide via halogen abstraction (Eq 12).[5d] This would introduce another competing chain reaction into a given probe experiment.

$$(c\text{-}C_6H_{11})_2P\bullet + RI \longrightarrow (c\text{-}C_6H_{11})_2PI + R\bullet \qquad \text{Eq. 12}$$

Rate Constants for S_H2 Reactions of Hydride Donors with Alkyl Radicals: Of the nucleophiles that have been investigated for potential SET reactions with alkyl halides, hydride donors are the best understood. For a simple alkyl radical reacting with a hydride donor, one can exclude an S_{RN} pathway (Eq 13) since the product (R-G-H)• would be a radical anion with an electron in a high energy σ^* orbital. If hydride donors are to react in chain reactions with

$$R\bullet + M^+(G\text{–}H)^- \not\longrightarrow M^+(R\text{–}G\text{–}H)^{-\bullet} \qquad \text{Eq. 13}$$

alkyl halides, the chain sequence must be that shown in Scheme 3. Steps (1) and (2) comprise the chain sequence when a neutral main group metal hydride such as R_3SnH or R_3GeH reduces an alkyl halide. The last step (3) shown in Scheme 3 is not required for the radical chain process and may or may not occur depending on the nature of the salt $M^+(G\text{-}X)^-$.

Scheme 3

$$R\bullet + M^+(G\text{–}H)^- \longrightarrow R\text{–}H + M^+G^{-\bullet} \qquad (1)$$

$$M^+G^{-\bullet} + R\text{–}X \longrightarrow M^+(G\text{–}X)^- + R\bullet \qquad (2)$$

$$M^+(G\text{–}X)^- \longrightarrow M^+X^- + G \qquad (3)$$

M = alkali metal, G = main group or transition metal

The mechanisms of reactions of alkyl halides with two classes of metal hydrides, transition metal hydride anions and Group III metal hydrides, have been studied with an eye to uncovering SET or radical processes. The transition metal hydride anion $CpV(CO)_3H^-$ was shown by Bergman to form radicals at least in part in reactions with R-X,[43] and more recently Darensbourg *et al.*[44,45] have provided evidence that a variety of transition metal hydride anions reduce alkyl halides rapidly by processes that can involve radicals. Kinetics of reactions of some transition metal hydride anions with alkyl bromide probes were studied by Ash, *et al.*[46] Using the rearrangements of radicals **10** and **27** as clocks, they found that two competing pathways, direct nucleophilic displacement and the radical chain reduction of Scheme 3, occurred. Rate constants for reactions for these transition metal hydride anions with alkyl radical **27** are given in Table IV. From these rate constants, one can conclude that, in a typical reaction of an alkyl halide with a transition metal hydride anion, hydrogen abstraction by an alkyl radical will probably be so fast that radical chain isomerization of the probe cannot compete. In addition, S_N2 reactions of transition metal hydride anions with unhindered alkyl halides are quite fast.[44–46] The initiation reactions for radical chain reduction of alkyl halides by transition metal hydride anions may involve an SET step, but since chain lengths for the S_H2 processes are not known, the extent of SET cannot yet be estimated.

The situation with Group III metal hydrides, $LiAlH_4$ and $NaBH_4$ and related reducing agents, is quite different. Several reports of SET in reactions of these reagents with alkyl halides based on the observation of probe rearranged products have appeared,[5] but in all cases the occurrence of SET should be reconsidered. Scheme 2, the radical chain isomerization of an alkyl halide probe, apparently can compete effectively in these reactions to produce substantial amounts of rearranged alkyl halides that can subsequently be reduced. The important rate constants for reaching this conclusion are those for reactions of the archetypal reagents with alkyl radicals (see Table IV). Russell and Guo showed that $NaBH_4$ reacted with 5-hexenyl radical (**10**) too slowly to prevent cyclization.[47] The rate constant for reaction of $LiAlH_4$ with an alkyl radical was derived by Park *et al.*[24] from the results of a study by Beckwith and Goh in which photo-initiated reductions of alkyl halides, including neophyl chloride, by $LiAlH_4$ were reported[48] and from the known rate of rearrangement of the neophyl radical (**29**).[30] Since the Group III metal hydrides cannot intercept an alkyl radical faster than it will abstract iodine atom from the alkyl iodide and because the overall nucleophilic substitution rates for reactions of these hydrides with alkyl halides are slow,[49] radical chain isomerization of alkyl iodide probes can be extensive in these reactions.

-INSERT TABLE IV-

Addition of Radicals to Nucleophiles (S_{RN}): A radical can add to an anionic nucleophile to give a radical anion product [Scheme 1, step (4)]. When alkyl halides are being studied, a subsequent one electron oxidation of the radical anion [Scheme 1, step (5)] could occur. These two steps comprise the chain sequence in an S_{RN} reaction mechanism. This sequence represents yet another potential problem in the qualitative application of alkyl halide probes; specifically, if an S_{RN} pathway exists for substitution, then *a small amount of initiation could lead to a substantial amount of radical formation if the chain reaction sequence has an appreciable length.* This possibility has seldom been addressed in qualitative studies of alkyl halide reactions with nucleophiles even when the addition of a radical to an anion [Scheme 1, step (4)] has been postulated.

The rates of addition of simple radicals to anions are not well understood, and progress in this area is required for quantitative treatments of potential SET reactions of alkyl halides. Important results in this area have come from Russell's laboratory, and some generalizations can be made. Low lying antibonding orbitals must be available in the radical anion product of step (4) [Scheme 1] so that the reaction is energetically feasible. The initial delocalization can originate on the radical or the nucleophile. For example, simple alkyl radicals add to nitronate anions but not to $(EtO)_2PO^-$ or $(EtO_2C)_2CR^-$,[50] whereas 2-nitro-2-propyl radical adds to all of these nucleophiles with comparable rates.[51]

In Russell and Khanna's studies of reactions of *tert*-butylmercuric chloride with carbanions, no simple relationship between anion structure or basicity and the rate of *tert*-butyl radical addition to the anion was found.[52] Assuming that *tert*-butyl radical adds to $Me_2C{=}NO_2^-$ with a rate constant equal to that for addition of the 5-hexenyl radical (**10**) to the same anion, approximate rates of addition of *tert*-butyl to several anions can be calculated from Russell and Khanna's results. Table V contains some examples. As in other radical reactions, aryl radicals are much more reactive than alkyl radicals in additions to anions as shown by the examples in Table V for two representative aryl radicals.

-INSERT TABLE V- (contains reference 53)

Radical-Radical Reactions: If SET between a nucleophile and an alkyl halide were to occur, then one radical would result from the nucleophile (Nu•) and one from the alkyl halide (R•). In some mechanistic studies it has been stated or implied that substitution products could form by coupling of these radicals [Scheme 1, step (3)]. There are two sets of conditions for which one should consider the possibility of radical-radical coupling reactions: (1) reactions occurring in solvent cages and (2) reactions involving free radicals. In either case, substantial amounts of rearranged substitution products in probe studies are not expected to arise from radical-radical coupling.

Where radical couplings occur in solvent cages, it is necessary that coupling be faster than the rate of diffusion. Since skeletal rearrangements of radicals are substantially slower than

diffusion, it is not possible for a mechanistic probe to give a rearranged product via radical coupling in the solvent cage. That is, mechanistic probe halides cannot give useful information for a reaction in which *free* radicals are not formed. The timing of one electron versus two electron processes in nucleophilic substitution reactions occurring within solvent cages remains an interesting problem; such reactions can be characterized by the application of Marcus theory and related approaches.[54]

When free radicals are formed in reactions of nucleophiles with alkyl halides, skeletal rearrangements of probes are possible. However, the formation of rearranged products by the radical-radical coupling in Eq 3 is not likely. If R–Nu arose from radical-radical coupling then R–R, Nu–Nu, and radical disproportionation products would also be expected. Moreover, one can often discount the possibility of radical-radical coupling by simple kinetic analysis. Consider the reaction of a nucleophile and an alkyl iodide probe (initially 0.1 M in both reactants) observed to give 50% yield of rearranged substitution products with a first half-life of 1000 s. In this case, 0.025 M substrate reacted via radical intermediates in 1000 s, or the velocity of the reactions involving radicals was 2.5×10^{-5} M^{-1} s^{-1}. During this first half-life, S_H2 iodine atom transfer ($k_{RI} > 2 \times 10^5$ M^{-1} s^{-1})to a rearranged radical sets the upper limit on the radical lifetime: since the mean concentration of RI was 0.075 M, that lifetime is:

$$\tau = 1/(k_{RI} \times [RI]) = < 7 \times 10^{-5} \text{ s.}$$

The mean concentration of radicals over the first half-life is given by the product of the velocity of the radical process and the lifetime of the radical; in this example, the mean radical concentration was $< 2 \times 10^{-9}$ M. Now, if SET processes were the origin of R• and Nu•, then an equal concentration of Nu• would have been formed since termination reactions are equally probable for each radical. If the diffusion constant is 1×10^{10} M^{-1} s^{-1}, the velocity of coupling of R• and Nu• is at least three orders of magnitude slower than the observed velocity of the overall reaction.

Conclusions and Recommendations

This account has surveyed the potentials pitfalls which can be encountered in the interpretation of "mechanistic probe" experiments designed to provide evidence for an SET mechanism. While the negative evidence provided by the lack of rearranged products in a probe study is always meaningful, the interpretation of the "positive" evidence provided by the observation of rearranged products is not straightforward. The observation of rearranged products does not justify the conclusion that an SET mechanism is operative.

As noted, the kinetic information now available permits some generalizations to be made regarding the use of alkyl halide probes in the studies of reactions with nucleophiles. Newcomb *et al.* concluded[35] that, due to the fast S_H2 iodine atom transfer rate, radical chain isomerizations of alkyl iodide probes could have chain lengths greater than 100. Thus, iodide probes cannot give useful results for SET studies unless the reaction of interest is fast (half-life 10 s or less). Fast reactions which proceed by SET will require the concentration of radicals to become high permitting radical coulping reactions to occur. Other radical reactions (i. e. S_H2 hydrogen atom transfer or S_{RN} reactions) can be studied conveniently with alkyl iodide probes when the velocity of the competing reaction is greater than that of iodine atom transfer.

The use of alkyl iodide probes solely to provide qualitative evidence (i. e. by the observation of a cyclic product) should be avoided. As a minimum requirement of evidence for SET, a series of probes should be studied to demonstrate that the product ratios correlate with the rates of rearrangement of the series.[55] In the competing atom transfer isomerization outlined in Scheme 2, the ratio of unrearranged to rearranged products depends not on the rate of rearrangement (provided it is not unreasonably slow) but on the viability of the atom transfer step. This can be controlled by the relative stability of the starting and final radicals. To suppress the atom transfer isomerization, probes should be employed in which the rearranged radical is significantly *more* stable than the starting radical.

S_H2 bromine atom transfer is slower than iodine atom transfer. Hence, the bromide probes are more useful. Radical isomerization chain lengths with bromides may be short. The formation

of R–Nu could possibly be accounted for by radical coupling.[56] Of course, other radical-radical reactions will also compete. However, if the overall velocity of the reaction of interest is quite slow (half-life ~hours), then the alkyl bromide probes will not be useful for SET studies because radical-radical couplings will fail to compete with simple chain transfer reactions. Because of the slow rates of S_H2 chlorine atom transfer, an alkyl chloride would not be expected to give an appreciable amount of product by the pathway outlined in Scheme 2.

In qualitative SET studies, we recommend the use of alkyl bromides and chlorides; alkyl iodide probes should be avoided in the absence of quantitative kinetic information. As noted above, it has not escaped our attention that there are cases where alkyl iodide probes give rearranged products in an SET probe study but alkyl bromides and chlorides give little or no rearrangement. We suggest in these cases that the evidence that SET processes represent a major pathway is not conclusive.

Reactions of nucleophiles with alkyl halides are typically conducted in ethereal solvents. S_H2 hydrogen atom transfer from THF (and, presumably, other ethers) to a radical is not expected to interfere with the use of alkyl halide mechanistic probes. This reaction is too slow to intercept most probe radicals before skeletal rearrangements occur, although S_H2 reaction of a radical with THF can compete with S_H2 halogen atom transfer to give a new chain sequence. If a substantial amount of unrearranged product is detected in a study, it is not appropriate to ascribe the origin of this product to the S_H2 reaction with THF.

The use of mechanistic probes for the detection of SET processes can be accompanied by serious complications. Available evidence on the nature of these complications has been summarized, and guidelines have been presented which are intended to help a reasearcher to avoid drawing erroneous conclusions from the results of past probes studies and to aid in the design of discerning experiments.

Acknowledgements: The work at Texas A&M was supported by the National Science Foundation, the Office of Naval Research, the Robert A. Welch Foundation, and the Petroleum

Research Fund administered by the American Chemical Society. The work at Pittsburgh was supported by the National Institutes of Health. D. P. C. is grateful to the Sloan Foundation for a Fellowship and to the Dreyfus Foundation for Young Investigator Award. Both authors thank the Dreyfus Foundation for Teacher Scholar Awards. The authors thank Professor Paul Dowd for a critical review of the manuscript.

References

1 Pross, A. *Acc. Chem. Res.* **1985**, *18*, 212.

2 For example, see: Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413. Kornblum, N. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 734. Russell, G. A.; Danen, W. C. *J. Am. Chem. Soc.* **1968**, *90*, 347. Kochi, J. K. "Oganometallic Reactions and Catalysis"; Academic Press: New York, 1978.

3 (a) Ashby, E. C.; Argyropoulos, J. N.; *J. Org. Chem.* **1986**, *51*, 3593. (b) Ashby, E. C.; Argyropoulos, J. N.; *J. Org. Chem.* **1986**, *51*,472. (c) Liotta, D., Saindane, M., Waykole, L. *J. Am. Chem. Soc.* **1983**, *105*, 2922.

4 Enolates: (a) Ashby, E. C.; Argyropoulos, J. N. *Tetrahedron Lett.* **1984**, *25*, 7. (b) Ashby, E. C.; Argyropoulos, J. N. *J. Org. Chem.* **1985**, *50*, 3274. Cuprates: (c) Ashby, E. C.; DePreist, R. N.; Tuncay, A.; Srivastava, S.*Tetrahedron Lett.* **1982**, *23*, 5251. Stannyl alkalis: (d) Ashby, E. C., DePreist, R. N. *J. Am. Chem. Soc.* **1982**, *104*, 6144. (e) Lee, K.-W.; San Filippo, J., Jr.*Organometallics* **1983**, *2*, 906. (f) Ashby, E. C., DePreist, R. N., Su, W.-Y *Organometallics* **1984**, *3*, 1718. (g) Ashby, E. C., Su, W.-Y., Pham, T. N. *Organometallics* **1985**, *4*, 1493. (h) Alnajjar, M. S., Kuivala, H. G. *J. Am. Chem. Soc.* **1985**, *107*, 416. Alkoxides: (i) Ashby, E. C., Bae, D.-H., Park, W.-S., DePreist, R. N., Su, W.-Y *Tetrahedron Lett.* **1984**, *25*, 5107.

5 (a) Ashby, E. C.; Depriest, R. N., Pham, T. N. *Tetrahedron Lett.* **1983**, *24*, 2825. (b) Ashby, E. C., Depriest, R. N.; Goel, A. B.; Wenderoth, B., Pham, T. N. *J. Org. Chem.*

1984, *49*, 3545. (c) Ashby, E. C.; Wenderoth, B.; Pham, T. N.; Park, W.-S. *J. Org. Chem.* **1984**, *49*, 4505. (d) Ashby, E. C.; Pham, T. N. *J. Org. Chem.* **1986**, *51*, 3598.

6 (a) Bailey, W. F.; Gagnier, R. P.; Patricia, J. J. *J. Org. Chem.* **1984**, *49*, 2098. (b) Ashby, E. C.; Pham, T. N.; Park, B. *Tetrahedron Lett.* **1985**, *26*, 4691. (c) Ashby, E. C.; Pham, T. N. *J. Org. Chem.* **1987**, *52*, 1291.

7 General references to free radical clocks: (a) Beckwith, A. L. J.; Ingold, K. U. in "Rearrangements in Ground and Excited States", deMayo, P., Ed.; Academic Press; NY, **1980**; Vol. 1, Essay 4. (b) Surzur, J. M. in "Reactive Intermediates", Abramovitch, R. A.; Ed.; Plenum Press; NY, **1981**; Vol. 2, Chapter 2.

8 We wish to draw a clear distinction between the use of intramolecular radical rearrangements as "free radical clocks" or as "mechanistic (or cyclizable) probes". The former provides quantitative information about the rate of a process known to proceed via a free radical intermediate by competition of this reaction with a rearrangement of known rate. The latter attempts to provide qualitative evidence that a mechanism under study proceeds via the intermediacy of a free radical.

9 For a recent compilation of references, see references 6b and 6c.

10 Indeed, two equivalents of t-butyllithium are often employed in preparative reactions of this nature. However, it has been proposed that the second equivalent of t-butyllithium serves to destroy the t-butyl halide produced in the halogen-metal exchange. Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210. Seebach, D. Neumann, H. *Chem. Ber.* **1974**, *107*, 847.

11 (a) Bailey, W. F.; Patricia, J. J.; DelGobbo, V. C. Jarret, R. M.; Okarma, P. J. *J. Am. Chem. Soc.* **1985**, *107*, 1999. (b) Garst, J. F.; Hines, J. B., Jr. *J. Am. Chem. Soc.* **1984**, *106*, 6443.

12 (a) Bailey, W. F.; Nurmi, T. T.; Patricia, J. J.; Wang, W. *J. Am. Chem. Soc.* **1987**, *109*, 2442. (b) Chamberlin, A. R.; Bloom, S. H. *Tetrahedron Lett.* **1986**, *27*, 551.

13 (a) Bailey, W. F.; Patricia, J. J.; Nurmi, T. T. Wang, W. *Tetrahedron Lett.* 1986, 27, 1861. (b) Bailey, W. F.; Patricia, J. J.; Nurmi, T. T. *Tetrahedron Lett.* **1986**, 27, 1865.

14 A growing body of evidence supports an "ate complex" mechanism. See: Reich, H. J.; Phillips, N. H.; Reich, E. L. *J. Am. Chem. Soc.* **1985**, *107*, 4101.

15 For example, with a chain length of 1000 and the observation of 10% rearrangement product in a study initially employing 0.1 M probe halide, only 1 x 10^{-5} moles of initiator per liter are indicated. If the test reagent was also 0.1 M, then as little as 0.01 mol-% of an impurity in the reagent acting as an initiator could account for all of the rearranged product.

16 Brace, N. O. *J. Org. Chem.* **1967**, *32*, 2711; *Ibid.* **1966**, *31*, 2879.

17 Hiatt, R.; Benson, S. W. *J. Am. Chem. Soc.* **1972**, *94*, 25

18 Castelhano, A. L.; Griller, D. *Ibid.* **1982**, *104*, 3655.

19 Review of halogen atom transfers: Danen, W. C. In *Methods in Free Radical Chemistry*; Huyser, E. S., Ed.; Marcel Dekker, New York, 1974; Vol. 5 pp 1-100

20 Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1986**, *108*, 2489

21 Curran, D. P.; Kim, D. *Tetrahedron Lett.* **1986**, *27*, 5821.

22 If the cyclic iodide is of greater polar reactivity than the starting iodide, it could conceivably consumed as fast as it is produced. In such as case, the intermediate cyclic iodide, although an actual intermediate, could not be detected.

23 On the other hand, the absence of cyclic products is always informative. This proves that a *free* radical with a lifetime greater than the probe rearrangement rate is not formed.

24 Park, S.-U, Chung, S.-K., Newcomb, M. E. *J. Org. Chem.* **1987**, *52*, 3000.

25 Park, S.-U, Chung, S.-K., Newcomb, M. E. *J. Am. Chem. Soc.* **1986**, *108*, 240

26 Mathew, L.; Warkentin, J. *J. Am. Chem. Soc.* **1986**, *108*, 7981.

27 Newcomb, M.; Williams, W. G. *Tetrahedron Lett.* **1985**, *26*, 1179. See ref. 28

28 The original values for these reactions were recalculated using the recently reported rate for the reactions of neopentyl radical with *n*-Bu_3SnH as the model reaction. cf. Johnson, L. J.

Lusztyk, J.; Wayner, D. D. M.; Abeywickreyma, A. N.; Beckwith, A. L. J.; Scaiano, J. C.; Ingold K. U. *J. Am. Chem. Soc.* **1985**, *107*, 4594.

29 Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C*J. Am. Chem. Soc.* **1981**, *103*, 7739.

30 Franz, J. A.; Barrows, R. D.; Camaioni, D. M. *J. Am. Chem. Soc.* **1984**, *106*, 3964; see ref. 28.

31 Wiberg, K. B.; Hess, A., Jr.; Ashe, A. J., III in "Carbonium Ions;" Olah, G. A.; Schleyer, P. V. R., Eds.; John Wiley & Sons: New York, 1972; Vol. 3, Chapter 26.

32 Hunter, D. H.; Stothers, J. B.; Warnhoff, E. W. in "Rearrangements in Ground and Excited States;" Mayo, P. D., Ed.; Academic Press: New York, 1980; Vol. 1, Essay 6.

33 Alnajjar, M. S.; Smith, G. F.; Duivila, H. G. *J. Org. Chem.* **1984**, *49*, 1271. Newcomb, M.; Smith, M. G. *J. Organomet. Chem.* **1982**, *228*, 61

34 Johnson, L.J.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1984**, *106*, 4877.

35 Newcomb, M.; Sanchez, R. M.; Kaplan, J. *J. Am. Chem. Soc.* **1987**, *109*, 1195.

36 Kryger, R. G.; Lorand, J. P.; Stevens, N. R.; Heron, N. R. *J. Am. Chem. Soc.* **1977**, *99*, 7589.

37 Scaiano, J. C.; Stewart, L. C. *J. Am. Chem. Soc.* **1983**, *105*, 3609.

38 Smith, G. F.; Kuivila, H. G.; Simon, R.; Sultan, L. *J. Am. Chem. Soc.* **1981**, *103*, 833.

39 Newcomb, M.; Park, S.-U. *J. Am. Chem. Soc.* **1986**, *108*, 4132.

40 Newcomb, M.; Kaplan, J. *Tetrahedron Lett.* **1987**, *28*, 1615.

41 Hawari, J. A.; Engel, P. S., Griller, D. *Int. J Chem. Kinet.* **1985**, *17*, 1215.

42 Newcomb, M., Kaplan, J. Unpublished results.

43 Kinney, R. J.; Jones, W. D.; Bergman, R. G. *J. Am. Chem. Soc.* **1978**, *100*, 7902.

44 Kao, S. C.; Spillet, C. T., Ash, C.; Lusk, R.; Park, Y. K.; Darensbourg, M. Y. *Organometallics* **1985**, *4*, 83.

45 Ash, C. E., Delord, T., Simmons, D.; Darensbourg, M. Y. *Ibid.* **1986**, *5*, 17.

46 Ash, C. E.; Hurd, P. W.; Darensbourg, M. Y.; Newcomb, M. *J. Am. Chem. Soc.* **1987**, *109*, 0000.

47 Russell, G. A.; Guo, D. *Tetrahedron Lett.* **1984**, *25*, 5239.

48 Beckwith, A. L. J.; Goh, S. H. *J. Chem. Soc., Chem. Commun.* **1983**, 907.

49 Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1980**, *45*, 849; *J. Org. Chem.* **1982**, *47*, 276; *J. Org. Chem.* **1983**, *48*, 3085.

50 Russell, G. A.; Hershberger, J.; Owens, K. *J. Organomet. Chem.* **1982**, *225*, 43.

51 Russell, G. A.; Ros, F.; Mudryk, B. *J. Am. Chem. Soc.* **1980**, *102*, 7601.

52 Russell, G. A.; Khanna, R. K. *Tetrahedron* **1985**, *41*, 4133.

53 Amatore, C.; Oturan, M. A.; Pinson, J.; Saveant, J. M.; Thiebault, A. *J. Am. Chem. Soc.* **1985**, *107*, 3451.

54 Eberson, L. *Adv. Phys. Org. Chem.* **1982**, *18*, 79-185. Eberson, L. *Acta Chem. Scand., B* **1984**, *B38*, 439-459. For a recent example, see Lund, T.; Lund, H. *Ibid.* **1986**,*B40*, 470.

55 For an example of precisely this technique, see: Garst, J. F.; Deutch, J. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1986**, *108*, 2490.

56 For example, in the sample calculation provided above, if an alkyl bromide is substituted for an alkyl iodide with the same constraints otherwise, one concludes that radical coupling would be fast enough to lead to an appreciable amount of R–Nu.

Table I. Rate Constants for Radical Rearrangements at 25 °C.

Reaction	k (s^{-1})	ref.
25 ---> 26	2.1×10^{8}	a
27 ---> 28	6.0×10^{6}	b
10 ---> 11	2.2×10^{5}	c
29 ---> 30	900	d

[a]Reference 26. [b]Reference 27. [c]Reference 29. [d]Reference 30.

Table II. Rate Constants for Halogen Atom Abstractions by Radicals.

Radical	Alkyl Halide	Temp. (°C)	k (M^{-1}, s^{-1})	ref.
phenyl	$(CH_3)_2CHI$	45	1.1×10^9	a
phenyl	$CH_3CH_2CH(CH_3)Br$	25	2.3×10^6	b
octyl	$(CH_3)_3CI$	50	3×10^6	c
octyl	$(CH_3)_2CHI$	50	8×10^5	c
octyl	$c\text{-}C_6H_{11}I$	50	5×10^5	c
octyl	CH_3CH_2I	50	2×10^5	c
octyl	$(CH_3)_3CBr$	50	5×10^3	c
octyl	$(CH_3)_2CHBr$	50	1×10^3	c
octyl	$n\text{-}C_6H_{11}Br$	50	1×10^3	c
octyl	$CH_3(CH_2)_3Br$	50	6×10^2	c
octyl	$(CH_3)_3CCl$	50	6×10^2	c

[a]Reference 36. [b]Reference 37. [c]Reference 35.

Table III. Rate Constants for Hydrogen Atom Transfer Reactions.

H-atom Donor	Radical	Temp. (°C)	k (M^{-1}, s^{-1})	ref.
$(CH_3)_3CSH$	27	32	1.1×10^7	a
$(c\text{-}C_6H_{11})_2PH$	27	27	1.0×10^6	a
	10	50	7×10^5	a
1,4-cyclohexadiene	ethyl	27	5.8×10^4	b
	t-butyl	27	9.4×10^3	b
	27	50	4.8×10^5	a
	10	50	2.3×10^5	a
THF	28	50	2×10^3 (s^{-1})	a
	11	50	6×10^3 (s^{-1})	a
	octyl	0	5×10^3 (s^{-1})	c
	phenyl	25	4.8×10^6	d

[a]Reference 39. [b]Reference 41. [c]Reference 42. [d]Reference 37.

Table IV. Rate Constants for Reactions of Metal Hydrides with Alkyl Radicals.

Metal Hydride[a]	Radical	Temp. (°C)	k (M^{-1} s^{-1})	ref.
$PPN^+HCr(CO)_5^-$	27	25	1.8×10^7	b
$PPN^+HW(CO)_5^-$	27	25	1.0×10^7	b
$PPN^+HW(CO)_4P(OMe)_3^-$	27	25	1.6×10^7	b
$Na^+HW(CO)_4P(OMe)_3^-$	27	25	1.8×10^6	b
$NaBH_4$	10	30	$< 1 \times 10^4$	c
$LiAlH_4$	29	25	ca. 4×10^3	d

[a] PPN^+ = bis(triphenylphosphine)iminium. [b]Reference 46. [c]Reference 47. [d]Reference 48, see text.

Table V. Representative Rate Constants for Addition of Radicals to Nucleophiles.

Radical	Nucleophile	Solvent	Temp. (°C)	k (M^{-1} s^{-1})	ref
$(CH_3)_3C^{\cdot}$	$Me_2C{=}NO_2^-$	DMSO	35	2×10^5	a
	$H_2C{=}NO_2^-$			7×10^6	a
	NO_2^-			8×10^4	a
	$PhCHCN^-$			$<2 \times 10^4$	a
	$PhC(O^-){=}C(CH_3)_2$			6×10^3	a
	$PhC(CO_2Et)_2^-$			4×10^3	a
	$(EtO)_2PO^-$			not observed	b
4-CN-$C_6H_4^{\cdot}$	$(EtO)_2PO^-$	NH_3	-38	1.4×10^9	c
	$CH_3C(O^-){=}CH_2$			2.6×10^9	c
1-naphthyl	$(EtO)_2PO^-$			3.2×10^{10}	c
	$CH_3C(O^-){=}CH_2$			4.2×10^{10}	c

[a]Calculated from the relative rate constants reported in ref. 52; the value for the rate constant of the reference reaction (line 1) was assumed, see text. [b]Reference 50. [c]Reference 53.

DL/1113/87/2

TECHNICAL REPORT DISTRIBUTION LIST, GEN

	No. Copies
Office of Naval Research Attn: Code 1113 800 N. Quincy Street Arlington, Virginia 22217-5000	2
Dr. Bernard Douda Naval Weapons Support Center Code 50C Crane, Indiana 47522-5050	1
Naval Civil Engineering Laboratory Attn: Dr. R. W. Drisko, Code L52 Port Hueneme, California 93401	1
Defense Technical Information Center Building 5, Cameron Station Alexandria, Virginia 22314	12 high quality
DTNSRDC Attn: Dr. H. Singerman Applied Chemistry Division Annapolis, Maryland 21401	1
Dr. William Tolles Superintendent Chemistry Division, Code 6100 Naval Research Laboratory Washington, D.C. 20375-5000	1
Dr. David Young Code 334 NORDA NSTL, Mississippi 39529	1
Naval Weapons Center Attn: Dr. Ron Atkins Chemistry Division China Lake, California 93555	1
Scientific Advisor Commandant of the Marine Corps Code RD-1 Washington, D.C. 20380	1
U.S. Army Research Office Attn: CRD-AA-IP P.O. Box 12211 Research Triangle Park, NC 27709	1
Mr. John Boyle Materials Branch Naval Ship Engineering Center Philadelphia, Pennsylvania 19112	1
Naval Ocean Systems Center Attn: Dr. S. Yamamoto Marine Sciences Division San Diego, California 91232	1

DL/1113/87/2

ABSTRACTS DISTRIBUTION LIST 053

Dr. M. F. Hawthorne
Department of Chemistry
University of California
Los Angeles, California 90024

Professor O. T. Beachley
Department of Chemistry
State University of New York
Buffalo, New York 14214

Dr. W. Hatfield
Department of Chemistry
University of North Carolina
Chapel Hill, North Carolina 27514

Professor R. Wells
Department of Chemistry
Duke University
Durham, North Carolina 27706

Professor K. Neidenzu
Department of Chemistry
University of Kentucky
Lexington, Kentucky 40506

Dr. Herbert C. Brown
Department of Chemistry
Purdue University
West Lafayette, IN 47907

Dr. J. Zuckerman
Department of Chemistry
University of Oklahoma
Norman, Oklahoma 73019

Professor R. Neilson
Department of Chemistry
Texas Christian University
Fort Worth, Texas 76129

Professor M. Newcomb
Department of Chemistry
Texas A&M University
College Station, Texas 77843

Professor L. Miller
Department of Chemistry
University of Minnesota
Minneapolis, Minnesota 55455

Professor K. O. Christe
Rockwell International
Canoga Park, California 91304

Dr. Margaret C. Etter
Department of Chemistry
University of Minnesota
Minneapolis, MN 55455

END

8-87

DTIC