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PROTON-IONIZABLE CROWN ETHERS.
A SHORT REVIEW.

by

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May 24, 1989

PROTON-IONIZABLE CROWN ETHERS. A SHORT REVIEW

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1. INTRODUCTION.

Since Pederson reported the synthesis and cation-complexing characteristics of the crown ethers in 1967¹, there has been increasing interest in these compounds as complexing agents for various metal and organic cations. Many different modifications of the crowns have been made to enhance their cation-complexing properties. Some of these modifications involve the use of alkyl substituents, aromatic subcyclic units, nitrogen and/or sulfur atoms substituted for oxygen in the macroring and other changes which provide crowns with unique complexing properties. A compilation of cation complexing properties of the crown ethers has been published.²

Macrocyclic crown ether ligands containing proton-ionizable groups are of interest because

Dedicated to the memory of Professor Tetsuji Kametani.

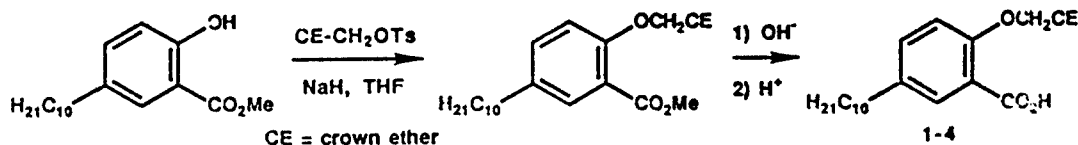
they alleviate the need for a counter anion in metal cation transport through a liquid membrane or in solvent extraction experiments. Often the cation-crown complex stability is increased when the crown is ionized.³ Transport of cations is, in many cases, also tied to the pH of the aqueous solutions in the liquid membrane system so that transport of cations can, in effect, be turned on and off by adjusting the pH.⁴⁻⁶ Proton-ionizable crown ligands have also been used spectrophotometrically to determine parts per million quantities of alkali and alkaline earth metal cations in solution.⁷⁻¹² Having macrocycles which show selectivity in complexation and transport of cations is also an objective in the syntheses of these types of crown ligands.¹³⁻¹⁸ This short review summarizes the syntheses of proton-ionizable crown ether ligands (PICE) to the end of 1988, gives a listing of these compounds and briefly reports on some of their uses (190) ↗

2. CROWN ETHERS CONTAINING A PROTON-IONIZABLE PENDANT ARM.

The modification of the basic crown ether ring structure by attaching a pendant ionizable group is designed to improve solvent extraction and transport of metal cations across bulk liquid and liquid surfactant membranes.^{17,19} This is done by using the ionized crown ligand as the anion thereby alleviating the need to co-transport hard anions such as chloride, nitrate, and sulfate.

Bartsch and his coworkers have synthesized a number of crown ethers of various ring sizes with attached pendant carboxylic acid groups.^{19,20} In general, these carboxylic acid-substituted crown ethers were synthesized by reacting the tosyloxymethyl-substituted crown ether (CE-CH₂OTs) with the hydroxy group of the appropriately substituted benzoic acid methyl ester using sodium hydride as the base in tetrahydrofuran. The methyl ester group was hydrolyzed to the carboxylic acid as shown in Procedure A for 1-4. Compounds 1-14 were synthesized in this manner (Figure I, Table 1).^{19,20}

Procedure A



Crown ether acids 1-4 were most selective for Li⁺, Na⁺, K⁺, and Cs⁺ ions, respectively, in solvent extraction studies of alkali metal chlorides from an aqueous phase into chloroform. All acids were lipophilic enough to remain in the organic phase even at pH ≥ 12.²⁰

Nakamura and Katayama have synthesized pendant proton-ionizable crown ethers (PICEs) with a

Table 1. Crown Ethers Containing Pendant Arm Ionizable Groups (Figure 1)

Number	CE	R ₁	R ₂	R ₃	R ₄	R ₅	mp(°C)	Yield(%)	Proc	Ref
1	12-Cr-4	H	H	n-C ₁₀ H ₂₁	H	CO ₂ H	54-56	83	A	20
2	15-Cr-5	H	H	n-C ₁₀ H ₂₁	H	CO ₂ H	42-44	84	A	20
3	18-Cr-6	H	H	n-C ₁₀ H ₂₁	H	CO ₂ H	oil	81	A	20
4	21-Cr-7	H	H	n-C ₁₀ H ₂₁	H	CO ₂ H	oil	79	A	20
5	13-Cr-4(2) ^a	H	H	n-C ₁₀ H ₂₁	H	CO ₂ H	46-48	47 ^b	A	19
6	13-Cr-4(3) ^a	H	H	n-C ₁₀ H ₂₁	H	CO ₂ H	yellow oil	20 ^b	A	19
7	14-Cr-4(2) ^a	H	H	n-C ₁₀ H ₂₁	H	CO ₂ H	yellow oil	24 ^b	A	19
8	14-Cr-4(3) ^a	H	H	n-C ₁₀ H ₂₁	H	CO ₂ H	yellow oil	33 ^b	A	19
9	15-Cr-4(3) ^a	H	H	n-C ₁₀ H ₂₁	H	CO ₂ H	yellow oil	22 ^b	A	19
10	16-Cr-5(3) ^a	H	H	n-C ₁₀ H ₂₁	H	CO ₂ H	colorless oil	30 ^b	A	19
11	19-Cr-6(2) ^a	H	H	n-C ₁₀ H ₂₁	H	CO ₂ H	yellow oil	65 ^b	A	19
12	24-Cr-8	H	H	n-C ₁₀ H ₂₁	H	CO ₂ H	yellow oil	52 ^b	A	19
13	27-Cr-9	H	H	n-C ₁₀ H ₂₁	H	CO ₂ H	colorless oil	66 ^b	A	19
14	30-Cr-10	H	H	n-C ₁₀ H ₂₁	H	CO ₂ H	colorless oil	50 ^b	A	19
15	15-Cr-5	H	NO ₂	H	NO ₂	OH	--	30	B	9
16	18-Cr-6	H	NO ₂	H	NO ₂	OH	--	25	B	9
17	15-Cr-5	H	H	H	H	OH	--	98	B	9
18	18-Cr-6	H	H	H	H	OH	180-200/0.84 Pa	47	B	9

^a 2 or 3 in parenthesis means attachment of the crown through one of the carbon atoms of a two carbon bridge or the central carbon atom of a 3 carbon bridge. ^b overall yield.

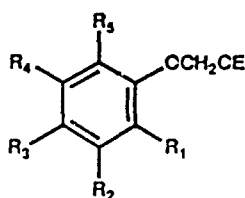


Figure 1

phenolic OH group as the ionizable part of the ligand.^{9,21} Some of the pendant arms were chromogenic. These PICEs were synthesized by the combination of guaiacolyl glyceryl ether and the glycol ditosylate of appropriate length with sodium hydride as the base in N,N-dimethylformamide (DMF). The methyl group is then cleaved by lithium aluminum hydride (LAH) in hexane at reflux temperature. The crown ether phenol is then ring substituted to obtain the desired product.

The synthesis of 15 is shown in Procedure B. Crown ether phenols 15-18 (Figure 1, Table 1) were obtained according to Procedure B in moderate yields. These ligands were all oils.

Procedure B

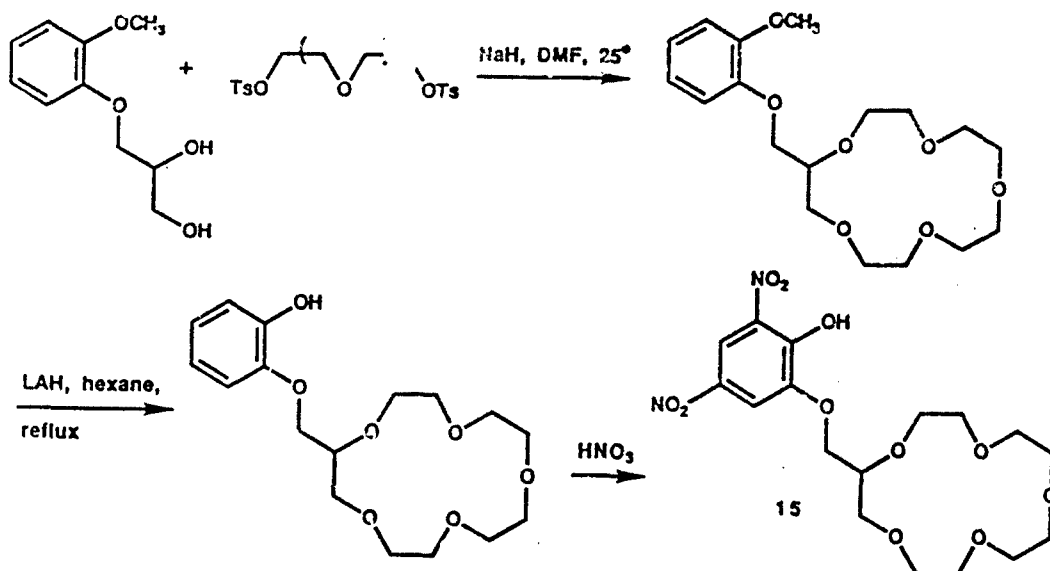


Table 2. Crown Ethers Containing A Pendant Arm Phenol Group (Figure II)

Number	CE	R ₁	R ₂	mp(°C)	Yield(%)	Proc	Ref
19	15-Cr-5	NO ₂	NO ₂	oil	96	B	21
20	18-Cr-6	NO ₂	NO ₂	oil	56	B	21
21	15-Cr-5	H	-N-N-4-nitrophenyl	powder	23	B	21
22	18-Cr-6	H	-N-N-4-nitrophenyl	powder	4.8	B	21
23	15-Cr-5	-N-N-4-nitrophenyl	-N-N-4-nitrophenyl	powder	14	B	21

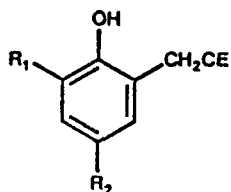


Figure II

Substitution on the phenol ring can be accomplished by aryl diazonium salts (21) as well as nitric acid (15) to give chromogenic ionizable crown ethers.²¹ Compounds 19-23 (Figure II, Table 2) were obtained by using the appropriate starting diol and glycol ditosylate. The starting diol was obtained by reacting methyl iodide with 2-allylphenol in the presence of sodium methoxide to obtain 2-allylanisole followed by oxidation with potassium permanganate to the diol.²¹ The diazophenol crowns 21-23 were obtained as brown powders.

PICE 15 was used to successfully determine sodium ion concentrations in human blood.⁹

Ligands 19-23 extracted alkali metal cations into 1,2-dichloroethane forming highly colored uncharged complexes.²¹

Crown ethers 24 and 25 (Figure III, Table 3) have a pendant ionizable arm connected through a nitrogen instead of an oxygen atom as in 15. The strongly electron withdrawing substituents on the benzene ring cause the aniline hydrogen to be acidic thus providing the PICE. Bubnis and Pacey have synthesized these ligands following the sequence outlined in Procedure C.²² The pK_a s

Procedure C

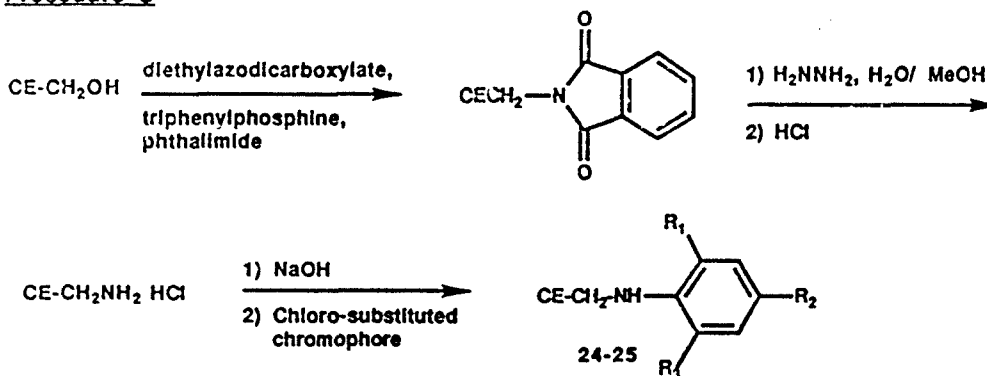


Table 3. Crown Ethers Containing a Pendant Ionizable Aniline Hydrogen (Figure III)

Number	CE	R ₁	R ₂	R ₃	mp(°C)	Yield(%)	Proc	Ref
24	12-Cr-4	NO ₂	NO ₂	CF ₃	86-88	60	C	22
25	15-Cr-5	NO ₂	NO ₂	NO ₂	187-188	60	C	22

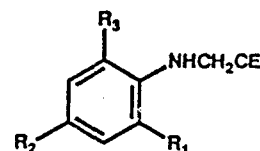


Figure III

for 24 and 25 were found to be 11.4 and 11.6 (40% acetonitrile/H₂O) respectively.²³ Alkali metal extraction and complexation studies determined that both 24 and 25 were more efficient extractors of K⁺ than of other alkali metal ions.²³

A series of PICEs based on 14-crown-4 with a substituted phenol on a pendant arm has also been reported (26-29, Figure IV, Table 4).¹⁸ These ligands were obtained using a modification of Procedure B. Instead of using a substituted ethylene glycol unit, the appropriately substituted 1,3-propylene glycol unit was used to combine with the glycol ditosylate. Sodium hydride was again used as the base in dioxane and lithium perchlorate was added for a template effect. The anisole methyl group was removed as outlined in Procedure B, except that heptane

Table 4. 14-Crown-4 Macrocycles with Pendant Proton-Ionizable Arms (Figure IV)

Number	R ₁	R ₂	Proc	Ref
26	H	H	B	18
27	NO ₂	H	B	18
28	H	NO ₂	B	18
29	NO ₂	NO ₂	B	18

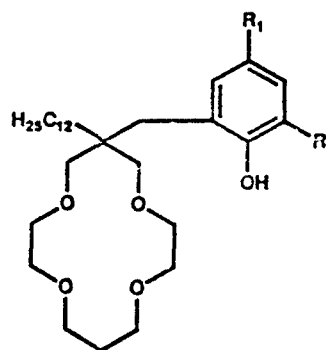


Figure IV

was used as the solvent. This afforded compound 26 which was then ring substituted using nitric acid to obtain 27-29. In proton-driven transport studies in a liquid membrane system, extremely high ratios of lithium over sodium were obtained using 27-29 as the carriers.¹⁸

3. AZA-CROWNS WITH PROTON-IONIZABLE PENDANT ARMS.

Modifications in the composition of the basic crown ether ring have also been made to change the behavior of PICEs toward complexation and transport of cations. Where one or two of the crown ring oxygen atoms have been replaced by nitrogen atoms, the proton-ionizable pendant arm can be attached through one or both nitrogen atoms. Preparation of diaza-crowns containing two carboxylic acid groups is the most obvious extension of this modification.

Diazadicarboxylic acid-containing ligands 30-32 (Figure V, Table 5) were synthesized by reacting the appropriate diaza-crown with the potassium salt of the appropriate ω -chlorocarboxylic acid in the presence of potassium hydroxide followed by acidification as outlined in Procedure D for compound 31.^{24,25} Crown ether 34 was obtained by a modified Procedure D.²⁰ Although ligand 33 is very similar to 30-32, it was obtained by reaction of the diaza-crown and two equivalents of acrylonitrile to form the diaza dinitrile crown. Subsequent hydrolysis produced the diacid 33 (Procedure E).²⁷

Monoaza-crowns 35-38 (Figure V, Table 5) were obtained by the reaction of 2-bromomethyl-4-nitrophenol and the appropriate aza-crown as shown in Procedure F for 35.^{8,21} Crowns 39-41 were

obtained by an extension of Procedure F. After obtaining the nitrophenol-substituted crown, the nitro group was reduced to the amine and the resulting compound was combined with picryl chloride to give the corresponding PICEs.²⁸

Proton-ionizable ligands 42-48 (Figure V, Table 5) were synthesized according to Procedure G shown for the synthesis of

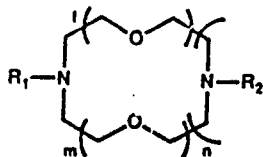


Figure V

Table 5. Aza-Crowns with Pendant Ionizable Arms (Figure V)

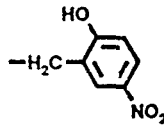
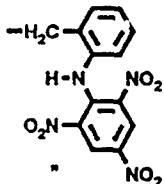
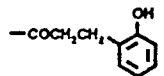
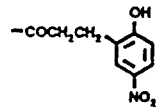
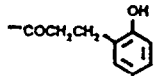
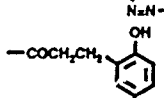
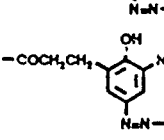
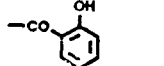
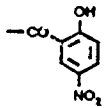
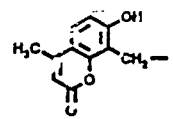
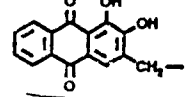
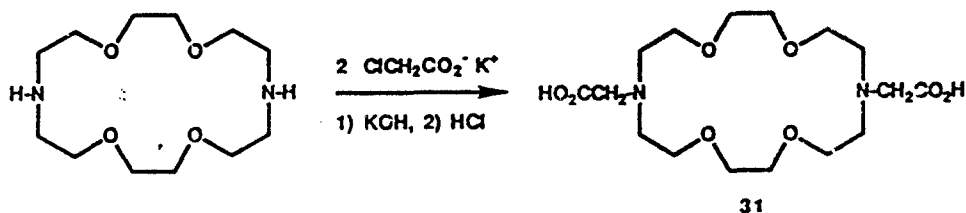
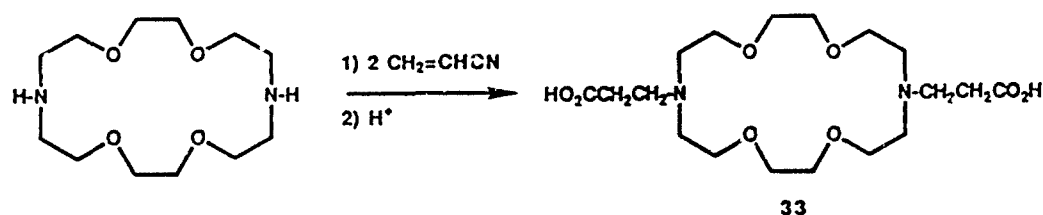
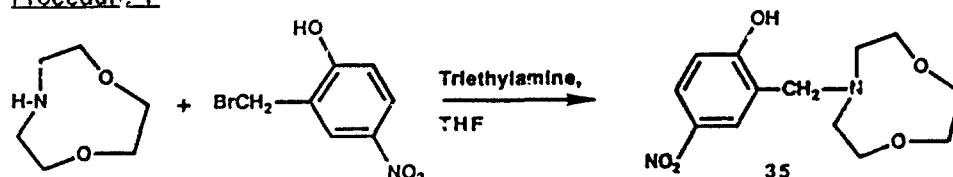
Number	l	m	n	R ₁	R ₂	mp(°C)	Yield(%)	Proc	Ref
30	2	1	1	-CH ₂ CO ₂ H	-CH ₂ CO ₂ H	--	--	D	24,25
31	2	2	1	-CH ₂ CO ₂ H	-CH ₂ CO ₂ H	--	--	D	24,25
32	1	1	1	-CH ₂ CO ₂ H	-CH ₂ CO ₂ H	--	--	D	24
33	2	2	1	CH ₂ CH ₂ CO ₂ H	- R ₁	128.5-130	65	E	27
34	2	2	1	CO(CH ₂) ₁₀ CH ₃	CH ₂ CO ₂ H	oil	17	D	26
35	1	1	0		--	89-90	57	F	21
36	1	2	0	"	--	82-83	71	F	21
37	1	3	0	"	--	--	91	F	8,21
38	1	4	0	"	--	--	87	F	8,21
39	2	2	0		--	orange crystal	48	F	28
40	2	1	1	"	- R ₁	--	30	F	28
41	2	2	1	"	- R ₁	207	32	F	28
42	2	2	1		- R ₁	131-131.5	80	G	29
43	2	2	1		- R ₁	124-125	48	G	29
44	2	2	1		- R ₁	88-92	43	G	29
45	2	2	1		- R ₁	196-203	49	G	29
46	2	2	1		- R ₁	144(dec)	14	G	29
47	2	2	1		- R ₁	141-142	36	G	29

Table 5 (continued)

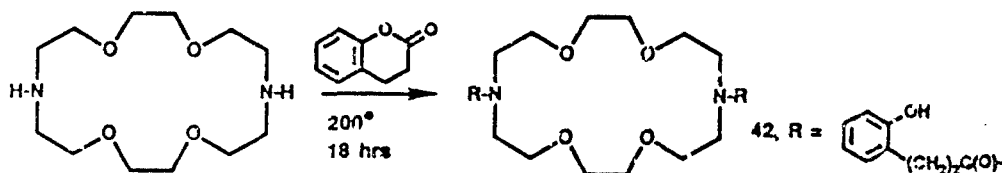
48	2	2	1		- R ₁	114-117	38	G	29
49	1	2	0		--	--	43	H	21
50	1	3	0	*	--	oil	47	H	21
51	1	4	0	*	--	oil	62	H	21
52	1	3	0		--	104	35	H	21
53	1	4	0	*	--	90-91	38	H	21

Procedure DProcedure EProcedure F

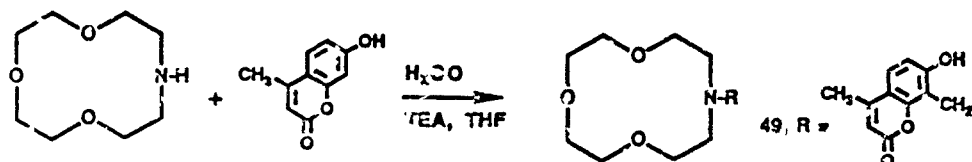
42.²⁹ Ligand 43 was obtained using the nitro-substituted dihydrocoumarin, 44-46 were obtained by subsequent aromatic ring substitution by the appropriate aryl diazonium salt, and 47 and 48 were obtained using a modified Procedure G with the phenyl ester instead of the lactone.²⁹

Chromogenic aza-crowns 49-53 (Figure V, Table 5) were obtained by the reaction of the

Procedure G



Procedure H



appropriate aza-crown, formaldehyde and a chromogenic group by the Mannich reaction in the presence of triethylamine (TEA) as the base.²¹ Procedure H illustrates this sequence with crown 45 as an example.

Ligands 30 and 31 were tested for transport and complexation properties with alkali, alkaline earth, some transition metal,²⁴ and some lanthanide metal ions.³⁰ Crowns 32-34 were only studied using alkali, alkaline earth, and some transition metal ions.^{26,27} The transport of cations by PICEs 33 and 34 was also studied using zwitterionic amino acid forms assisted by Ca^{2+} ions. The extraction of alkali metal cations into 1,2-dichloroethane by 35-38 and 49-53 was studied and the chromogenic crowns formed highly colored uncharged metal complexes.²¹ Ligands 37 and 38 were selective for Li^+ and K^+ respectively and 37 was useful in determining parts per million concentrations of Li^+ as well as concentrating Li^+ from dilute solutions.⁸ Of compounds 44-48, only 46 was found to extract alkali or alkaline earth metal cations.²⁹

4. TARTARIC ACID DERIVED PROTON-IONIZABLE CROWN ETHERS.

Fyles and Lehn have synthesized a series of lipophilic carboxylic acid crown ethers derived from one or two tartaric acid residues. These syntheses gave crowns with a specific set of stereoisomers for complexation and cation transport studies.³¹ The starting N,N,N',N'-tetramethyldiamide of tartaric acid was obtained from the (2R,3R)-isomer of tartaric acid. Thallium ethoxide, which was compatible with the easily racemized chiral centers,³¹ was employed as the base in this modification of the Williamson ether synthesis. The general synthetic method is shown in Procedure I using 34 as an example. Lipophilic acid ligands 34-68 (Figure VI, Table 6) were obtained in this manner using the appropriate glycol diiodide and by making

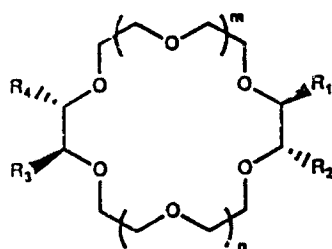


Figure VI

the appropriate substitutions.³¹⁻³⁵ Tetrasubstituted crown ethers 69-91 (Figure VI, Table 6) were also synthesized according to general Procedure I but modifications were made to obtain some of the products.^{5,33,36-38} Compound 80, for example, was obtained by the reaction of the *N,N,N',N'*-tetramethyldiamide of tartaric acid and 1-iodo-3-oxa-5-benzoyloxypentane in the presence of thallium ethoxide in DMF to obtain the bis-benzyl blocked pentaethylene glycol. This material was deblocked, brominated, then iodinated

Table 6. Tartaric Acid Derived Proton-Ionizable Crown Ethers (Figure VI)

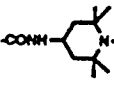
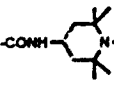
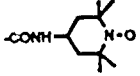
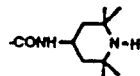
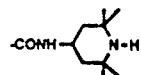
Number	m	n	R ₁	R ₂	R ₃	R ₄	mp(°C)	Yield(%)	Proc	Ref
54	0	1	H	H	CONH(CH ₂) ₇ CH ₃	CO ₂ H	oil	70	I	31
55	0	1	H	H	CONH(CH ₂) ₁₃ CH ₃	CO ₂ H	wax	60	I	31
56	0	1	H	H	CONH(CH ₂) ₁₇ CH ₃	CO ₂ H	57°	78	I	31
57	1	1	H	H	CONH(CH ₂) ₇ CH ₃	CO ₂ H	wax	80	I	31
58	1	1	H	H	CONH(CH ₂) ₁₃ CH ₃	CO ₂ H	oil	61	I	31
59	1	1	H	H	CONH(CH ₂) ₁₇ CH ₃	CO ₂ H	wax	58	I	31
60	1	1	H	H	CONH(CH ₂) ₃ CH ₃	CO ₂ H	93	90	I	31
61	0	1	H	H	CO ₂ H	CO ₂ H	60	65	I	31
62	1	1	H	H	CO ₂ H	CO ₂ H	103	75	I	31
63	0	1	H	H	CON(C ₈ H ₁₇) ₂	CO ₂ H	--	--	I	32
64	1	1	H	H	CON(C ₈ H ₁₇) ₂	CO ₂ H	--	--	I	32
65	1	1	H	H	CO ₂ H		--	--	I	33
66	1	1	H	H	CO ₂ H		162-163	90	I	33
67	1	1	H	H	^a PCONHCH ₂ CH ₂ NHCO	CO ₂ H	--	60	I	35
68	0	1	CO ₂ H	CON[(CH ₂) ₇ CH ₃] ₂	H	H	--	--	I	34
69	1	1	A ^b	CO ₂ H	CO ₂ H	A ^b	--	--	I	5
70	1	1	CO ₂ H	CONHPh	CO ₂ H	CONHPh	256	44	I	36
71	1	1	CO ₂ H	CONH-4-Phenyl-azo-1-Naphthyl	CO ₂ H	= R ₂	--	--	I	36

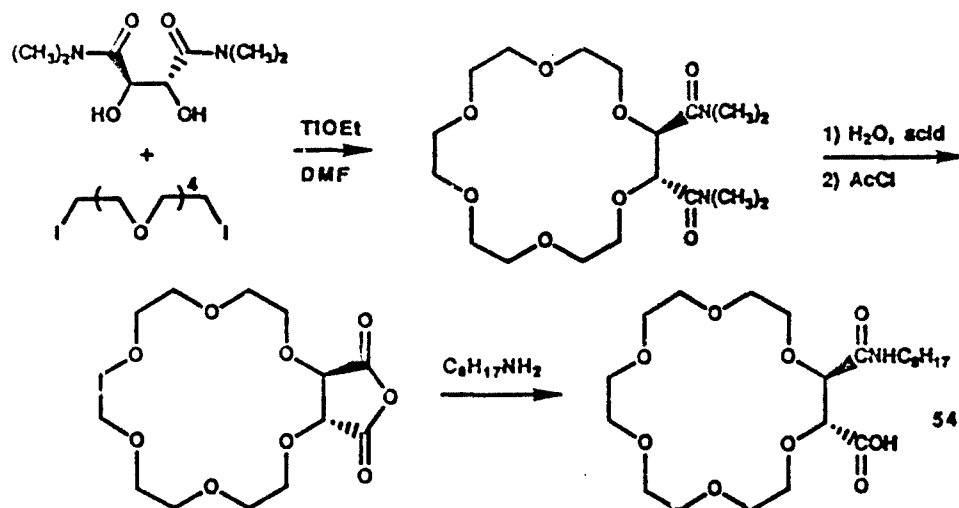
Table 6 (continued)

72	1	1	CO ₂ H	CONH-4-Iodo-phenyl	CO ₂ H	- R ₂	--	--	I	36
73	1	1	CO ₂ H	CONH-1-Napthyl	CO ₂ H	- R ₂	--	--	I	36
74	1	1	CONHPh	CO ₂ H	CO ₂ H	- R ₁	110(dec)	47	I	36
75	1	1	CONH-4-Phenyl-azo-1-Napthyl	CO ₂ H	CO ₂ H	- R ₁	--	--	I	36
76	1	1	CONH-4-Iodo-phenyl	CO ₂ H	CO ₂ H	- R ₁	--	--	I	36
77	1	1	CONH-9-Phenanthryl	CO ₂ H	CO ₂ H	- R ₁	--	--	I	36
78	1	1	CONH-1-Napthyl	CO ₂ H	CO ₂ H	- R ₁	--	--	I	36
79	1	1	CO ₂ H	CONH-9-Phenanthryl	CO ₂ H	- R ₁	--	--	I	36
80	1	1	C ₁₀ H ₂₁	C ₁₀ H ₂₁	CO ₂ H	CO ₂ H	glass	92	I	37
81	1	1	CON(C ₈ H ₁₇) ₂	- R ₁	CO ₂ H	CO ₂ H	--	97	I	37
82	1	1	CONHC ₈ H ₁₇	CO ₂ H	CO ₂ H	- R ₁	180-183	--	I	37
83	1	1	CONHC ₈ H ₁₇	CO ₂ H	- R ₁	CO ₂ H	74-78	--	I	37
84	1	1	CON(C ₈ H ₁₇) ₂	CO ₂ H	CO ₂ H	- R ₁	--	--	I	37
85	1	1	CON(C ₈ H ₁₇) ₂	CO ₂ H	- R ₁	CO ₂ H	--	--	I	37
86	1	1		CO ₂ H	CO ₂ H	- R ₁	--	--	I	37
87	1	1	"	CO ₂ H	- R ₁	CO ₂ H	--	--	I	37
88	1	1		CO ₂ H	- R ₂	- R ₁	190(dec)	95	I	33
89	1	1	CO ₂ H		- R ₁	- R ₂	oil	83	I	33
90	1	1	CO ₂ H	CO ₂ H	CO ₂ H	CO ₂ H	213	>95	I	38
91	1	1	CH ₂ CO ₂ H	- R ₁	- R ₁	- R ₁	197-201	95	I	38

^a P - Polyaramid Support. ^b A - CON(n-Pr)CH₂CH₂OCH₂CH₂N(n-Pr)CO₂CH₂C₆H₆

to obtain the bis-iodo compound. Reaction with didecylethylene glycol in the presence of thallium ethoxide and DMF followed by the work up outlined in Procedure I gave 80.³⁷ An analogous modification of Procedure I, used to obtain 81, started with 1,4-dibenzyl-1-threitol and 1-iodo-3-oxa-5-tetrahydropyranyloxypentane.³⁷ Ionizable crown 92 (Figure VII) was obtained

Procedure I



from three equivalents of diethyleneglycol diiodide in the presence of thallium ethoxide/DMF followed by hydrolysis of the amide to the acid.³⁸

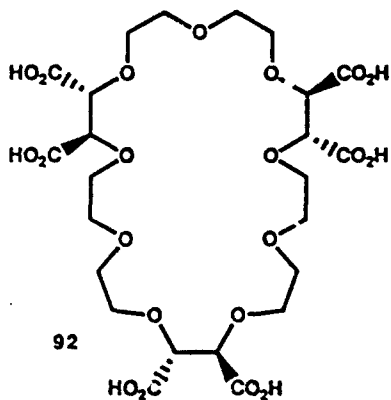


Figure VII

Complexation by these crowns has been extensively studied. Complexation and transport studies have been done using these ligands with the alkali and alkaline earth metal cations. Kinetic and mechanistic studies for their use in the transport of metal ions have been carried out. Preferences of certain ligands for particular cations and transport rates of those cations have been determined.^{32-35,38,39-43} Ionizable crown 67 was attached to a polymer support and its cation separation properties were studied.³⁵

5. CROWN ETHERS WITH PROTON-IONIZABLE CHROMOGENIC PENDANT ARMS.

Proton-ionizable crown ethers containing chromogenic pendant arms are unique in that spectrophotometric analysis can be done upon deprotonation and complexation with a metal cation. Some of these chromogenic proton-ionizable crown ethers have already been discussed and others will be discussed at a later point in this article. The compounds discussed here either have an ionizable phenolic proton or an amine hydrogen made ionizable by strong electron withdrawing substituents on the neighboring benzene substituent.

Chromogenic ionizable crowns 93-106 (Figure VIII, Table 7) were synthesized by modification of Procedure A. The substituted aminophenol was combined with the appropriate tosyloxymethyl

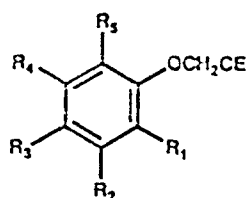


Figure VIII

substituted crown ether in the presence of sodium hydride in THF to obtain the crown ether containing the aniline pendant arm. This material was then coupled with the appropriate chloride (i.e. picryl chloride) to obtain the product.⁴⁴ Crowns 107 and 108 were obtained according to Procedure B except that the corresponding diazonium salt was used instead of nitric acid.⁹

Table 7. Crown Ethers with Chromogenic Ionizable Pendant Groups (Figure VIII)

Number	CE	A	B	C	D	E	mp(°C)	Yield(%)	Proc	Ref
		R ₁ -		R ₂ - R ₃ - R ₄ - R ₅ - H						
93	15-C-5	NO ₂	H	NO ₂	H	NO ₂	119-121	89	A	44
94	15-C-5	NO ₂	H	NO ₂	H	CN	red glass	92	A	44
95	15-C-5	NO ₂	H	NO ₂	H	CF ₃	red oil	96	A	44
96	15-C-5	CF ₃	H	NO ₂	H	NO ₂	72.5-74.5	90	A	44
		R ₁ - same as above, R ₂ - R ₃ - R ₅ - H, R ₄ - NO ₂								
97	15-C-5	NO ₂	H	NO ₂	H	NO ₂	red oil	47	A	44
98	15-C-5	NO ₂	H	NO ₂	H	CF ₃	red glass	48	A	44
		R ₁ - same as above, R ₂ - R ₄ - NO ₂ , R ₃ - R ₅ - H								
99	15-C-5	NO ₂	H	CN	H	NO ₂	164-166	80	A	44
		R ₁ - same as above, R ₂ - R ₃ - R ₄ - R ₅ - H								
100	16-C-5	CF ₃	H	NO ₂	H	NO ₂	orange oil	47	A	44
101	18-C-6	CF ₃	H	NO ₂	H	NO ₂	red oil	67	A	44
102	19-C-6	CF ₃	H	NO ₂	H	NO ₂	red oil	94	A	44
103	21-C-7	CF ₃	H	NO ₂	H	NO ₂	red oil	51	A	44
104	30-C-10	CF ₃	H	NO ₂	H	NO ₂	red oil	66	A	44
		R ₂ -		R ₁ - R ₃ - R ₄ - R ₅ - H						
105	15-C-5	CF ₃	H	NO ₂	H	NO ₂	red oil	69	A	44
106	18-C-6	CF ₃	H	NO ₂	H	NO ₂	red oil	67	A	44
		R ₂ -		R ₁ - R ₃ - R ₄ - H, R ₅ - OH						
107	15-C-5	H	H	NO ₂	H	H	45-55	49	B	9
108	18-C-6	H	H	NO ₂	H	H	88-89	70	B	9

6. SUBSTITUTED BENZO-CROWN ETHERS

This section covers PICEs with one benzene ring incorporated into the crown as a subcyclic unit. Alkanoic acid groups as well as aromatic chromogenic groups have been substituted onto the benzene ring. Crowns 109-112 (Figure IX, Table 8) were synthesized as shown in Procedure J using 109 as an example. The hydroxymethyl substituted benzocrown ether was reacted with the

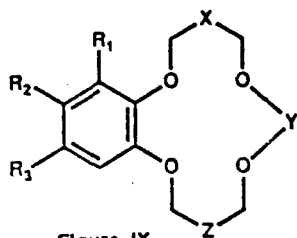


Figure IX

corresponding bromo-substituted carboxylic acid and, after protonation, benzocrown 109 was obtained. Crown 110 was obtained by a modification of Procedure J in that the tosyloxymethyl crown and hydroxy-substituted carboxylic acid were used to obtain the product.^{19,45} Acid crowns 113 and 114 were obtained by oxidation of the corresponding acetyl derivative (Procedure K).⁴⁶⁻⁴⁸

Phenolic crowns 115 and 116 were obtained by a modified Procedure K. Instead of oxidizing the acetyl derivative to the carboxylic acid, the acetyl group was subjected to Baeyer-Villiger oxidation conditions to obtain the corresponding acetate. The acetate was then hydrolyzed to obtain the phenol.⁴⁹

Table 8. Substituted Benzo Crown Ethers (NA = No Atom, E = CH₂CH₂) (Figure IX)

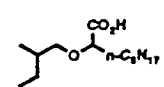
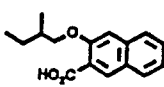
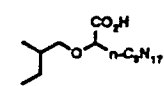
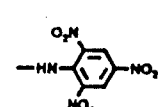
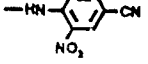
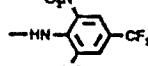
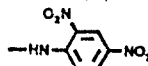
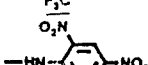
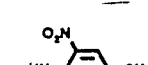
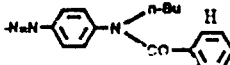
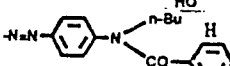
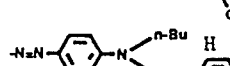
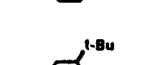
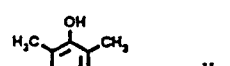
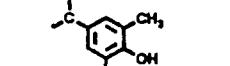
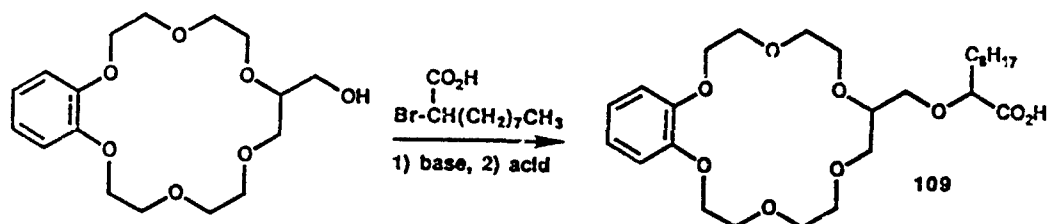
Number	R ₁	R ₂	R ₃	X	Y	Z	mp(°C)	Yield(%)	Proc	Ref
109	H	H	H	CH ₂ OCH ₂		CH ₂ OCH ₂	oil	47	J	45
110	H	H	H	CH ₂ OCH ₂		CH ₂ OCH ₂	oil	58	J	45
111	H	H	H	NA		NA	oil	63	J	19
112	H	H	H	CH ₂	"	CH ₂	oil	47	J	19
113	H	CO ₂ H	H	NA	EOE	NA	183-185	89	K	46,48
114	H	CO ₂ H	H	CH ₂ OCH ₂	CH ₂ OCH ₂	NA	118-120	80	K	47
115	H	-OH	H	NA	EOE	NA	101-103	93	K (mod.)	49
116	H	-OH	H	NA	EOEOE	NA	52	82	K (mod.)	49
117	H		H	NA	EOE	NA	155	72	L	11

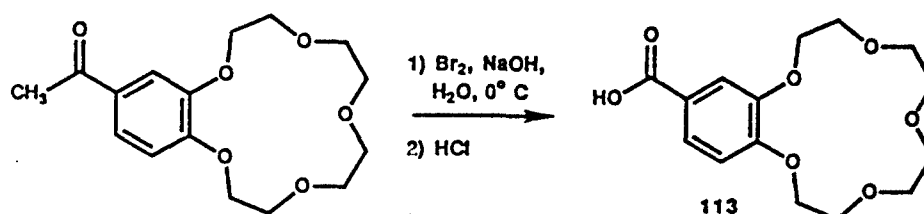
Table 8 (continued)

118	H		NO ₂	NA	EOE	NA	208-209	82	L	11
119	H		Br	NA	EOE	NA	216-217	60	L	11
120	H		H	NA	EOE	NA	--	--	L	50
121	H		H	NA	EOE	NA	--	--	L	50
122	H		H	NA	EOE	NA	--	--	L	50
123	H		H	NA	EOE	NA	--	--	L	50
124	H		H	NA	EOEOE	NA	55-56	45	L	29
125	H		NO ₂	NA	EOEOE	NA	160-161	32	L	29
126	H		H	NA	EOEOE	NA	75-78	17	L	51
127	H		H	NA	EOEOE	NA	150-152	32	L	51
128	H		H	NA	EOEOE	NA	120-123	77	L	51
129	H		H	NA	EOE	NA	162-163	66	L	29
130	H		H	NA	EOE	NA	72-74	11	L	29
131	H		H	NA	EOE	NA	107-108	34	L	29
132	H		H	NA	EOE	NA	62-64	11	L (mod.)	29
133	H		H	NA	EOE	NA	244-245	90	M	29
134	H		H	NA	EOE	NA	171-172	42	M	29

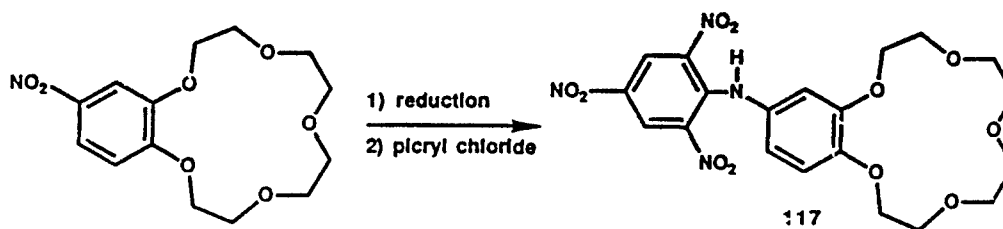
Procedure J



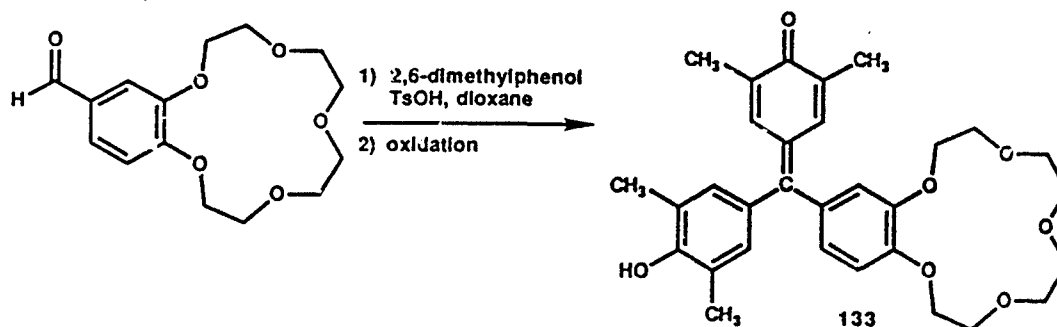
Procedure K



Procedure L



Procedure M



Chromogenic ionizable crowns 117-125 (Figure IX, Table 8) were prepared according to Procedure L. The appropriately substituted nitrobenzocrowns were catalytically reduced to the amine followed by coupling with the corresponding chloride.^{11,29,50} Azocrowns 126-132 were obtained by modifying Procedure L. The amine function was converted to a diazonium salt and

then combined with the appropriate aromatic substrate to yield the proton-ionizable chromogenic crown ether.⁵¹ Crowns 133 and 134 were obtained as shown in Procedure M.²⁹

The transport of alkali and alkaline earth metals by these PICEs has been studied.⁴⁵ Crown ethers 126-128 were used in studies demonstrating the first example of light driven Ca^{2+} transport across a liquid membrane.⁵¹ UV light caused the crowns to isomerize from the *trans* to the *cis* configuration which puts the phenol group above the macrocyclic cavity and in a position to assist in complexation and transport.⁵¹

7. CARBOXYLIC ACID-SUBSTITUTED DIBENZO-CROWN ETHERS.

Dibenzo-crown ethers are a natural extension of the work done with the benzo-crown ethers. These compounds have alkyl and carboxylic acid substituents and one crown (159) is chromogenic.

Dibenzo-crowns containing carboxylic acid substituents (135-148) (Figure X, Table 9) were obtained by combining the various hydroxydibenzo-crown ethers with the corresponding bromoalkyl carboxylic acid in the presence of sodium hydride in THF as illustrated in Procedure J.⁵²⁻⁵⁴ Propionic acid-containing crown 149, homologous to acid crowns 135-148, was prepared via the

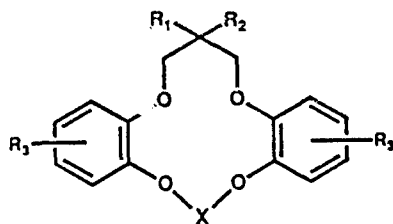


Figure X

appropriate hydroxydibenzo-crown ether and allyl bromide or ethyl acrylate as shown in Procedure N.^{52,56} Disulfonic acid-crowns 150-152 were prepared from the corresponding carboxylic acid-crowns (Procedure J) by sulfonation of the benzene rings using sulfuric acid, acetic anhydride, and acetic acid in chloroform.⁵⁷

Crowns 153-156 were obtained by reacting the dibenzo-crown containing a ketone function on the propylene bridge with the appropriate Grignard reagent to give alkyl and hydroxy substitution on the same carbon as shown in Procedure O.⁵⁴ Procedure J was then followed as outlined before to obtain the acid crowns. Alkylsulfonic acid crown 157 was obtained by a modification of Procedure J in that the hydroxy crown was first combined with sodium hydride in THF to give the sodium alkoxide followed by the addition of 1,3-propane sultone. Hydrogen chloride gas was then bubbled through the reaction mixture to protonate the salt.⁵⁶ Dicyclohexano-crown carboxylic acid 158 (Figure XI) was prepared according to Procedure J but first the benzene rings on the corresponding hydroxy-crown were reduced to cyclohexane rings using hydrogen and ruthenium on carbon in ethanol.⁵⁴

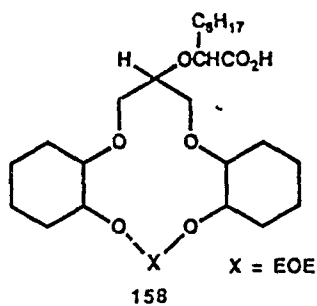
Crown 159 (Figure XII) was the only chromogenic proton-ionizable dibenzo crown ether reported. It was prepared according to Procedure L except that the corresponding nitro-substituted dibenzo-crown was used.²⁹

Table 9. Dibenzo Acid Crowns (E = CH₂CH₂, P = CH₂CH₂CH₂) (Figure X)

Number	R ₁	R ₂	R ₃	X	mp(°C)	Yield(%)	Proc	Ref
135	H	-OCH ₂ CO ₂ H	H	E	129	76	J	52
136	H	-OCH ₂ CO ₂ H	H	P	140-141	80	J	52
137	H	-OCH ₂ CO ₂ H	H	EOE	166	82	J	52
138	H	-OCH ₂ CO ₂ H	H	EOEOE	95-96	66	J	52
139	H	-OCH(C ₂ H ₅)CO ₂ H	H	EOE	93-95	40	J	52
140	H	-OCH(n-C ₄ H ₉)CO ₂ H	H	EOE	93-95	40	J	52
141	H	-OCH(n-C ₆ H ₁₃)CO ₂ H	H	EOE	75-77.5	23	J	52
142	H	-OCH(n-C ₈ H ₁₇)CO ₂ H	H	EOE	87-88	27	J	52
143	H	-O(CH ₂) ₄ CO ₂ H	H	EOE	97-98	76	J	52
144	H	-OCH ₂ CO ₂ H	t-Bu	EOE	55-56	86	J	53
145	H	-OCH(n-C ₈ H ₁₇)CO ₂ H	H	P	74.5-76.5	46	J	54
146	H	-OCH(n-C ₈ H ₁₇)CO ₂ H	H	EOEOE	oil	35	J	54
147	H	-OCH(n-C ₈ H ₁₇)CO ₂ H	H	EOEOEOE	oil	38	J	54
148	H	-OCH ₂ (CH ₂) ₄ CO ₂ H	H	P	50	70	J	55
149	H	-C(CH ₂) ₂ CO ₂ H	H	EOE	116-119	6	N	52,56
150	H	-OCH ₂ CO ₂ H	-SO ₃ H	EOE	127-128	93	J	57
151	CH ₃	-OCH ₂ CO ₂ H	-SO ₃ H	EOE	110-111	86	J	57
152	n-C ₄ H ₉	-OCH ₂ CO ₂ H	-SO ₃ H	EOE	173-175	82	J	57
153	n-C ₄ H ₉	-OCH ₂ CO ₂ H	H	EOE	145-146	quan.	O	54
154	n-C ₈ H ₁₇	-OCH ₂ CO ₂ H	H	EOE	95.5-97.5	quan.	O	54
155	n-C ₁₄ H ₂₉	-OCH ₂ CO ₂ H	H	EOE	107-108	quan.	O	54
156	n-C ₈ H ₁₇	-OCH ₂ CO ₂ H	H	EOEOE	oil	78	O	54
157	H	-O(CH ₂) ₃ SO ₃ H	H	EOE	60-70	80	J	56

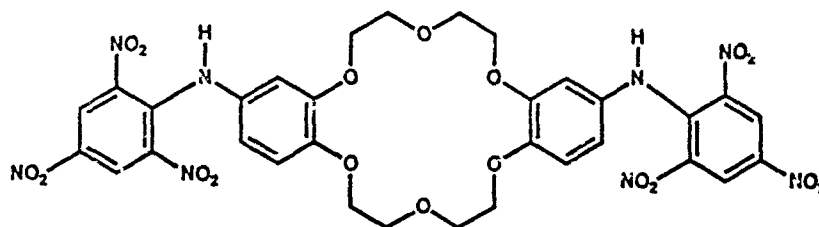
Metal cation complexation by many of these compounds has been studied extensively. The pK_a values for many of them have been determined.^{52,56,58} Using these dibenzo-crown carboxylic acids, transport of alkali, alkaline earth, some transition metal, and lanthanide metal ions has been studied as a function of pH, metal ion concentration, and the nature of the organic phase in single ion as well as competitive ion experiments in bulk and emulsion liquid membrane systems.^{3,4,16,53,57,59-68} Some of these crown acids have been used in the study of the

transport of praseodymium (III) across phosphatidyl choline vesicles.⁶⁹ Thermodynamic studies have also been carried out, and ΔH , ΔG , and $T\Delta S$ values have been determined for crown-metal ion complexes.^{56,58,70,71}



yield: 41%, mp: oil, ref.: 54

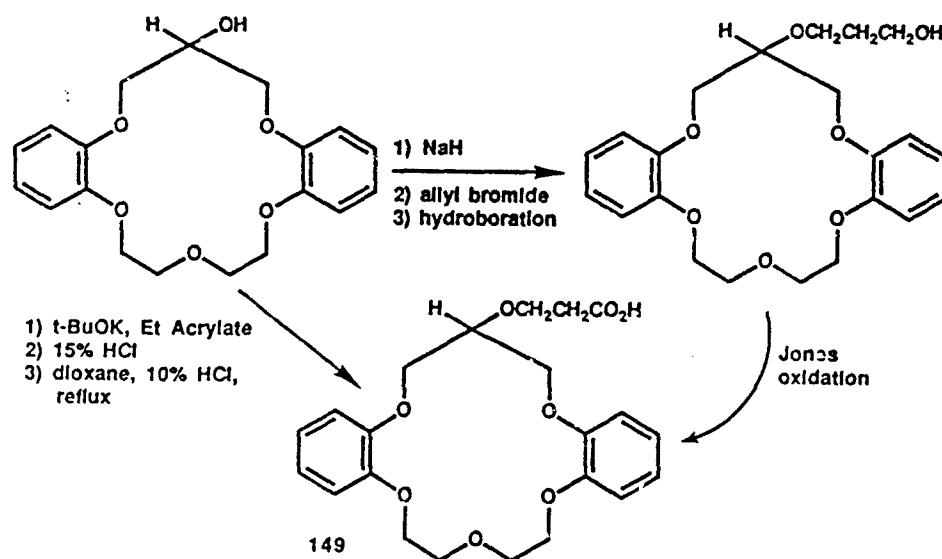
Figure XI



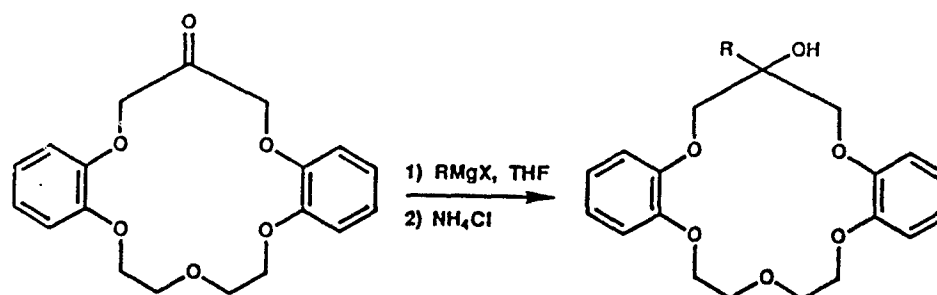
159) yield: 67%, mp: 222-226°C, Proc. D, Ref. 29

Figure XII

Procedure N



Procedure O



8. PROTON-IONIZABLE CROWN ETHERS CONTAINING THE BINAPHTHYL SUBCYCLIC UNIT.

The PICEs containing a binaphthyl unit were among the first proton-ionizable crowns synthesized. Gram and coworkers have studied a large number of these compounds for metal cation complexation as well as molecular recognition.^{72,73}

Binaphtho-crowns 160-161 (Figure XIII, Table 10) were synthesized from the combination of 2,2'-bis-methoxy-3,3'-bis-(hydroxymethyl)-1,1'-binaphthyl and the appropriate glycol ditosylate followed by the cleavage of the methyl group to give the bis-naphthol compound as outlined in Procedure P for compound 160.⁷²

Table 10. Binaphthyl Ionizable Crown Ethers
with Intraannular Hydroxy Groups

(Procedure P, Reference 72) (Figure XIII)

Number	n	mp(°C)	Yield(%)
160	2	214-215	40
161	3	188-189	40
162	4	162-163	15

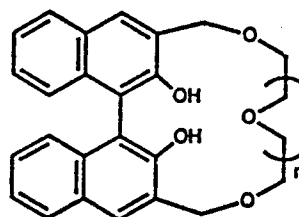
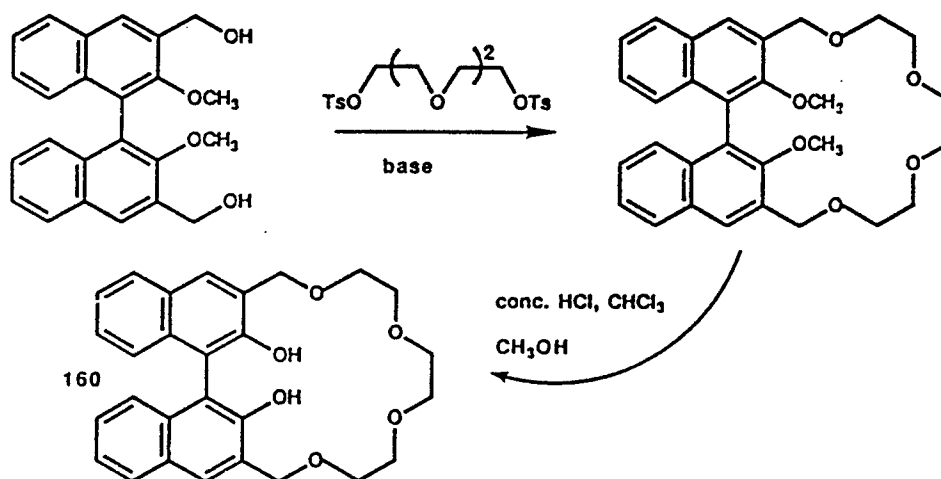


Figure XIII

Procedure P



Binaphtho-crown ethers 163-184 (Figure XIV, Table 11) have the crown ring attachment at the 2,2'-positions instead of the 3,3'-positions as in 160-162. The general procedure for the synthesis of proton-ionizable binaphtho-crown ethers 163-174 is given in Procedure Q using crown 163 as an example.^{74,75} The synthetic pathway to obtain the appropriately substituted starting binaphtho-crown is somewhat similar to Procedure P.⁷⁴ Once the precursor binaphtho-crown was

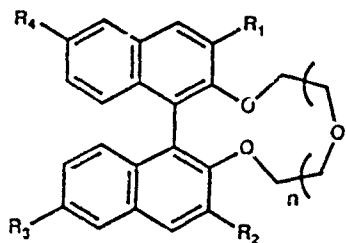


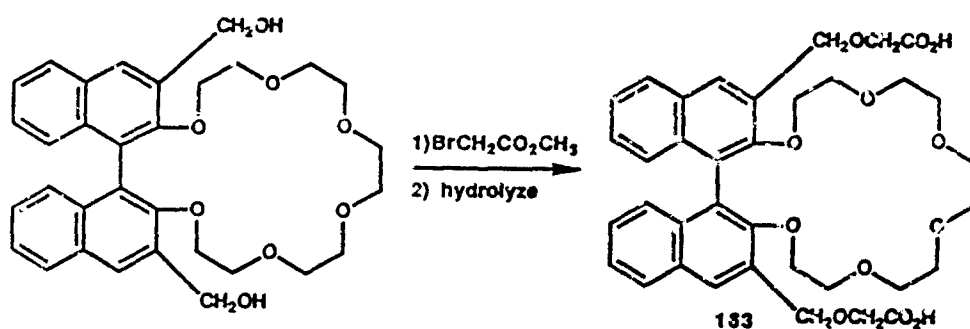
Figure XIV

obtained, it was coupled with bromoacetic acid methyl ester and subsequent hydrolysis and acidification provides the binaphtho-crown acid.^{74,75} Binaphtho-crown acids 175-180 containing a sulfur atom in the alkyl acid chain were obtained by modifying Procedure Q. Reaction of the 3,3'-bis(chloromethyl) binaphtho-crown ether with an ω -sulfhydryl alkanolic acid in the presence of base followed by acidification gave the sulfur-containing

Table 11. Binaphthyl Ionizable Crown Ethers (A = $\text{OCH}_2\text{CO}_2\text{H}$ M = ) (Figure XIV)

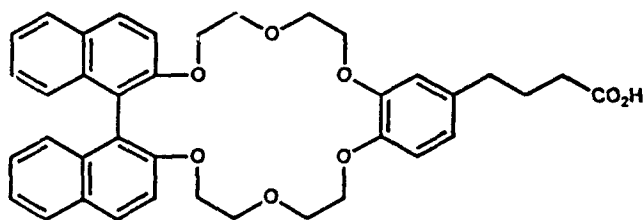
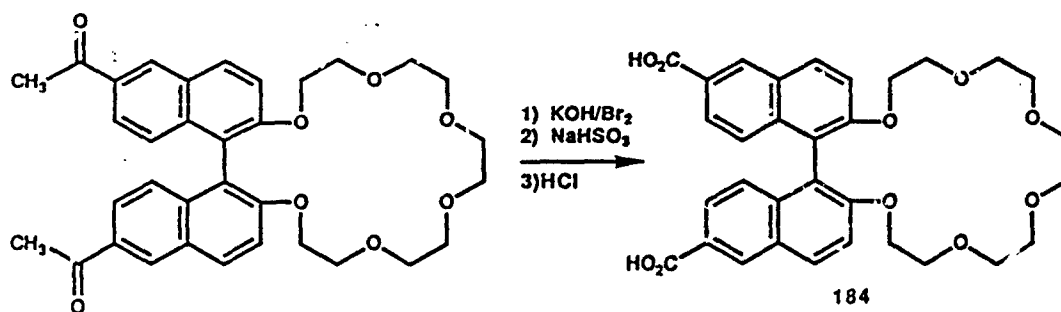
Number	n	R ₁	R ₂	R ₃	R ₄	mp(°C)	Yield(%)	Proc	Ref
163	4	CH ₂ A	CH ₂ A	H	H	oil	80	Q	74,75
164	4	H	CH ₂ A	H	H	oil	70	Q	74
165	4	CH ₂ M	CH ₂ A	H	H	oil	65	Q	74
166	3	CH ₂ A	CH ₂ A	H	H	oil	85	Q	74
167	5	CH ₂ A	CH ₂ A	H	H	oil	75	Q	74
168(-)-(S)	4	CH ₂ A	CH ₂ A	H	H	glass	90	Q	75
169(-)-(S)	3	CH ₂ A	CH ₂ A	H	H	glass	65	Q	75
170(-)-(R)	5	CH ₂ A	CH ₂ A	H	H	glass	50	Q	75
171	3	CH ₂ A	H	H	H	128-130	35	Q	75
172	4	CH ₂ A	CH ₃	H	H	glass	85	Q	75
173	4	CH ₂ A	CH ₂ OH	H	H	glass	77	Q	75
174	4	H	H	CH ₂ A	CH ₂ A	glass	75	Q	75
175	4	CH ₂ SCH ₂ CO ₂ H	- R ₁	H	H	glass	96	Q	75
176(+)-(S)	4	CH ₂ SCH ₂ CO ₂ H	- R ₁	H	H	glass	72	Q	75
177	4	CH ₂ SCH ₂ CH ₂ CO ₂ H	- R ₁	H	H	glass	97	Q	75
178(-)-(S)	4	CH ₂ SCH ₂ CH ₂ CO ₂ H	- R ₁	H	H	glass	58	Q	75
179	4	H	H	CH ₂ SCH ₂ CO ₂ H	- R ₃	oil	75	Q	75
180	4	CH ₂ SCH ₂ CO ₂ H	- R ₁	- R ₁	- R ₁	glass	96	Q	75
181	4	CH ₂ CH(CO ₂ H) ₂	- R ₁	H	H	140	91	Q	75
182	4	CH ₂ CH ₂ CO ₂ H	- R ₁	H	H	glass	92	Q	75
183(-)-(S)	4	CH ₂ CH ₂ CO ₂ H	- R ₁	H	H	glass	85	Q	75
184	4	H	H	CO ₂ H	CO ₂ H	291-2	84	R	75

Procedure Q



binaphtho-crown acid.⁷⁵ Compounds 181-183 were also obtained starting from 3,3'-bis(chloromethyl) binaphtho-crown and dimethyl malonate followed by subsequent workup.⁷⁵ Diacid 184 was obtained by the sequence shown in Procedure R.⁷⁵ Compound 185 (Figure XV) was obtained using Procedure Q.⁷⁴

Procedure R



185) yield: 70%, mp: oil, ref. 74
Figure XV

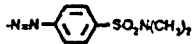
The binaphthylene unit of the crown ethers just described is a steric barrier whose 3- and 3'-positions direct the attached side chains over and under the cavity of the crown ether. This provides additional binding sites for complexation.⁷⁴ These crowns were

able to extract metal cations into organic phases and they provided optical resolution through differential complexation of the enantiomers of the α -amino acids.⁷²⁻⁷⁶

9. PROTON-IONIZABLE BENZO-CROWNS CONTAINING AN INTRAANNULAR HYDROXY GROUP.

Although many of the PICEs already discussed contain phenol groups, this section will discuss PICEs which contain a phenol hydroxy group inside the crown ether cavity. The general synthesis is shown in Procedure S with compound 186 as an illustration.⁷⁷ Crown phenols 186-196 (Figure XVI, Table 12) were synthesized according to this procedure, some with slight

Table 12. Crown Ethers Containing Intraannular Phenol Hydroxy Groups (Figure XVI)

Number	m	n	R	X	mp(°C)	Yield(%)	Proc	Ref
186	0	1	H	O	66-66.5	91	S	77
187	0	1	NO ₂	O	105.5-106	92	S	77
188	1	1	H	O	48-49	92	S	77
189	1	1	NO ₂	O	91-91.5	93	S	77
190	2	1	H	O	oil	70	S	77
191	2	1	NO ₂	O	73-75.5	92	S	77
192	1	1	Cl	O	62-65	22	S	78
193	2	1	Cl	O	oil	70	S	78
194	3	1	Cl	O	oil	64	S	78
195	4	1	Cl	O	5*	87	S	78
196	5	1	Cl	O	--	65	S	78
197	0	1	-N-N-2,4-dinitrophenyl	O	167.5-168.5	--	S	7,10,79
198	1	1	"	O	109.5-110	--	S	7,79
199	0	1	-N-N-4-methoxyphenyl	O	136-137	--	S	80
200	1	1	"	O	95.5-96.5	--	S	80
201	1	1		O	143.5-144.5	--	S	80
202	0	1	OH	O	151-152	quan	S	81
203	1	1	OH	O	76-80	quan	S	81
204	3	0	OH	O	68-70	92	S	82
205	2	0	H	O	57-58	82	T	82
206	3	0	H	O	oil	81	T	82
207	4	0	H	O	oil	86	V	82
208	2	1	H	NH	oil	11	U	83

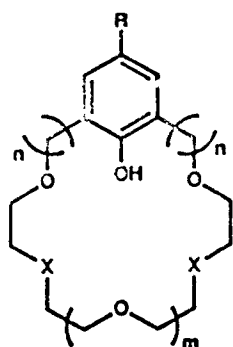
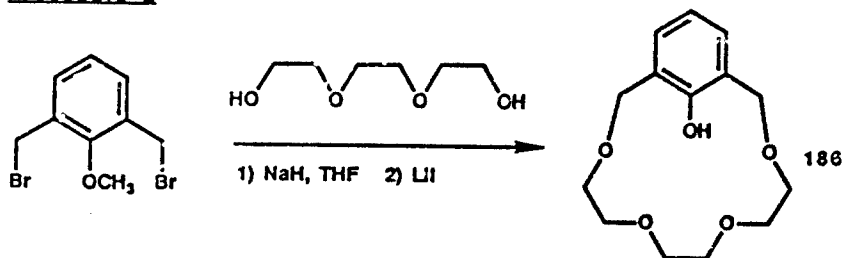


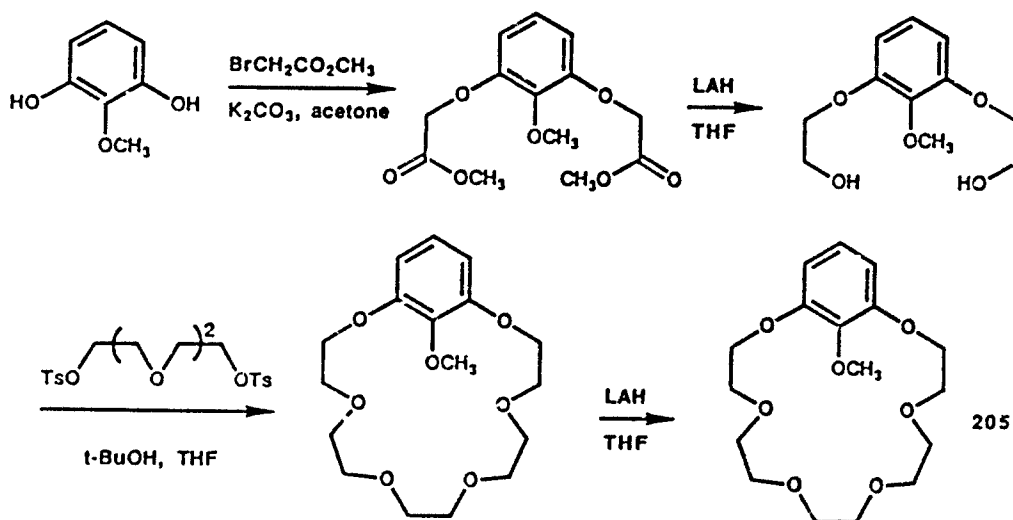
Figure XVI

modifications. The crowns containing a nitro-substituent were prepared by nitrating the initially formed crown phenol using sodium nitrite and nitric acid.³⁰ The macrocycles containing the 4-chloro-substituent were obtained from 1-allyloxy-4-chloro-2,6-bis-(hydroxymethyl)benzene which was converted to the dibromide followed by ring closure to obtain the crown. The allyl blocking group was later removed.⁷⁸ Azo-substituted crowns 197-201 (Figure XVI, Table 12) were obtained according to Procedure S followed by reaction with the appropriate diazonium salt.^{79,80} Crown hydroquinones 202-204 were also obtained by a modification of Procedure S. 1,4-Dimethoxy-2,6-

Procedure S



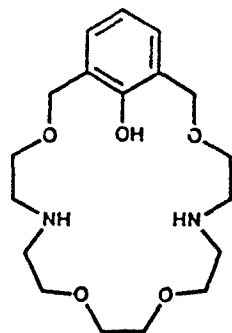
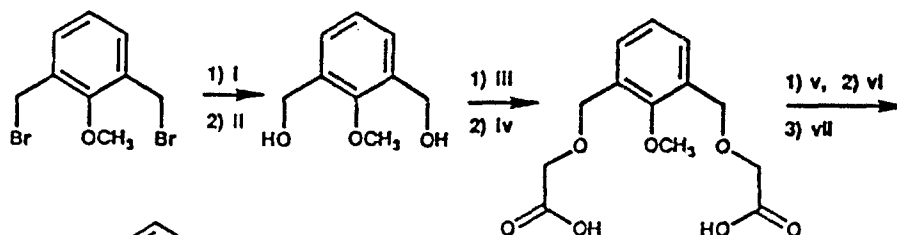
Procedure T



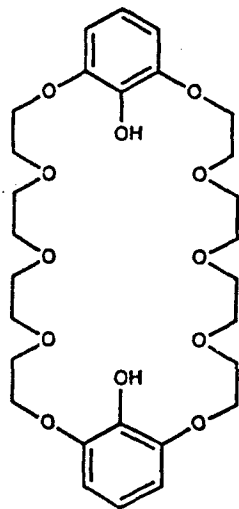
bis-(hydroxymethyl)benzene was used to form the crown using the appropriate glycol ditosylate. The dimethoxybenzene residue was oxidized to the quinone with ceric ammonium nitrate then reduced to the hydroquinone with sodium dithionite.^{81,82} Crown phenols 205-207 were obtained

according to Procedure T.⁸² Diaza-crown phenol 208 was obtained as outlined in Procedure U.⁸³ Crowns 209 and 210 (Figure XVII) were synthesized by a modification of Procedures T and U.^{78,82}

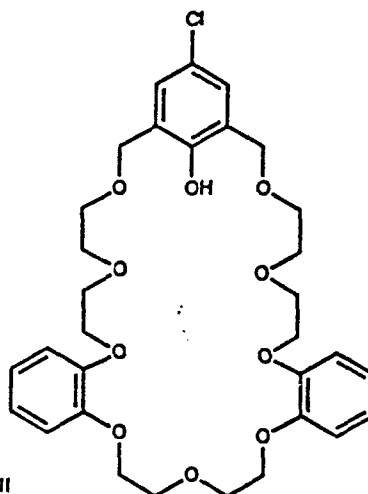
Procedure U



(I) AcOK, AcOH; (II) NaOH, EtOH_(aq);
(III) ClCH₂CO₂H, t-BuOK, t-BuOH,
then PTSA, EtOH; (iv) NaOH,
EtOH_(aq), then HCl; (v) (COCl)₂, C₆H₆;
(vi) NH₂CH₂CH₂OCH₂CH₂OCH₂CH₂NH₂,
Et₃N, toluene; (vii) LAH, THF



209) 61%, mp: 91-93°C, ref. 82



210) 64%, oil, ref. 78

Figure XVII

These PICEs have been studied to determine acid dissociation constants and complexation properties with amines, transition metal ions, heavy metal ions, and alkali and alkaline earth metal ions.^{7,74,77-80,84} Some of the crowns have been used to determine the presence of specific cations. The chromogenic crown phenols change color upon formation of a complex.

10. PROTON-IONIZABLE BENZO-CROWNS CONTAINING AN INTRAANNULAR CARBOXYLIC ACID.

Many of the PICEs already described contain benzoic acid type functions but the compounds discussed in this section have an intraannular carboxylic acid group attached directly to a

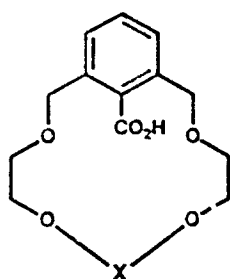


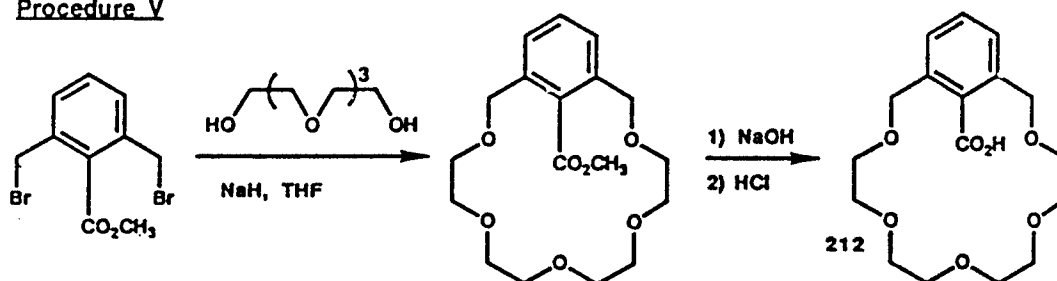
Figure XVIII

benzene ring. Benzoic acid-containing crowns 211-213, 216, 218, and 219 (Figure XVIII, Table 13) were prepared either by Procedure V or by a modification of Procedure V.⁸⁵⁻⁸⁷ Compound 212 is shown as an example. Most of these crown acids were also prepared by Procedure W.⁸⁶⁻⁸⁸ Complexation and transport of Li^+ , Na^+ , K^+ , and Ca^{2+} by these intraannular carboxylic acid-containing crowns have been studied.^{86,89}

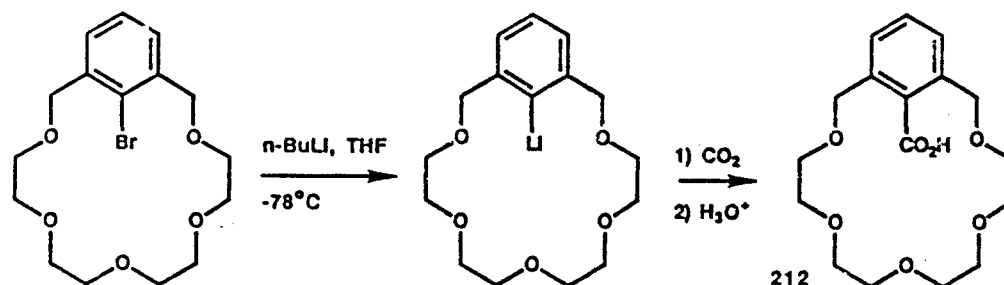
Table 13. Crown Ethers With an Intraannular Carboxylic Acid Group (E = CH_2CH_2) (Figure XVIII)

Number	X	mp($^{\circ}\text{C}$)	Yield(%)	Proc	Ref
211	E	106-112	34	V,B	86,87
212	EOE	100-101	82	V,B	86,87
213	EOEOE	86-95	68	V,B	86,87
214	EOEOEOE	78-79	55	B	87,88
215	EOEOEOEOE	oil	58	B	87,88
216	EOEOEOEOEOE	oil	34	V,B	86
217	EOEOEOEOEOEOE	oil	36	B	87,88
218		213-214	70	V	85
219		172-181	98	V	85

Procedure V



Procedure W



11. PROTON-IONIZABLE CROWN ETHERS CONTAINING PHOSPHOROUS.

Phosphoric acid-containing ionizable crown ethers are more acidic than their carboxylic acid counterparts and some have more than one ionizable proton. Hydrogen phosphate crowns 220-225 (Figure XIX, Table 14) have the ionizable group as an intraannular hydroxy. These ligands

Table 14. Dialkyl Hydrogen Phosphate Crown Ethers
(Reference 90) (Figure XIX)

Number	n	R	mp(°C)	Yield(%)
220	1	H	104-106	33
221	1	n-octyl	oil	47
222	2	H	106-108	75
223	2	n-octyl	88-89	65
224	2	n-decyl	89-91	73
225	2	n-hexadecyl	98-100	77

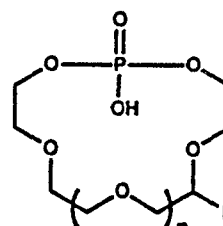
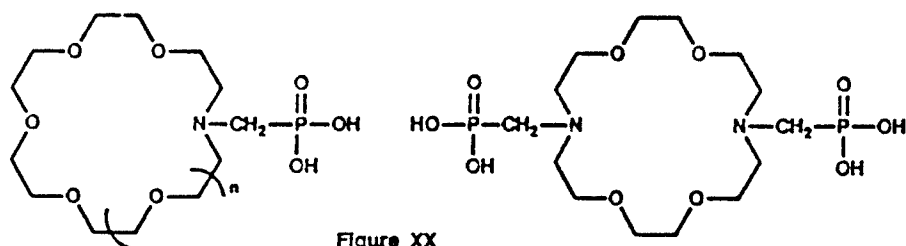


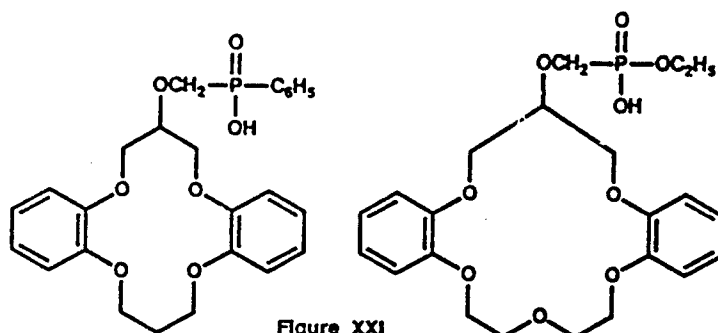
Figure XIX

were obtained by combining the appropriate glycol with phosphorous oxychloride at -70°C in dichloro-methane. The resulting crowns containing phosphorous chloride group were hydrolyzed to the hydrogen phosphate crowns by water in dioxane.⁹⁰ Phosphonomethyl-containing aza-crowns 226-228 (Figure XX) were obtained by reacting the corresponding aza-crown with phosphoric acid, formaldehyde, hydrochloric acid, and water.²⁵ Dibenzo-crown phosphinic acid 229 (Figure XXI) and crown phosphonic acid 230 were prepared by reacting the hydroxy dibenzo-crown ether with chloromethylphenyl phosphinic acid and monoethyl iodomethyl phosphonic acid respectively.^{56,91}



226) $n=0$,
227) $n=1$, yield: 74%, mp: 74-78°C, ref. 25

228) ref. 25



229) yield: 40%, mp:
170.5-171°C, ref. 91

230) yield: 88%, mp:
48-52°C, ref. 56

Figure XXI

These phosphoric acid-containing crowns were studied in transport experiments with alkali metal ions and with Zn^{2+} , Ag^+ , Pb^{2+} , Mg^{2+} , Cd^{2+} , and Ni^{2+} .^{90,92} Thermodynamic and kinetic studies were carried out on the side arm interactions of 229.⁵⁶

12. CROWN ETHERS CONTAINING A PROTON-IONIZABLE PYRIDINE-DERIVED SUBCYCLIC UNIT.

Crown ethers containing a proton-ionizable subcyclic unit are unique in that the anion formed upon removal of the proton is actually part of the crown ether ring. Thus, after complexation, a negative charge is in close proximity to the positively charged cation in the cavity of the macrocycle. Crown ethers 231-245 (Figure XXII, Table 15) have an ionizable proton on the ring nitrogen. The pyridine of the crown ether is in the 4-pyridone form, as shown, as determined by an x-ray crystal structure analysis.⁹³ The general synthetic procedure is

outlined in Procedure X.⁹³⁻⁹⁵ The synthesis of compound 232 is given as an example. Using the same synthetic procedure, 4-pyridono-14-crown-4 compounds 246-248 (Figure XXIII, Table 16) were also obtained.⁹⁶

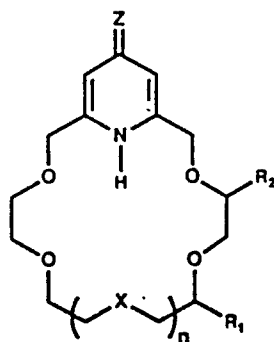


Figure XXII

As an extension of the synthesis of the above pyridono-crown ethers, pyridone-N-hydroxide-containing compounds 249-252 (Figure XXIV, Table 17) were prepared. The crown N-hydroxides were obtained using a modification of Procedure X. The crown was purified as the THP-protected material and subjected to oxidation

Table 15. Crown Ethers Containing the 4-Pyridone Subcyclic Unit (Procedure X) (Figure XXII)

Number	n	R ₁	R ₂	X	Z	mp(°C)	Yield(%)	Ref
231	0	H	H	O	O	150-151	14	93
232	1	H	H	O	O	104-105	26	93
233	2	H	H	O	O	oil	23	93
234	1	-n-C ₈ H ₁₇	H	O	O	41.5-43	38	93
235	0	-n-C ₈ H ₁₇	H	O	O	wax	52	94
236	1	-C ₆ H ₆	H	O	O	90.5-93	29	94
237	2	-n-C ₈ H ₁₇	H	O	O	oil	28	94
238	1	H	H	S	O	63-64	11	93
239	0	H	H	O	S	153-155	46	94
240	0	-n-C ₈ H ₁₇	H	O	S	82-85	8	94
241	1	H	H	O	S	182-183	62	94
242	1	-n-C ₈ H ₁₇	H	O	S	118-120	40	94
243	1	-C ₆ H ₆	H	O	S	145-148	12	94
244	0	H	-CH ₂ OCH ₂ CH-CH ₂	O	O	oil	38	95
245	1	-CH ₂ OCH ₂ CH-CH ₂ H	H	O	O	77	35	95

Table 16. 14-Crown-4 Macrocycles Containing the 4-Pyridone Subcyclic Unit (Procedure X, Reference 96) (Figure XXIII)

Number	R	Yield (%)	mp(°C)
246	H	28	179-180
247	n-C ₈ H ₁₇	35	123.5-124.5
248	-CH ₂ C ₆ H ₆	21	168-169

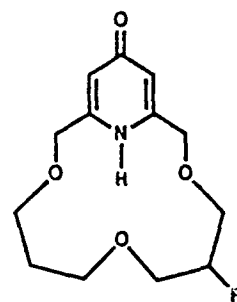


Figure XXIII

using meta-chloroperoxybenzoic acid in methylene chloride at 0°C.⁹⁷ It was determined that these compounds exist as shown in Figure XXIV in solution but in the solid state, they exist as the crown 4-hydroxypyridine-N-oxide.⁹⁷

Several proton-ionizable pyridino diester-crown ethers have also been synthesized. These compounds have been shown to exist in the 4-hydroxypyridine form, unlike the non-ester 4-

Procedure X

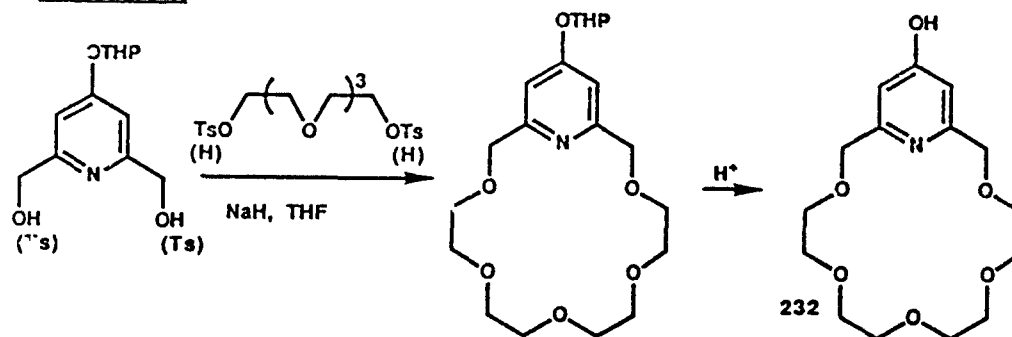


Table 17. Crown Ethers Containing the 4-Pyridone-N-Hydroxide

Subcyclic Unit (Procedure X, modified) (Reference 17) (Figure XXIV)

Number	x	mp(°C)	Yield(%)
249	-CH ₂ CH ₂ CH ₂ OCH ₂ CH ₂ CH ₂ -	205-206(dec)	10
250	-CH ₂ CH ₂ CH ₂ OCH ₂ CH(n-C ₈ H ₁₇)CH ₂ -	147-148.5	15
251	-CH ₂ CH ₂ OCH ₂ CH ₂ OCH ₂ CH ₂ -	135	4
252	-CH ₂ CH ₂ OCH ₂ CH ₂ OCH ₂ CH ₂ OCH ₂ CH ₂ -	166	5

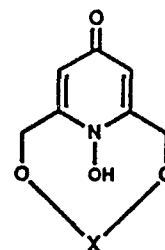


Figure XXIV

Table 18. 4-Hydroxypyridine Diester Crown Ethers (Procedure Y, Reference 98) (Figure XXV)

Number	n	R	mp(°C)	Yield(%)
253	1	H	142-143	76
254	1	CH ₃ (S,S)	95-97	30
255	1	Ph(S,S)	119-122	3.1
256	2	H	85-89	78

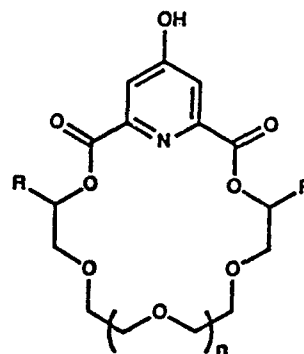
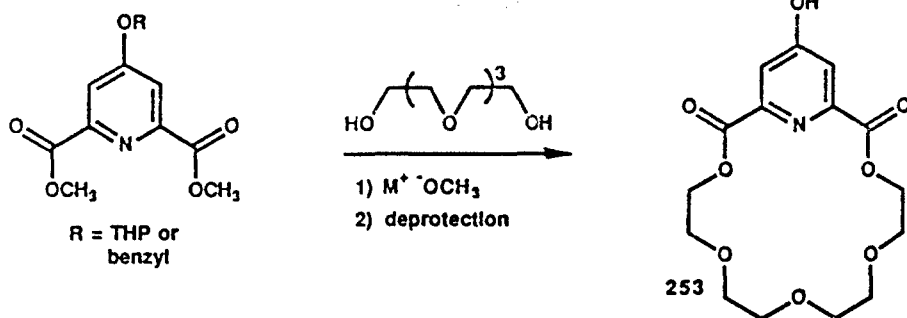


Figure XXV

pyridone crowns.⁹⁸ Macrocycles 253-255 (Figure XXV, Table 18) were obtained by transesterification of 4-O-protected dimethyl chelidamate and the appropriate glycol (Procedure Y) using a metal methoxide base and molecular sieves to remove the methanol. Subsequent deprotection yielded the 4-hydroxypyridine diester-crown ethers.⁹⁸

These proton-ionizable pyridine-containing macrocycles have been examined as carriers in transport studies with alkali, alkaline earth, and some transition metal cations using bulk liquid and emulsion liquid membrane systems. The crowns containing chiral substituents were

Procedure Y



also used in chiral molecular recognition experiments. Acid dissociation constants have been determined as well. It has been shown that transport can be "switched" on or off by adjusting the pH of the aqueous phase.^{6,14,93,95-101} Because of the lability of the ester function, these crowns were not as effective in transporting metal ions as the corresponding polyether crowns.

13. PROTON-IONIZABLE CROWN ETHERS CONTAINING A TRIAZOLE SUBCYCLIC UNIT.

The triazole unit provides another way of incorporating a proton-ionizable subcyclic unit into a crown ether so that, upon ionization, the negative charge is on the macrocyclic ring itself. Triazolo-crowns 256-267 (Figure XXVI, Table 19) were synthesized according to the

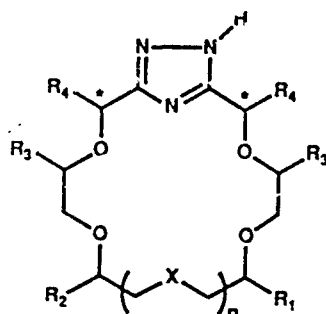


Figure XXVI

sequence shown in Procedure Z.^{13,95,102} Two separate solutions, one containing the THP-protected bis-(chloromethyl)-1,2,4-triazole in THF and another containing the dipotassium glycooxide in THF were added simultaneously to refluxing THF to obtain the protected crown. Deprotection using methanolic HCl provided the proton-ionizable crown. Triazole crowns 268 and 269 were obtained by a different method as shown in Procedure AA.¹⁰³ The overall yields for Procedure Z were somewhat higher

Procedure Z

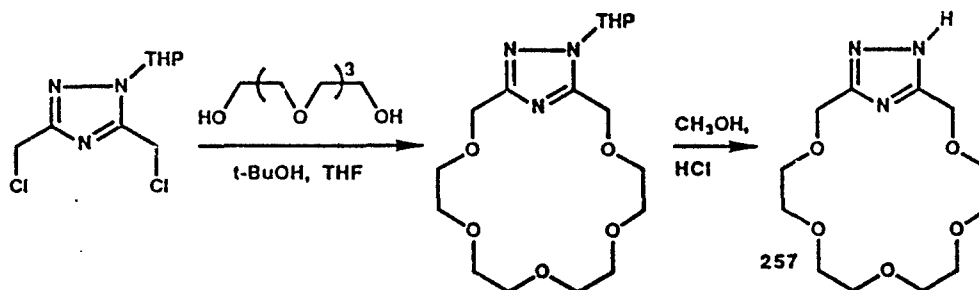
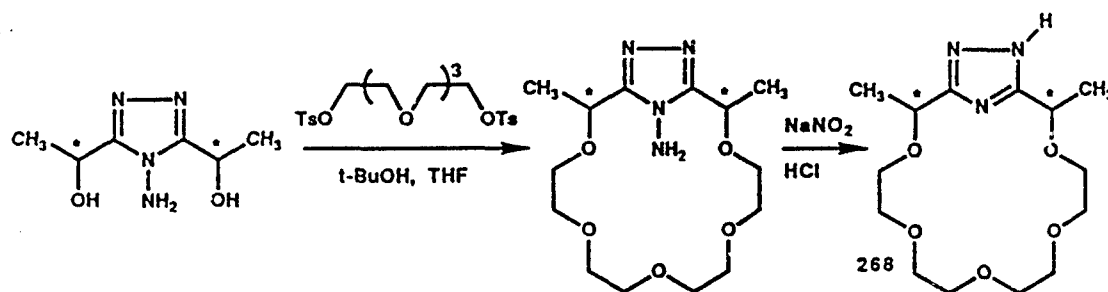


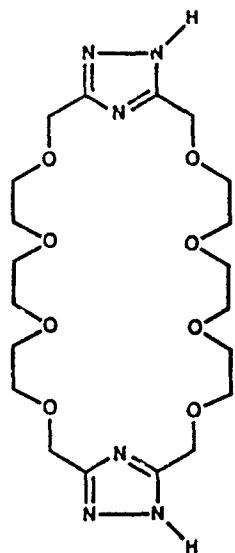
Table 19. Crown Ethers Containing the 1,2,4-Triazole Subcyclic Unit (Figure XXVI)

Number	n	R ₁	R ₂	R ₃	R ₄	X	mp(°C)	Yield(%)	Proc	Ref
256	0	H	H	H	H	O	90-92	1.1	Z	102
257	1	H	H	H	H	O	112-114	33	Z	102
258	2	H	H	H	H	O	71-72	15	Z	102
259	1	H	H	CH ₃ (S,S)	H	O	oil	33	Z	102
260	0	n-C ₈ H ₁₇	H	H	H	O	oil	24	Z	13
261	1	n-C ₈ H ₁₇	H	H	H	O	wax	36	Z	13
262	1	C ₆ H ₆	H	H	H	O	oil	48	Z	13
263	1	H	H	n-C ₈ H ₁₇	H	O	syrup	25	Z	13
264	0	n-C ₁₁ H ₂₃	n-C ₁₁ H ₂₅	H	H	O	70	26	Z	95
265	1	n-C ₁₂ H ₂₅	n-C ₁₂ H ₅	H	H	O	77.5-79	48	Z	95
266	1	H	H	H	H	S	95.5-97	17	Z	13
267	1	n-C ₈ H ₁₇	H	H	H	S	oil	9	Z	13
268	1	H	H	H	CH ₃ (S,S)	O	110	32 ^a	AA	103
269	1	H	H	H	CH ₃ (R,R)	O	oil	89 ^a	AA	103

^a Yield on last step.Procedure AA

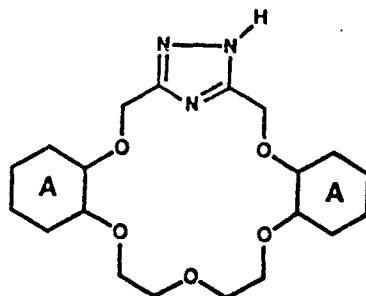
than those for Procedure AA. Triazolo-Crown 270 (Figure XXVII) was isolated and characterized in addition to crown 256.¹⁰² Dibenzo-crown 271 and dicyclohexano-crown 272 (Figure XXVIII) were obtained by Procedure Z also using the appropriate glycols.¹³

Three triazolo diester-crowns, 273-275 (Figure XXIX, Table 20), were also synthesized using the same procedure described for the hydroxypyridino diester-crowns, Procedure Y, but starting with dimethyl 1-benzyl-1H-1,2,4-triazole-3,5-dicarboxylate.^{104,105} By x-ray crystal structure analysis, it was shown that the triazole ring hydrogen is located on the nitrogen of the



270) yield: 7.4%, mp:
128-9°C, ref. 102

Figure XXVII



271) A= benzo, yield: 71%, mp:
203.5-204.5°C, ref. 103
272) A= cyclohexano, yield: 40%,
ref. 103

Figure XXVIII

Single ion transport as well as competitive ion transport studies were carried out. Some triazolo-crowns had a special affinity for silver cations. Molecular recognition for the enantiomers of chiral

triazole ring as shown in Figure XXIX for the diester crowns and on one of the outside nitrogens in the triazole-containing polyether crowns as shown in Figure XXVI.^{102,104}

The triazolo-crowns have been used to transport alkali, alkaline earth, and transition metal cations in the bulk liquid and emulsion liquid membrane systems.

Table 20. 1,2,4-Triazole Diester Crown Ethers

(Procedure Y, Reference 104) (Figure XXIX)

Number	n	R	mp(°C)	Yield(%)
273	1	H	140-142.5	16
274	2	H	132.5-134	19
275	1	CH ₃ (S,S)	114-116	22

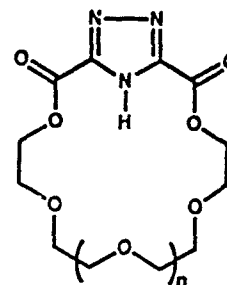


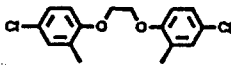
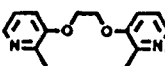
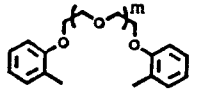
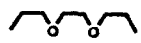
Figure XXIX

amines by the triazolo-crowns having chiral substituents was studied. Thermodynamic studies to determine acid dissociation constants and cation complex stabilities have also been performed.^{15,95,103-107}

14. PROTON-IONIZABLE CROWN ETHERS CONTAINING SULFONAMIDE GROUPS.

Another group of proton-ionizable crown ethers in which the anion is a member of the macrocyclic ring are the sulfonamido-crowns. The proton on one or both of the sulfonamide groups of compounds 276-290 (Figure XXX, Table 21) can be removed to provide better ligating sites for metal cations. Sulfonamide crowns 276-290 were obtained by following the general procedure shown in Procedure BB.¹⁰⁷⁻¹⁰⁹ The starting bis-(sulfonylchloride) compound was

Table 21. Crown Ethers Containing the Sulfonamide Group (Procedure BB)
(Figure XXX)

Number	n	X	mp(°C)	Yield(%)	Ref
276	1		268-271	23	107
277	2	"	302-305	10	107
278	1		232-234	10	108
279	2	"	305-306	19	108
280	1		131-133	1	108
281	0		290-293	25	108
282	0		253-256	6	108
283	1		230-232	12	109
284	2	"	256-259	17	109
285	1		183-186	8.8	109
286	0	 m - 0	229	70	109
287	0	" m - 1	277-279	6	109
288	1	" m - 0	183	91	109
289	1	" m - 1	164-165	10	109
290	0		252	72	109

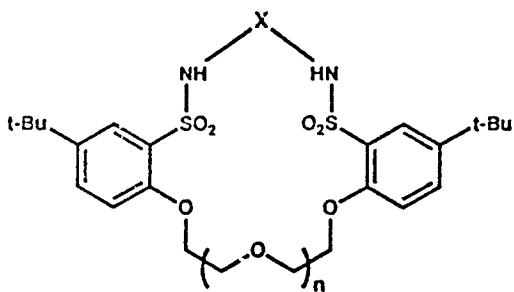
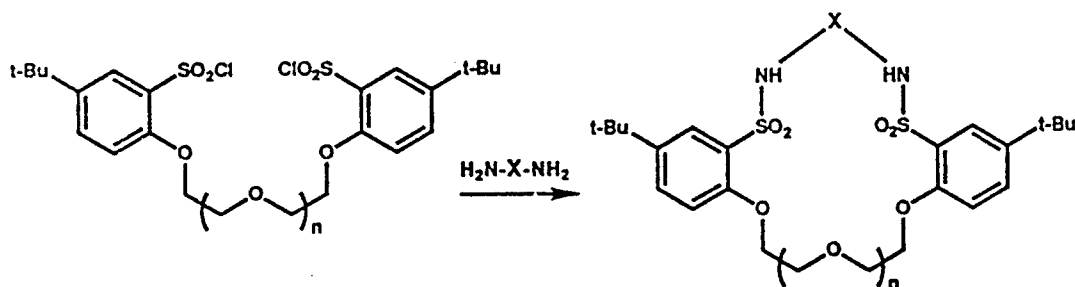


Figure XXX

combined with the appropriate diamine in dichloromethane to provide the sulfonamido-crown. The starting bis-(sulfonylchloride) was obtained by reacting p-*t*-butylphenol and the appropriate glycol dichloride. Addition of chlorosulfonic acid to the resulting bis-phenol provided the starting material for the sulfonamido-crowns.¹⁰⁷

These ionizable sulfonamido-crown ethers were

Procedure BB

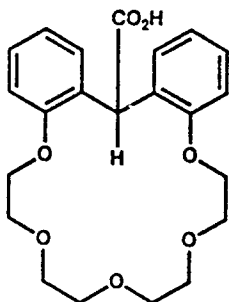


tested as carriers for the alkali metal cations in bulk liquid membrane transport systems. X-ray crystal structure analysis was performed to determine the conformation of these carriers. Also thermodynamic studies were done to determine acid dissociation constants. It was shown that ionization of both protons is required for cation transport.¹⁰⁷⁻¹¹⁰

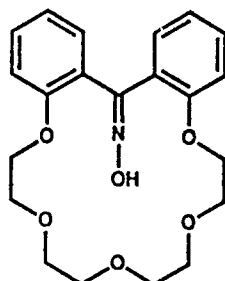
15. MISCELLANEOUS PROTON-IONIZABLE CROWN ETHERS.

Proton-ionizable crown ethers 291-307 did not easily fit into any of the categories

previously discussed so they will be described here. Crowns 291 and 292 (Figure XXXI) were synthesized and used in a study of carbocations, carbanions, and carbenes as ring members in crown ethers.¹¹¹ Bis-(crown ether) dyes 293-297 (Figure XXXII) were synthesized with expectations that they would show very different complexation properties from the corresponding monocyclic crown dyes. The bis-(crown ether) effect was not very remarkable.^{44,80} These crowns

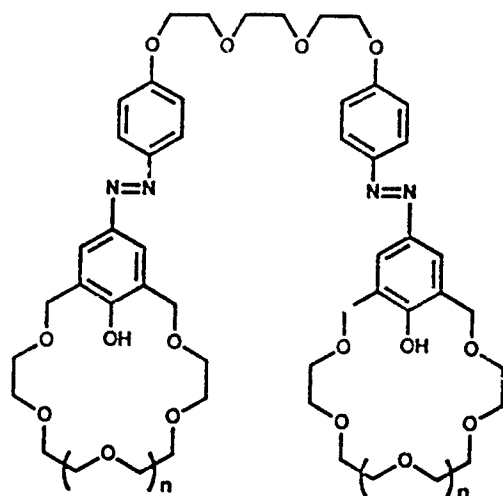


291) yield: 90%, mp: 177°C, ref. 112.

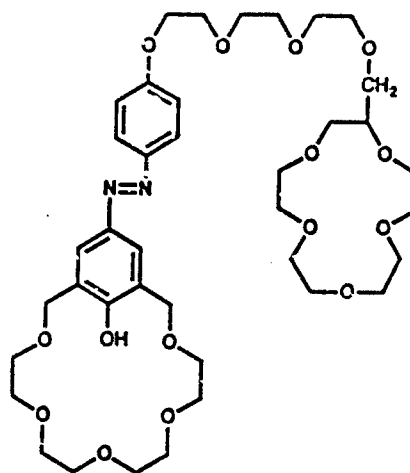


292) yield: 91%, mp: 173-4°C, ref. 112

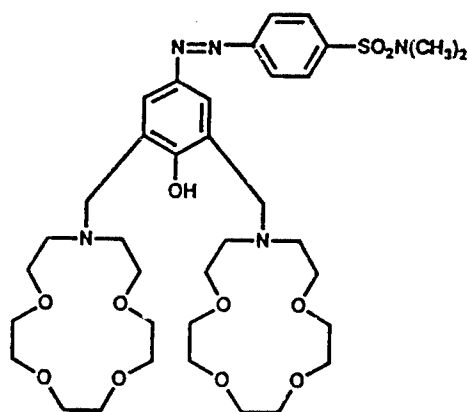
Figure XXXI



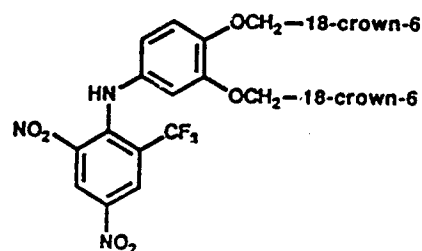
293) $n = 0$; mp: 150°C (dec); Ref. 80
 294) $n = 1$; mp: 123°C (dec); Ref. 80



295) oil; Ref. 80



296) oil; Ref. 80



297) yield 71%; oil; Ref.44

Figure XXXII

were synthesized in a similar manner to crowns already discussed. Crown acids 298-304 (Figure XXXIII, Table 22) containing an intraannular sulfonic acid group were synthesized by Procedure W using sulfur dioxide instead of carbon dioxide.⁸⁷ PICE 305 (Figure XXXIV) was obtained using Procedure J.^{17,19} Thiacrowns 306 and 307 (Figure XXXV, Table 23) were obtained as outlined in Procedure CC and tested for the extraction of silver.¹¹²

Table 22. Crown Ethers Containing an
Intraannular Sulfonic Acid Group
(Procedure D, Reference 87) (Figure XXXIII)

Number	n	mp(°C)	Yield(%)
298	0	162-104	59
299	1	101-104	67
300	2	oil	72
301	3	oil	71
302	4	oil	42
303	5	oil	70
304	6	oil	74

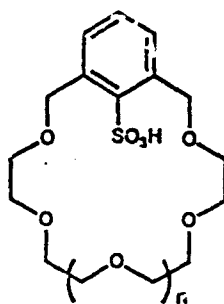
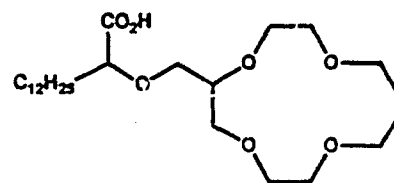


Figure XXXIII



305) oil; yield 27%; ref. 17, 19

Figure XXXIV

Table 23. Chromogenic Thiacrowns (Procedure CC,
Reference 112) (Figure XXXV)

Number	R ₁	R ₂	R ₃	mp(°C)	Yield(%)
306	H	OH	H	133-134	51
307	OH	H	Cl	133-134	53

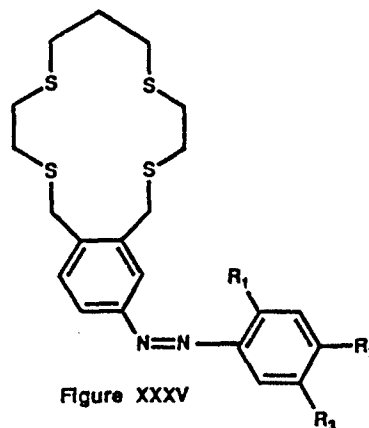
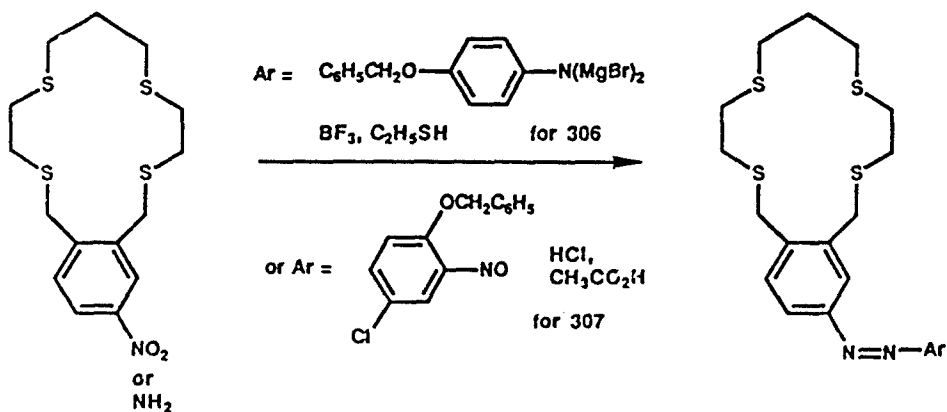


Figure XXXV

Procedure CC



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