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METAL ION COMPLEXATION BY IONIZABLE CROWN ETHERS

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I. ABSTRACT

During the report period a variety of new lipophilic ionizable crown ethers with pendent proton-ionizable groups has been synthesized. The ligands possess one or more ionizable group (carboxylic acid, phosphonic acid monoethyl ester, para-nitrophenol, phosphonic acid) attached to crown ether, monoazacrown ether or diazacrown ether frameworks. These novel chelating agents have either pendent or inward-facing proton-ionizable groups. Such lipophilic proton-ionizable crown ethers are designed for use in multiphase metal ion separations (solvent extraction, liquid membrane transport). In addition a series of proton-ionizable crown ethers without lipophilic groups was prepared to study how structural variations within the ligand influence metal ion complexation in homogeneous media as assessed by NMR spectroscopy or titration calorimetry. A third class of new metal ion-complexing agents is a series of lipophilic acyclic polyether dicarboxylic acids.

Competitive solvent extractions of alkali metal and alkaline earth cations and of the mixed species have been conducted to reveal the influence of ring size, nature and attachment site of the lipophilic group, sidearm length, and proton-ionizable group identity and location upon the selectivity and efficiency of metal ion complexation. In addition to such studies of structural variation within the lipophilic proton-ionizable crown ether, the effect of changing the organic solvent and variation of the stripping conditions have been assessed. The influence of structural variations within lipophilic acyclic polyether dicarboxylic acids upon competitive solvent extraction of alkaline earth cations has been probed. Also a new chromogenic, di-ionizable crown ether with extremely high selectivity for Hg^{2+} has been discovered.

Complexation of alkali metal cations by proton-ionizable crown ethers in homogeneous media has been probed by ^1H NMR spectroscopy and titration

calorimetry to provide information about the conformational rigidity of complexes in solution as well as quantitative data concerning the thermodynamics of the metal ion complexation process.

The ability of proton-ionizable crown ethers to function as selective metal ion carriers in liquid membrane transport processes has been examined in both bulk liquid membrane and polymer-supported liquid membrane transport systems. Variation of experimental parameters, such as the organic solvent in the liquid membrane, pH of the source and receiving aqueous phases, etc., provides important insight into the controlling factors for the proton-coupled metal ion transport process.

New acyclic and cyclic polyether carboxylic acid resins have been prepared by condensation polymerization and characterized. Alkali metal cation sorption by such resins is found to be strongly influenced by the incorporation of cyclic polyether sites for metal ion complexation.

II. RESULTS AND DISCUSSION

A. Synthesis of Proton-Ionizable Cyclic and Acyclic Polyether Ligands

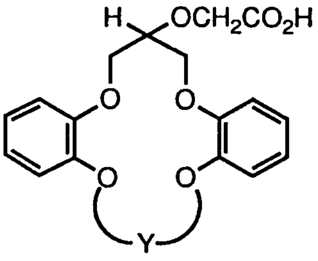
To probe the effects of structural variation within the complexing agent upon metal ion complexation by proton-ionizable polyethers, a variety of new cyclic and acyclic ligands has been prepared. The common features of these ligands include the presence of one or more ionizable group (carboxylic acid, phosphonic acid monoethyl ester, para-nitrophenol, phosphonic acid) and at least two ethereal oxygen atoms. Cyclic polyethers with either pendent or inward-facing, proton-ionizable groups are included. Ligands which are to be utilized in multiphase separations (e.g. solvent extraction or liquid membrane transport of metal ions) often have a lipophilic alkyl group attached to retain the complexing agent in the organic phase. On the other hand, for ligands whose metal ion complexation behavior is to be assessed in homogeneous media by nuclear magnetic resonance spectroscopy or by titration calorimetry, such lipophilic groups are not necessary.

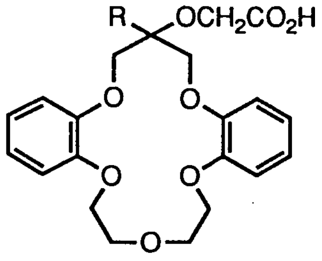
1. Mono-Ionizable Crown Ethers with Pendent Acid Groups

Our first proton-ionizable crown ethers were crown ether carboxylic acids **1-4**.[1-3] The dibenzocrown ether ring system is readily accessible and amenable to the study of structural variations within the ligand upon the efficiency and selectivity of monovalent metal ion complexation. Such structural variations include the influence of ring size, the attachment site(s) for one or more lipophilic groups, the length of the sidearm which attaches the proton-ionizable group to the crown ether ring, and the identity of the proton-ionizable group.[4-6]

For derivatives of sym-dibenzo-16-crown-5-oxyacetic acid (**3**), the highest Na^+ selectivity in competitive solvent extraction of alkali metal cations from aqueous solution into chloroform was observed when an eight-carbon lipophilic group was attached to the center carbon of the three-carbon bridge (i.e. in **11**) rather than to the carbon adjacent to the carboxyl group in the sidearm or when two four-carbon lipophilic groups were attached to the two benzene rings.[5,6] It was proposed that the enhanced Na^+ selectivity results from extension of the lipophilic group away from the polar polyether ring which orients the carboxyl group of the sidearm over the crown ether cavity and provides pre-organization of the binding site.

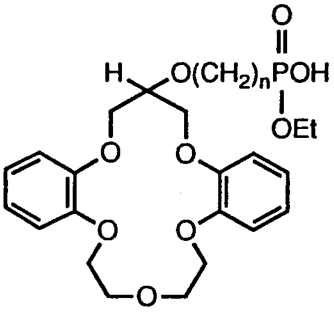
To examine the influence of structural variation within a lipophilic group attached to the center carbon of the three-carbon bridge, the new dibenzo-16-crown-5 carboxylic acids **5-7,9-10,12-14,16-21** were synthesized. When considered in combination with previously-prepared crown ether carboxylic acids **8,11,15**, the lipophilic group is systematically varied from methyl to



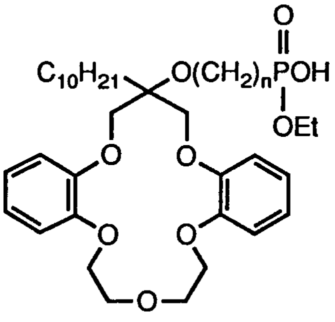


	Y
1	$-CH_2CH_2-$
2	$-CH_2CH_2CH_2-$
3	$-CH_2CH_2OCH_2CH_2-$
4	$-CH_2(CH_2OCH_2)_2CH_2-$

	R
5	$-CH_3$
6	$-C_2H_5$
7	$-C_3H_7$
8	$-C_4H_9$
9	$-C_5H_{11}$
10	$-C_6H_{13}$
11	$-C_8H_{17}$
12	$-CH(C_2H_5)(C_5H_{11})$
13	$-C_{10}H_{21}$
14	$-C_{12}H_{23}$
15	$-C_{14}H_{29}$
16	$-C_{16}H_{33}$
17	$-C_{18}H_{37}$
18	$-C_{20}H_{41}$
19	$-C_3F_7$
20	$-C_6F_{13}$
21	$-C_8F_{17}$



22 (n = 1-4)



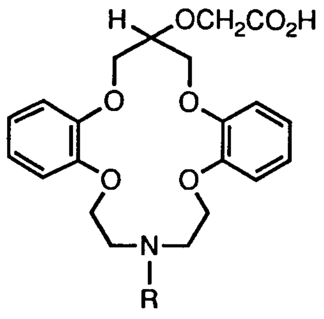
23 (n = 1-4)

ethyl to propyl to butyl to pentyl to hexyl and then by two carbon units from hexyl to $C_{20}H_{41}$. Compounds **11** and **12** are structural isomers in which the linear octyl group in **11** is replaced with a branched 2-ethylhexyl group in **12**. In **19-21**, the alkyl group has been replaced with fluoroalkyl groups of varying lengths. It is anticipated that the lipophilic group variation in **5-21** will alter the interfacial behavior of these metal ion complexing agents in solvent extraction and liquid membrane transport processes.

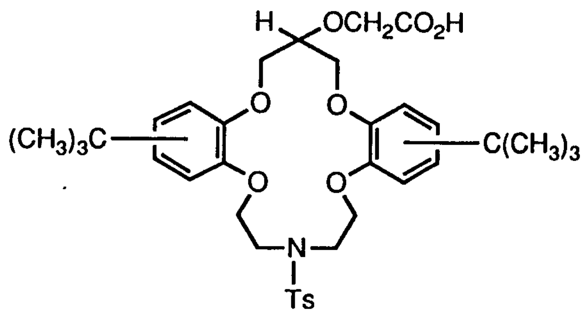
In earlier work we examined the influence of sidearm length variation upon alkali metal cation solvent extraction selectivity and efficiency by the lipophilic dibenzo-16-crown-5 phosphonic acid monoethyl esters **22**.[7] Varying the number of sidearm methylene groups from 1-4 markedly affected both the extraction selectivity and efficiency. Anticipating that the attachment of the lipophilic group to the center carbon of the three-carbon bridge might better position the proton-ionizable group over the polyether cavity, the new series of lipophilic dibenzo-16-crown-5 phosphonic acid monoethyl esters **23** with n = 1-4 has been prepared for evaluation in the solvent extraction of alkali metal cations.

Ligands **24-26** are dibenzo-16-crown-5-oxyacetic acid derivatives in which one polyether ring oxygen has been replaced with a nitrogen. For **24** and **26**, the attached tosyl group will withdraw electron density from the ring nitrogen. In **25**, the decyl group will donate electron density onto the ring nitrogen.

The proton-ionizable dibenzocrown ethers **1-23** all have attachment of the sidearm to the polyether ring through an oxygen atom of the sidearm. To determine the effect of the structural variation in which this linkage is through a carbon atom, two new series of dibenzocrown ether carboxylic acids were prepared. In comparison with **2** and **3**, a methylene group has been inserted at the sidearm attachment sites in **28** and **29**. (Attempts to synthesize



	R
24	-Ts
25	$-C_{10}H_{21}$



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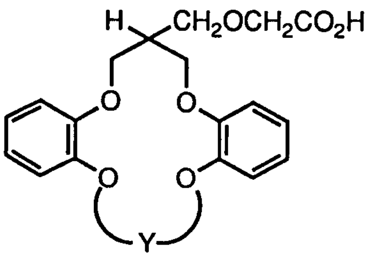
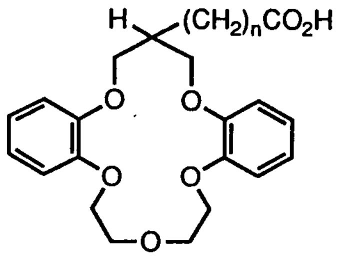
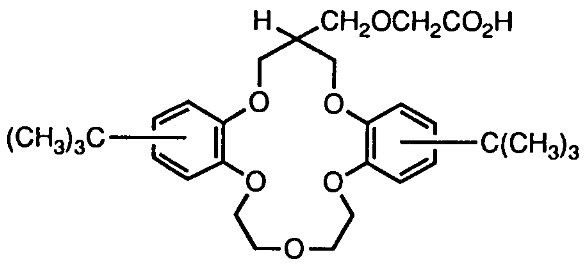


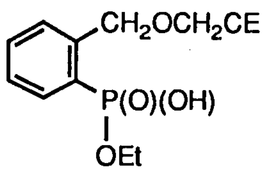
	Y
27	$-CH_2CH_2-$
28	$-CH_2CH_2CH_2-$
29	$-CH_2CH_2OCH_2CH_2-$



	n
30	0
31	1
32	2



33



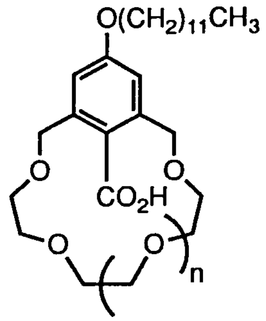
	CE
34	15-Crown-5
35	18-Crown-6

the dibenzo-13-crown-4 analog **27** were unsuccessful.) For **31** and **32**, ether oxygens have been removed completely from the sidearm. (Attempts to synthesize the analog **30** in which the proton-ionizable group is directly attached to the polyether ring were unsuccessful.) Although alkali metal cation complexation by **28,29,31,32** was to be studied in homogeneous solution by titration calorimetry, compound **33**, a lipophilic derivative of **29**, was also prepared for examination by solvent extraction.

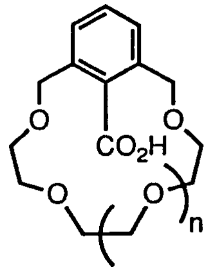
For use in ^1H NMR spectroscopic studies of the ligand conformation in alkali metal complexes, crown ether phosphonic acid monoethyl esters **34** and **35** were synthesized. In these ligands if both the ionized sidearm and the polyether ring simultaneously coordinate with an alkali metal cation, rotation about the C-C and C-O bonds in the sidearm will be restricted. This would produce non-equivalence of the diastereotopic benzylic hydrogens and a distinctive AB ^1H NMR absorption pattern.

2. Mono-Ionizable Crown Ethers with Inward-Facing Acid Groups

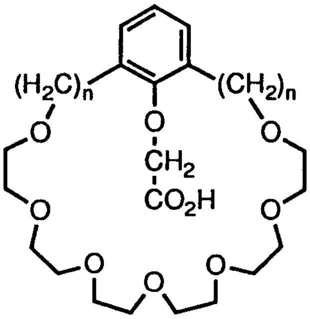
Our earlier studies have involved proton-ionizable crown ethers in which the acidic functional group was attached to the polyether framework with a flexible arm. To examine the structural variation of fixing the acidic group position so it is pointed into the polyether ring, the series of lipophilic crown ether benzoic acids **36-39** was prepared for use in studies of alkali metal cation solvent extraction. The non-lipophilic analogs **40-42** were reported by Cram and coworkers[8] and **40-43** by Reinhoudt and coworkers.[9,10] By adaptation of the procedure of Reinhoudt and coworkers,[9,10] the series of crown ethers with inward-facing carboxylic acid groups **36-39** was realized. In addition, the non-lipophilic analogs **40-43** were synthesized for investigations of the thermodynamics of alkali metal cation complexation by the corresponding crown ether carboxylates using titration calorimetry.



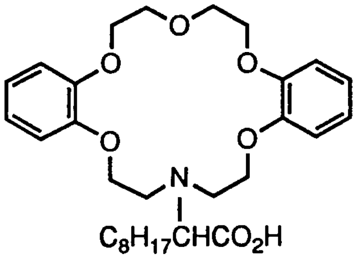
	n
36	1
37	2
38	3
39	4



	n
40	1
41	2
42	3
43	4



	n
44	0
45	1



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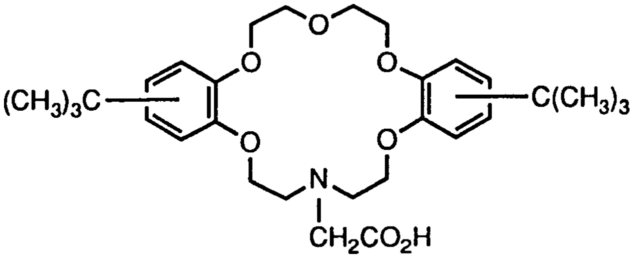


47

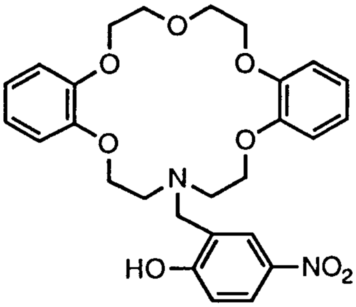
For ^{1}H NMR spectroscopic investigations of the corresponding alkali metal carboxylate salts, large ring crown ethers **44** and **45** with inward-facing oxyacetic acid groups were prepared. Ligands **44** and **45** differ in the atoms which connect the polyether portion to the benzene ring change from oxygen in the former to carbon in the latter. Of particular interest for these compounds is whether or not the oxyacetate group in an alkali metal carboxylate complex will have restricted rotation due to coordination with the polyether-bound metal ion.

3. Mono-Ionizable Monoazacrown Ethers with Pendent Acid Groups

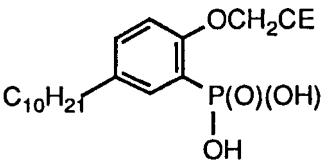
All of the crown ethers with pendent acid groups described above are examples of "C-pivot" lariat ethers in which the sidearm is attached to a carbon atom of the polyether ring. Previously we reported the synthesis of lipophilic crown ether amino acid **46** in which the sidearm is attached to the nitrogen atom of a monoazacrown ether.[11] To provide addition examples of such proton-ionizable N-pivot lariat ethers from which structure-complexation behavior relationships may be assessed, ligands **47** and **48** were prepared. Compounds **46** and **47** are structural isomers in which the attachment site of the lipophilic group is varied. In compound **48**, the proton-ionizable group has been changed to para-nitrophenol.

4. Di-Ionizable Crown Ethers with Pendent Acidic Groups

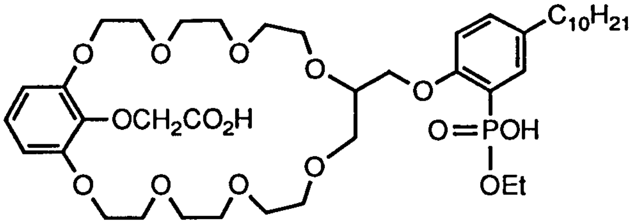
Di-ionizable crown ethers can form electroneutral complexes with divalent metal ions. The series of lipophilic crown ether phosphonic acids **49-53** was prepared which possess a single, di-ionizable group and crown ether ring sizes that vary from 14-crown-4 to 15-crown-5 to 18-crown-6 to 21-crown-7 to 24-crown-8.



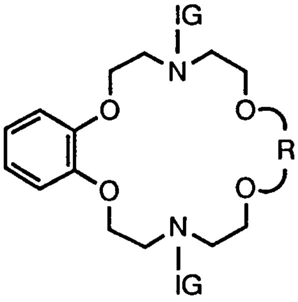
48

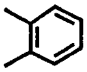
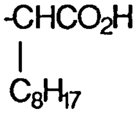
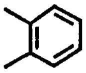
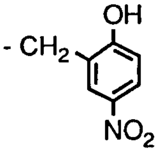
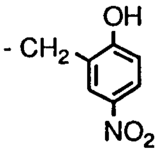


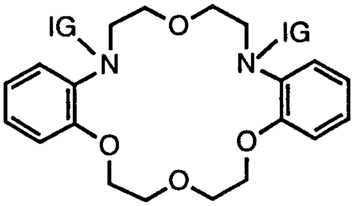
	CE
49	14-Crown-4
50	15-Crown-5
51	18-Crown-6
52	21-Crown-7
53	24-Crown-8

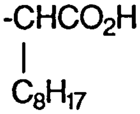
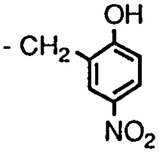


54



	R	IG
55		 $-\underset{C_8H_{17}}{\underset{\vert}{CHCO_2H}}$
56		
57		



	IG
58	 $-\underset{C_8H_{17}}{\underset{\vert}{CHCO_2H}}$
59	

5. A Di-Ionizable Crown Ether with Pendent and Inward-Facing Acidic Groups of Different Types

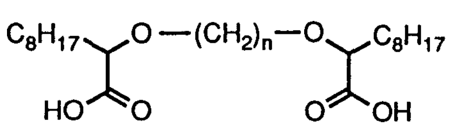
The sophisticated, lipophilic, di-ionizable crown ether **54** was also synthesized. This chelating agent possesses an inward-facing oxyacetic acid group and a pendent phosphonic acid monoethyl ester group. Since the latter is the more acidic of the two proton-ionizable functions, the metal ion complexing properties of compound **54** can be varied by pH adjustment of contacting aqueous solutions. When the solutions are acidic, only the pendent phosphonic acid monoethyl ester group will be ionized. On the other hand for basic solutions, both of the proton-ionizable groups will be dissociated.

6. Di-Ionizable Diazacrown Ethers with Pendent Acid Groups

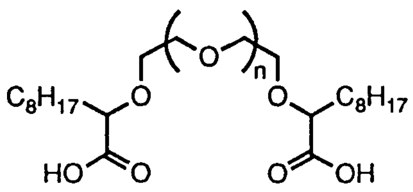
Attachment of acid group-containing sidearms to the nitrogen atoms of a diazacrown ether is an alternative synthetic route to di-ionizable ligands. Such ligands are of the N-pivot type. For evaluation of their metal ion complexation properties, novel di-ionizable crown ethers were prepared from two different diazadibenzo-18-crown-6 compounds. From 1,10-diazadibenzo-18-crown-6, both the lipophilic di-amino acid **55** and the di(para-nitrophenol)-substituted derivative **56** were synthesized. From 1,7-diazadibenzo-18-crown-6 which has less basic alkyl aryl amine nitrogens, the di(para-nitrophenol)-substituted derivative **59** was prepared. However attempts to form the lipophilic di-amino acid **58** were unsuccessful, giving only the mono-substituted product. Presumably the combination of a bulkyl lipophilic group and the reduced nucleophilicity of alkyl aryl amine nitrogens prevented the second substitution reaction. Di-ionizable crown ether **57** which is derived from 1,7-diaza-5,6-benzo-16-crown-5 was also prepared.

7. Lipophilic Di-Ionizable Acyclic Polyethers

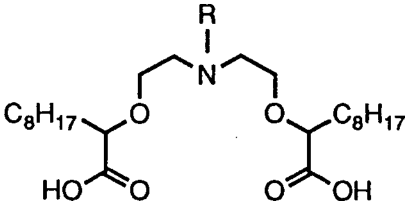
A versatile synthetic route to a variety of lipophilic acyclic polyether dicarboxylic acids was discovered and developed. The lipophilic



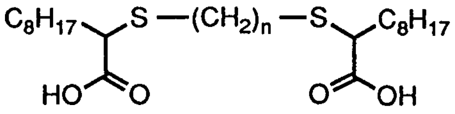
	n
60	2
61	3
62	4



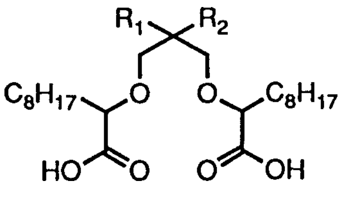
	n
63	1
64	2



	R
65	-Ts
66	$-C_6H_5$



	n
67	2
68	3



	R1	R2
69	-H	$-CH_3$
70	-H	$-CH_2C_6H_5$
71	-H	$-C_6H_5$
72	-H	$-C(C_6H_5)_3$
73	-H	$-C_{10}H_{33}$
74	$-CH_3$	$-CH_3$
75	$-CH_2CH_2-$	
76	$-CH_2CH_2CH_2-$	

acyclic polyether dicarboxylic acids **60-76** provide an excellent series with which structural variation within the ligands upon the selectivity and efficiency of alkaline earth cation complexation may be assessed. In **60-62** the number of methylene groups which separate the ether oxygens is changed from one to three. Compounds **60,63,64** provide a series in which the number of potential ether oxygen chelating sites is systematically varied. Comparison of results for compounds **63,65,66** will allow the influence of replacing one ether oxygen in **63** with a nitrogen atom for which the electron density may be altered. In **65** the electron density on the nitrogen atom will be much less than in **66** due to the strongly electron withdrawing tosyl group of the former. Lipophilic dicarboxylic acids **67** and **68** closely resemble **60** and **61** except for the replacement of the two ether coordinating sites in the latter with thioether ligation sites in the former.

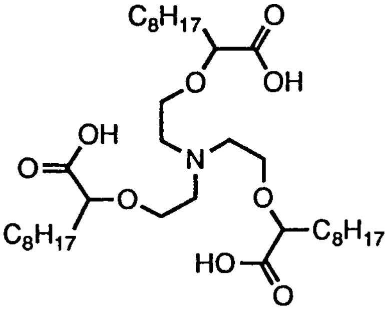
For the series of lipophilic acyclic diether carboxylic acids **61,69-76**, the substituents on the center carbon of the three-carbon bridge are varied widely. Such changes will alter the possible conformations of the acyclic di-ionizable polyether ligands.

8. A Lipophilic Tri-Ionizable Acyclic Polyether

Extension of the new synthetic method allowed the novel lipophilic acyclic polyether tricarboxylic acid **77** to be prepared. Examination of CPK space filling models suggests that **77** will be an efficient chelator for trivalent metal ions.

B. Acidities of Lipophilic Proton-Ionizable Crown Ethers

Since proton-ionizable crown ethers are effective metal ion complexing agents only in the dissociated form, knowledge of the pK_a values for such ligands is important for their application in separation processes. Unfortunately, the high lipophilicity of the proton-ionizable crown ethers



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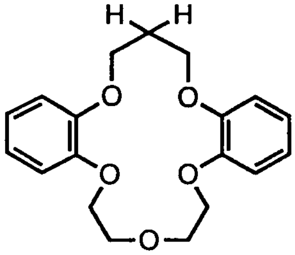

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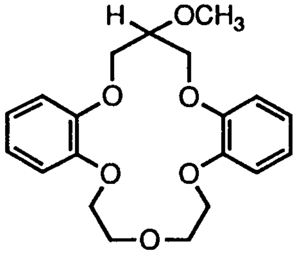

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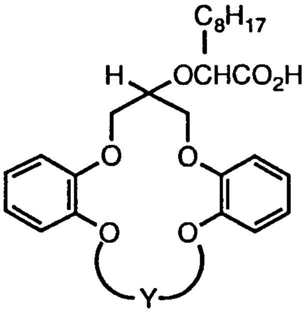
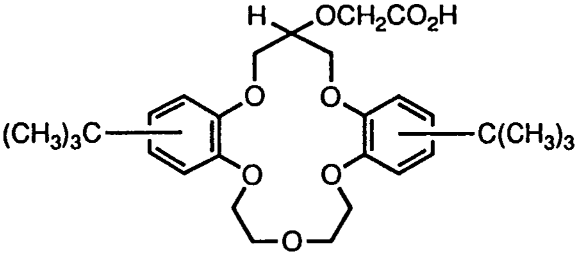


Y

80	$-CH_2CH_2CH_2-$
81	$-CH_2CH_2OCH_2CH_2-$
82	$-CH_2(CH_2OCH_2)_2CH_2-$



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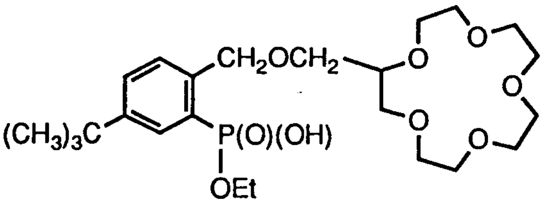
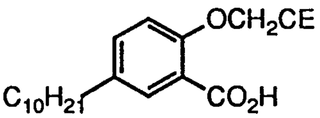


84



85 (CE = Crown Ether)

which we have designed and synthesized for use in solvent extraction and liquid membrane transport of metal ions makes it impossible to directly determine their pK_a values in water. To circumvent such difficulties, a technique for measuring the pK_a values in 70% dioxane-water (by volume) was developed.[12] In this mixed solvent system, dissociative behavior for 14 proton-ionizable crown ether compounds at 25.0 °C has been determined which allows the influence of structural variation (ring size, lipophilic group size and attachment site, identity of the proton-ionizable group) upon acidity to be assessed.[13] For six of the compounds, the dissociation behavior was also studied at 35.0 °C in 70% dioxane-water and the thermodynamic functions, ΔG°, ΔH° and ΔS°, for ionization were calculated.[13] By extension of this work to a series of dioxane-water mixtures with lesser proportions of the organic solvent (i.e. down to 40% dioxane), it is possible to extrapolate to pK_a values in water for certain crown carboxylic acids.

C. Metal Ion Complexation by Proton-Ionizable Crown Ethers Assessed by Titration Calorimetry

To provide information about metal ion complexation by ionized crown ethers in homogeneous solution, the thermodynamics of alkali metal cation complexation by anionic forms of proton-ionizable crown ethers are being determined by titration calorimetry. Preliminary studies revealed that a mixed solvent of 90% methanol-10% water (v/v) is appropriate for the measurements. The experimental procedure consists of titrating at 25.00 ± 0.02 °C an aqueous methanolic solution which is 4.0 mM in the proton-ionizable crown ether and 5.0 mM in tetramethylammonium hydroxide with an aqueous methanolic solution which is 4.0 mM in an alkali metal chloride and 5.0 mM in tetramethylammonium hydroxide. Heats of dilution are determined by titrating the aqueous methanolic solution of the alkali metal chloride (4.0 mM) and the tetramethylammonium hydroxide (5.0 mM) into a 5.0 mM solution of tetramethylammonium hydroxide in 90% methanol-10% water in the absence of the ligand. When this titration was repeated but with no alkali metal chloride in the titrant, the heat of dilution was negligible.

The resulting titration curves from addition of the aqueous methanolic solution of alkali metal chloride and tetramethylammonium hydroxide to the aqueous methanolic solution of the proton-ionizable crown ether and tetramethylammonium hydroxide are analyzed by a least-squares method to obtain log K, ΔG, ΔH and TΔS.[14] The values of log K and ΔH are corrected to their thermodynamic values using the Debye-Hückel relationship with 4.5 Å as the distance of closest approach in 90% methanol-10% water.[15]

Using this method, values of log K, ΔG, ΔH and ΔS have been and continue to be determined for complexation of Li^+, Na^+, K^+, Rb^+ and Cs^+ by the ionized forms of proton-ionizable crown ethers. Some of the log K values which have been determined are collected in Tables 1-3.

The data presented in Table 1 clearly demonstrates the enhancement in metal cation binding which takes place when a pendent ionized group is attached to the dibenzo-16-crown-5 ring. Data are presented for dibenzo-16-crown-5 itself (**78**), sym-(methoxy)dibenzo-16-crown-5 (**79**), and sym-dibenzo-16-crown-5-oxyacetic acid (**3**). For the two model non-ionizable crown ether compounds **78** and **79**, the former exhibits strongest complexation for Na^+ as would be predicted for the dibenzo-16-crown-5 ring size. The change to somewhat stronger binding of K^+ than Na^+ by **79** suggests a perching complex in which the K^+, which is too small to fit within the polyether cavity, rests on top of the ring oxygens and also coordinates with the oxygen of the pendent methoxyl group. Compared with **79**, the carboxylate form of crown ether carboxylic acid **3** exhibits a 1.6 log unit increase in association for Na^+ and a 0.9 log unit enhancement in K^+ binding. Thus the presence of the pendent ionizable group not only improves the metal ion binding but also appears to accentuate the cavity size-metal ion diameter relationship.

The effect of varying the lipophilic group attachment site upon the strength of alkali metal cation binding by sym-dibenzo-16-crown-5-oxyacetic acid derivatives in homogeneous media is shown by the data in Table 2. Crown ether carboxylic acids **81, 83** and **11** are structural isomers which possess a common sym-dibenzo-15-crown-5-oxyacetic acid **(3)** framework but have one or two lipophilic groups with a total of eight carbon atoms attached at different locations on the framework. In **81** an eight-carbon chain is attached to the carbon atom adjacent to the carboxyl group in the sidearm. For **83** a tert-butyl group is attached to each of the two benzo groups. Finally in **11** an eight carbon chain is attached to the same polyether ring carbon as the oxyacetic acid group. For these three structural isomers, the highest log K value was obtained for complexation of Na^+ by **11**. Since **11** also exhibits the highest Na^+ selectivity of the three structural isomers in competitive alkali metal cation solvent extraction into chloroform,[5,6] the present results establish that the selectivity arises from structural features of the ligand rather than some unusual aspect of the two-phase solvent extraction system. Thus the quantitative data regarding metal ion complexation by proton-ionizable crown ethers which results from titration calorimetry provides valuable support for the more qualitative results which we have obtained in two-phase (or three-phase) separation systems.

Table 3 provides information about the influence of ring size variation upon the alkali metal cation complexation properties of the lipophilic crown ether carboxylic acid series **80-82**. As the polyether ring size is varied from 14-crown-4 to 16-crown-5 to 19-crown-6, the best complexed alkali metal cation changes from Na^+ to $Na^+=K^+$ to K^+, respectively. These results parallel those

Table 1. Effect of a Pendent Proton-Ionizable Group upon Alkali Metal Cation Complexation by Dibenzo-16-crown-5 Compounds in 90% Methanol-10% Water

	log K				
Crown Ether	Li^+	Na^+	K^+	Rb^+	Cs^+
78	ND[a]	2.61	2.19	ND[a]	ND[a]
79	1.18	2.07	2.35	1.28	IN[b]
3	IN[b]	3.69	3.27	2.63	2.43

[a] ND = Not determined. [b] Insufficient heat change for reliable calculations.

Table 2. Effect of Lipophilic Group Attachment Site upon Alkali Metal Cation Complexation by sym-Dibenzo-16-crown-5-oxyacetic Acid Derivatives in 90% Methanol-10% Water.

	log K				
Crown Ether	Li^+	Na^+	K^+	Rb^+	Cs^+
81	IN[a]	3.56	3.53	2.30	UA[b]
83	IN[a]	3.67	3.50	3.10	UA[b]
11	IN[a]	4.40	3.42	2.87	2.34

[a] IN = Insufficient heat change for reliable calculation. [b] UA = Unreliable answer. Sufficient heat was generated, but the calculation gave an anomalously high value.

Table 3. Effect of Ring Size upon Alkali Metal Cation Complexation by Dibenzocrown Ether Carboxylic Acids in 90% Methanol-10% Water.

	log K				
Crown Ether	Li^+	Na^+	K^+	Rb^+	Cs^+
80	IN[a]	3.82	3.57	2.85	1.96
81	IN[a]	3.56	3.53	2.30	UA[b]
82	IN[a]	3.37	3.88	3.70	3.18

[a] IN = Insufficient heat change for reliable calculation. [b] UA = Unreliable answer. Sufficient heat was generated, but the calculation gave an anomalously high value.

found in competitive alkali metal cation solvent extraction with the exception of **81** which is clearly Na^+ selective in solvent extraction.[5]

Through a comparison of the changes in ΔH and ΔS values for structural variation within the proton-ionizable crown ethers, detailed understanding of the influence of enthalpic and entropic factors upon the association constants may be obtained.

D. Metal Ion Complexation by Proton-Ionizable Crown Ethers as Assessed by Proton Magnetic Resonance Spectroscopy

In earlier published work, we examined the 100 MHz proton magnetic resonance spectra of crown ether phosphonic acid monoethyl ester **84** and its lithium, sodium and potassium salts in $CDCl_3$.[16] In the acid **84** and its lithium and potassium salts, the absorption for the diastereotopic benzylic protons was found to be a singlet for **84** and a slightly broadened singlet for the lithium and potassium salts. However for the sodium salt of **84**, the benzylic proton absorption was an AB quartet caused by restricted rotation of the sidearm. Thus it was demonstrated for the sodium salt of **84** that the cation is simultaneously complexed by the 15-crown-5 ring and the pendent ionized group.[16]

With the availability of higher field NMR spectrometers this phenomena was re-examined for the 15-crown-5 and 18-crown-6 phosphonic acid monoethyl esters **34** and **35**, respectively. For the proton-ionizable 15-crown-5 compound **34**, the 300 MHz ^1H NMR absorption for the benzylic protons was a singlet in $CDCl_3$. On the other hand for the lithium, sodium and potassium salts, AB quartets were observed in all cases. The coupling constants J_{AB} varied widely and were 21.6, 54.8 and 34.7 Hz for the lithium, sodium, and potassium salts, respectively. Thus even though restricted sidearm rotation is evident for all three salts, the coupling constant is highest for the sodium salt in which the metal ion would be strongly coordinated within the crown ether cavity and the sidearm would be highly constrained.

For the analogous 18-crown-6 phosphonic acid monoethyl ester **35** at 300 MHz, the ^{1}H NMR absorption for the benzylic protons shows a very narrow AB quartet in the protonated form. This suggests intramolecular hydrogen bonding between the acidic group and the oxygens in the crown ether ring. The coupling constants J_{AB} for the sodium and potassium salts were 63.6 and 62.4 Hz. These large and essentially equal coupling constants indicate that rotation of the sidearm is highly restricted for both the sodium and potassium salts.

In contrast with these results which were obtained for crown ethers with pendent acid groups, restricted rotation was not evident in the carboxylic acid or alkali metal carboxylate forms of compounds **44** and **45** which have inward-facing proton-ionizable groups. Thus the 300 MHz ^{1}H NMR absorptions for the methylene group protons in the oxyacetic acid and oxyacetate forms of **44** and **45** appeared only as singlets.

E. Metal Ion Complexation by Proton-Ionizable and Neutral Crown Ethers in Polymeric Membrane Electrodes

In a collaborative research project with Professor Gary D. Christian and his coworkers, the behavior of several of our neutral and proton-ionizable crown ethers in polymeric membrane electrodes has been examined.[17,18] Of particular interest was the behavior of crown ether compounds with four ring oxygen atoms and different pendent groups in potential ion selective electrodes for Li^+. When compared with solvent extraction data, the electrode selectivities exhibited a general correlation which demonstrates that solvent extraction selectivity data can aid in the design and performance prediction of electrode ionophores.[17]

F. Metal Ion Complexation by Proton-Ionizable Crown Ethers Assessed by Solvent Extraction

Solvent extraction experiments were utilized extensively to evaluate the selectivity and efficiency of metal ion complexation by lipophilic, proton-ionizable crown ether ligands. Extractions of alkali metal cations, alkaline earth cations, and mixtures of alkali metal and alkaline earth cations into chloroform by crown ether carboxylic acids were examined. The effect of organic solvent variation upon the selectivity and efficiency of alkali metal cation extraction by a lipophilic crown ether carboxylic acid was explored. In addition the effect of stripping phase pH upon the release of complexed alkali metal cations from a chloroform phase into the aqueous stripping solution was determined. For chromogenic di-ionizable ligands derived from diazacrown ethers, the propensity of extraction of a wide variety of divalent metal cations into 1,2-dichloroethane was probed and a reagent with very high selectivity for Hg^{2+} was discovered.

1. Alkali Metal Cations

The influence of structural variation within lipophilic crown ether carboxylic acids upon the selectivity and efficiency of alkali metal cation extraction into chloroform has been summarized.[5] In addition the extraction selectivities and efficiencies have been examined in detail for a series of nine lipophilic dibenzocrown ether carboxylic acids[6] and a series of 14 lipophilic salicylic acid crown compounds 85.[19] For the dibenzocrown ether carboxylic acid compounds, the structural variations were the crown ether ring size and the lipophilic group attachment site. sym-(Decyl)dibenzo-16-crown-5-oxyacetic (13) acid was found to exhibit excellent Na^+ selectivity in competitive alkali metal cation extraction into chloroform. For the analogous 14-crown-4 and 19-crown-6 compounds, good extraction selectivity for Li^+ and K^+ was observed.

For the series of lipophilic crown ether carboxylic acids **85**, the structural change was systematic variation of the crown ether ring size: 12-crown-4, 13-crown-4, 14-crown-4, 15-crown-4, 15-crown-5, 16-crown-5, 18-crown-6, 19-crown-6, 21-crown-7, 24-crown-8, 27-crown-9, and 30-crown-10. Chelating reagents with excellent extraction selectivity for Li^+ and good selectivities for Na^+, K^+ and Cs^+ were obtained.[5,19]

The influence of R group variation for sym-(R)dibenzo-16-crown-5-oxyacetic acids for competitive alkali metal cation extraction into chloroform was probed with compounds **7**, **11**, **12**, **13** and **19**. For **7**, **11**, and **13** in which R is changed from propyl to octyl to decyl, competitive extraction of alkali metal cations into chloroform gave 100% loading of the organic phase (assuming a 1:1 complex) in all cases. However, the selectivity for Na^+ over the second-best extracted cation increased as the alkyl group became longer. Crown carboxylic acids **11** and **12** are structural isomers in which R is octyl in the former and 2-ethylhexyl in the latter. Both the maximum organic phase metals loading and Na^+/K^+ selectivity were somewhat higher for **11** than **12**, which demonstrates that an unbranched R group gives higher extraction efficiency and selectivity than a branched one. The comparison of **7** and **19** involves the replacement of a propyl group with a perfluoropropyl group. Although the maximum organic phase metals loading for both complexing agents were quantitative, the Na^+/Li^+ selectivity (Li^+ was the second-best extracted cation) was markedly diminished in going from **7** to **19**. Thus replacement of an alkyl group with a perfluoroalkyl group does not affect the extraction efficiency, but it does markedly influence the selectivity. Examination of CPK space-filling models indicates that when R is a long, unbranched alkyl chain, it prefers to point away from the polar polyether portion of the ligand which orients the pendent carboxylic acid group directly over the crown ether cavity. Such pre-organization of the binding site apparently produces the highest Na^+ selectivity in these solvent extraction experiments. When a hydrocarbon group is replaced by a more polar perfluoroalkyl group, the strong orientation of the R group away from the polyether ring is lost and the Na^+ extraction selectivity is reduced.

To probe the influence of the structural change from a pendent carboxylic acid group to an inward-facing carboxylic acid function, competitive solvent extraction of alkali metal cations into chloroform by the lipophilic crown ether carboxylic acids **36-39** was examined. For the series **36-39**, the crown ether ring size is systematically increased from 15-crown-4 to 18-crown-5 to 21-crown-6 to 24-crown-7. For competitive solvent extraction of alkali metal cations into chloroform the extraction selectivities were: $Li^+ > Na^+ > K^+ > Rb^+ \sim Cs^+$ for **36**; $Li^+ > K^+ > Na^+ > Rb^+ > Cs^+$ for **37**; $Cs^+ > Rb^+ > K^+ > Na^+ > Li^+$ for **38** and $Cs^+ > Rb^+ \sim K^+ > Li^+ \sim Na^+$ for **39**. Even though these results demonstrate that the extraction selectivity is influenced by ring size variation, the relationship is more complicated than that reported earlier for crown carboxylic acids with pendent ionizable groups, such as **13** and its 14-crown-4 and 19-crown-6 analogs.[5,6] Clearly the inward-facing carboxyl groups in **36-39** are a complicating factor.

The influence of varying the identity of the proton-ionizable group upon solvent extraction behavior was also assessed. Compounds **13** and **23** (n=1) are structurally the same except for the change from a crown ether carboxylic acid in the former to a crown ether phosphonic acid monoethyl ester in the latter. For competitive solvent extractions of alkali metal cations into chloroform by crown ether carboxylic acid **13**, the maximum organic phase loading was 100% and the extraction selectivity order was $Na^+ >> K^+ > Li^+$ with no detectable Rb^+ or Cs^+. With **23** (n=1), the maximum organic phase loading was 93% and the extraction selectivity order was $Na^+ > K^+ > Rb^+ > Cs^+ > Li^+$. Although alkali metal cation extraction by crown ether carboxylic acid **13** is more efficient and selective than that for crown ether phosphonic acid monoethyl ester **23** (n=1), the more acidic ionizable group in the latter allows alkali metal cations to be extracted from reasonably acidic aqueous solutions as well as neutral and basic solutions. Thus when the aqueous solution of alkali metal chlorides was pH=4, the organic phase loading was approximately 50% for **23** (n=1), but less than 5% for **13**.

Crown ether carboxylic acids **24-26** bear a close structural relationship to previously-investigated dibenzo-16-crown-5 crown ether carboxylic acids such as **13** and **83**, which possess only oxygen heteroatoms in the macrocyclic ring. Hence for **24-26** the structural variation is that an oxygen atom of the polyether ring has been replaced with a nitrogen atom. Also the requisite lipophilic group for retention of the extractant in the organic phase during solvent extraction is now attached to nitrogen rather than carbon. For competitive solvent extraction of alkali metal cations into chloroform, crown ether carboxylic acid **25** provides outstanding selectivity for Na^+ which surpasses even the very high Na^+ extraction selectivity ($Na^+ >> Li^+, K^+, Rb^+, Cs^+$) exhibited by the all-oxygen crown carboxylic acid **13**. In contrast for **24** and **26**, the extraction selectivity was much poorer and the selectivity order was $Li^+ > Na^+ > K^+ > Rb^+, Cs^+$ for both compounds. This marked change in extraction selectivity when the group attached to the ring nitrogen is changed from decyl to tosyl can be readily understood by considering the strong electron-withdrawing properties of the latter. Hence in **24** and **26**, sufficient electron density is removed from the ring nitrogen that it is no longer a metal ion coordination site. The four oxygens form a distorted crown-4 structure which prefers complexation of Li^+.

Lipophilic crown carboxylic acids **46** and **47** are derived from mono-azadibenzo-18-crown-6. For competitive solvent extraction of alkali metal cations into chloroform, both **46** and **47** exhibited extraction selectivity orders of $Na^+ > K^+ > Li^+, Rb^+, Cs^+$. The extraction selectivity for Na^+ is surprising since selectivity for K^+ would be predicted for this ring size.

To probe the effect of solvent variation, competitive extractions of alkali metal cations by solutions of crown carboxylic acid **13** in eleven different chlorocarbon and hydrocarbon solvents were conducted. The solvents included: dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethan, 1,1,1-trichloroethane, 1,2-dichlorobenzene, chlorobenzene, benzene, toluene, para-xylene and tetrahydronaphthalene. For all eleven solvents, 100% loading of the organic phase was observed (assuming a 1:1 metal ion-crown carboxylate extraction complex). For the extractions from aqueous solutions containing all five alkali metal-cations, Na^+ selectivity was observed, as would be predicted for the ring size of crown carboxylic acid **13**. Very high selectivities for Na^+ over K^+ (the second best extracted cation) were noted when the extraction solvents were dichloromethane, chloroform and 1,2-dichloroethane. For the other solvents, Li^+ was the second best extracted cation and Na^+/Li^+ ratios were 2.9-5.7. Very good correlation between extraction selectivity and E_T (Dimroth's emperical parameter of solvent polarity) was noted for solvents of similar chemical structure, i.e. families of chlorinated methanes, chlorinated ethanes and the aromatic compounds.

To examine the possibility of selectivity in the stripping of alkali metal cations from crown ether carboxylate complexes, the five alkali metal cation-crown ether carboxylate complexes of **13** were prepared. Chloroform solutions which contained equimolar amounts of the five complexes (0.01 M in each) were shaken with equal volumes of aqueous HCl solutions of varying strengths to determine the extent of metal ion release into the aqueous phase and the relative concentrations of the alkali metal cations in the aqueous phase. When the HCl solution was 0.01, 0.02, 0.03, 0.05 and 0.10 M the percentages of stripped metals were 17, 32, 50, 88 and 98%, respectively.

With concentrations of HCl above 0.10 M, the stripping was quantitative. A plot of the concentrations of stripped alkali metal cations vs. the pH of the stripping solution gave a different curve for each alkali metal cation. At pH=2.0 the order of concentrations for stripped alkali metal cations was $Cs^+ > Rb^+ > Li^+ > K^+ > Na^+$ which is just the opposite of the competitive extraction selectivity.[5,6] Thus the stronger complexation which produces higher extraction of an alkali metal cation also results in poorer release in stripping. However by use of a 0.50 M aqueous HCl solution for stripping, quantitative release of the complexed metal ions is assured.

Competitive solvent extractions of alkali metal cations into chloroform by crown ether dicarboxylic acid **55** gave biphasic extraction selectivity orders of $Na^+ > K^+ > Li^+ > Rb^+ > Cs^+$ at pH 6-8 and $Li^+ > K^+ > Na^+ > Rb^+ > Cs^+$ at pH 9-12. The high extractability of Li^+ by **55** at alkaline pH suggests cooperative complexation of Li^+ by the two carboxylate anions outside the polyether cavity.

2. Alkaline Earth Cations

The influence of ionizable group variation was also examined for solvent extraction of alkaline earth cations from aqueous solutions into chloroform by lipophilic crown ether carboxylic acid **13** and lipophilic crown ether phosphonic acid monoethyl ester **23** (n=1). For divalent metal cations and mono-ionizable crown compounds, the extraction complex would be $M^{2+}(A^-)_2$, where A^- is the ionized crown ether. Assuming such a 1:2 extraction complex, the maximum organic phase loadings for **13** and **23** (n=1) were 86% and 96%, respectively. In contrast to the similarity in extraction efficiencies, selectivities were markedly different. For **13** the selectivity order was $Ba^{2+} > Ca^{2+} > Sr^{2+} > Mg^{2+}$; whereas for **23** (n=1) the selectivity order was $Mg^{2+} > Ca^{2+}$ with no detectable Sr^{2+} or Ba^{2+} in the chloroform phase. Hence the identity of the ionizable group is demonstrated to have a strong influence upon the selectivity of alkaline earth cation extraction by mono-ionizable crown compounds.

Competitive solvent extractions of alkaline earth cations into chloroform by proton-ionizable crown ethers with a pendent di-ionizable group was examined with lipophilic crown ether phosphonic acids **49-53**. For **49-53** the crown ether ring size is systematically varied from 14-crown-4 to 15-crown-5 to 18-crown-6 to 21-crown-7 to 24-crown-8. For **49** in which the crown ether ring size is 14-crown-4, the extraction selectivity order was Ca^{2+}> Mg^{2+},Ba^{2+}>Sr^{2+}. However the extraction selectivity orders for **50-53** exhibited biphasic behavior with different orders when the aqueous solutions were acidic and alkaline (Table 4).

Table 4. Selectivity Order for Competitive Solvent Extraction of Alkaline Earth Cations from Aqueous Solutions into Chloroform by Lipophilic Crown Ether Phosphonic Acids 49-53.

Crown Ether	Ring Size	Selectivity Order pH 3-6	Selectivity Order pH 8-10
49	14C4	$Ca^{2+} > Mg^{2+}, Ba^{2+} > Sr^{2+}$	$Ca^{2+} > Mg^{2+}, Ba^{2+} > Sr^{2+}$
50	15C5	$Ba^{2+} >> Ca^{2+}, Sr^{2+} > Mg^{2+}$	$Ca^{2+} > Sr^{2+} > Ba^{2+} > Mg^{2+}$
51	18C6	$Ba^{2+} > Sr^{2+} > Ca^{2+} > Mg^{2+}$	$Ca^{2+} > Ba^{2+} > Sr^{2+} > Mg^{2+}$
52	21C7	$Ba^{2+} > Ca^{2+} > Sr^{2+} > Mg^{2+}$	$Ca^{2+} > Ba^{2+} > Sr^{2+} > Mg^{2+}$
53	24C8	$Ba^{2+} > Ca^{2+} > Sr^{2+} > Mg^{2+}$	$Ca^{2+} > Ba^{2+} > Sr^{2+} > Mg^{2+}$

Lipophilic crown ether phosphonic acid **49** exhibits selectivity for Ca^{2+} which is too large to be accommodated within the crown ether cavity. For **50-53**, greater or lesser selectivity for Ba^{2+} is noted at acidic pH and greater or lesser selectivity for Ca^{2+} at basic pH. Presumably, the Ba^{2+} selectivity at acidic pH arises from ionization of only one proton from the phosphonic acid groups which requires formation of a 2:1 extraction complex. On the other hand, the Ca^{2+} selectivity at alkaline pH for all five crown phosphonic acids strongly suggest primary coordination of the metal ion outside the polyether ring.

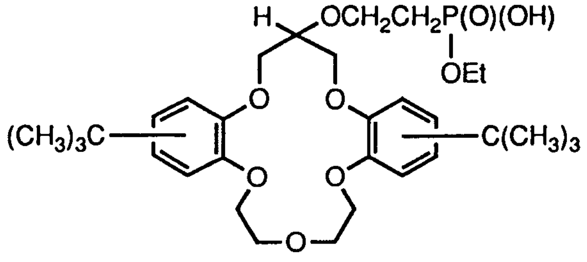
3. Mixed Alkali Metal and Alkaline Earth Cations

Since mixtures of alkali metal and alkaline earth cations are often encountered in practical separation problems, a study of solvent extractions of such mixed cationic species into chloroform by lipophilic, proton-ionizable crown ethers was undertaken. Results obtained for the five lipophilic, mono-ionizable crown ethers **13**, **23** (n=1), **81**, **83** and **86** reveal that structural variation within the extractant has a marked effect upon the extraction selectivity and efficiency. Results are recorded in Table 5.

Table 5. Competitive Solvent Extraction of Alkali Metal and Alkaline Earth Cations into Chloroform by Lipophilic Mono-Ionizable Crown Ethers

Crown Ether	Extraction Selectivity Order at pH=9.0	Maximum Metals Loading, %
<u>13</u>	$Na^+ >>> Ba^{2+}$ (no $Li^=, K^+, Rb^+, Cs^+, Mg^{2+}, Ca^{2+}, Sr^{2+}$)	32
<u>81</u>	$Na^+ > Sr^{2+} > Ca^{2+} > K^+ > Li^+ > Rb^+ > Ba^{2+}, Ca^{2+}$	61
<u>83</u>	$Ba^{2+} > Ca^{2+} > Na^+, Sr^{2+} > K^+ > Mg^{2+} > Rb^+ > Li^+, Cs^+$	69
<u>23</u> (n=1)	$Na^+ >> Mg^{2+}, Ca^{2+}, K^+, Rb^+$ (no $Li^+, Cs^+, Sr^{2+}, Ba^{2+}$)	83
<u>86</u>	$Na^+ >> Mg^{2+} > Ca^{2+}$ (no $Li^+, K^+, Rb^+, Cs^+, Sr^{2+}, Ba^{2+}$)	69

Dibenzo-16-crown-5 carboxylic acids **13**, **81** and **83** have very similar structures except for the positioning of the lipophilic group(s). However their selectivities in competitive alkali metal and alkaline earth cation extractions into chloroform are very different. Thus when the lipophilic group is attached to the polyether ring carbon which bears the sidearm or is attached to the sidearm selectivity for Na^+ extraction is observed. In contrast, when a tert-butyl group is attached to each of the benzo substituents of the polyether ring, extraction selectivity for Ba^{2+} is noted.



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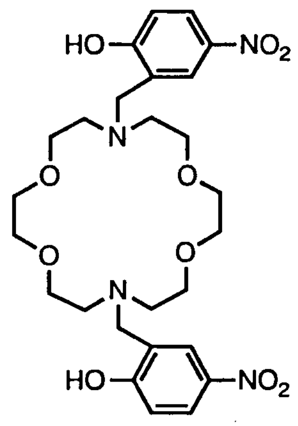

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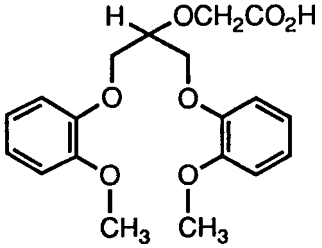

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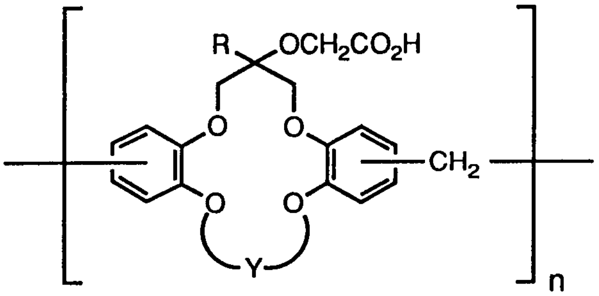

	R	Y
89	-H	$-CH_3$ CH_3-
90	-H	$-CH_2CH_2OCH_2CH_2-$
91	$-C_3H_7$	$-CH_2CH_2OCH_2CH_2-$

For mono-ionizable crown ethers **13** and **23** (n=1), the structural variation is the change of ionizable group from carboxylic acid in the former to phosphonic acid monoethyl ester in the latter. Although both compounds exhibit selectivity for Na^+ extraction, there is a marked difference in extraction of other metal ions such as Ba^{2+} which is the second best extracted species for **13** but is not extracted by **23** (n=1).

The structural variations in going from **83** to **86** are a change in the proton-ionizable group and a lengthening of the sidearm by a methylene unit in the latter. It is readily evident from the data presented in Table 5 that the extraction selectivities are very different.

Although these results clearly establish a marked influence of structural variations within lipophilic mono-ionizable crown ethers upon the selectivity and efficiency of competitive alkali metal and alkaline earth cation extraction into chloroform, the number of compounds examined is too limited for generalizations to be drawn at this stage.

Of the proton-ionizable crown ethers that we have prepared, compound **54** is unique in that it possesses two different mono-ionizable groups and one is pendent and the other is inward-facing. Solvent extractions into chloroform were conducted for alkali metal cations, alkaline earth cations, and mixed alkali metal and alkaline earth cations. For the alkali metal cations, the extraction selectivity order at pH=7.0 was $K^+>Rb^+>Na^+>Li^+,Cs^+$. Although the metals loading increased smoothly as the pH of the aqueous phase was increased from 3.5 to 7.0, at higher pH the extraction efficiency dropped precipitously indicating loss of the extractant into the alkaline aqueous phase when both acid groups are ionized. For the alkaline earth cations, the extraction selectivity order was $Ca^{2+}>>Ba^{2+}>Sr^{2+}>>Mg^{2+}$ with no apparent loss of the extractant upon contact with alkaline aqueous phases. Retention of the di-ionized chelating agent in the chloroform phase suggests simultaneous coordination of the divalent metal ion with both ionized groups to form a more compact lipophilic complex than that derived from two alkali metal cations. For extraction of the mixed alkali metal and alkaline earth cations into chloroform, the selectivity at pH=9.0 was $Ca^{2+} >> Ba^{2+} > Sr^{2+} >> Mg^{+}, K^{+}, Rb^{+}, Na^{+}, Li^{+}, Cs^{+}$ which is consistent with formation of stronger complexes with the divalent cations.

4. Alkaline Earth Cations and Divalent Heavy Metal and Transition Metal Cations

Compared with the reported chromogenic di-ionizable, diaza-18-crown-6 compound **87**, the dibenzodiaza-18-crown-6 analog **56** which we synthesized has a more rigid polyether structure due to the benzo groups. On the other hand, replacement of four dialkyl ether oxygens with alkyl aryl ether oxygens should reduce the basicity of the oxygen coordination sites. To investigate the effects of these structural variations upon the extraction of divalent metal cations, solvent extractions of $Ba^{2+}, Ca^{2+}, Cd^{2+}, Cu^{2+}, Hg^{2+}, Pb^{2+}$ and Sr^{2+} into 1,2-dichloroethane by **56** were conducted using the method reported[20] for **87**. The extraction constants were found to be 2-3 orders of magnitude lower for **56** than has been reported for **87** with all of the divalent metal cations except Hg^{2+}. This demonstrates the importance of oxygen basicity upon extraction efficiency. In sharp contrast, Hg^{2+} was extracted five orders of magnitude better by **56** than **87**. The extraction selectivity order for **56** was $Hg^{2+} >>> Pb^{2+} > Cu^{2+} > Cd^{2+} >> Ca^{2+} > Sr^{2+} > Ba^{2+}$. The calculated extraction selectivity for Hg^{2+} over Pb^{2+} was 10^7 and for Hg^{2+} over Ca^{2+} was 10^{15}! Hence the new chromogenic di-ionizable crown ether **56** possesses an amazing selectivity for Hg^{2+} and may have potential application in lead removal from biological systems (i.e. treatment of lead poisoning) where high Hg^{2+}/Ca^{2+} selectivity is required.

Due to the extremely high extraction selectivity for Hg^{2+} exhibited by chromogenic di-ionizable crown ether **56**, single species extractions into chloroform were also conducted with the structural isomer **59** and the closely-related compound **57**. In contrast with **56**, structural isomer **59** distributed badly into the aqueous layer during attempted extraction. On the other hand, **57** was much better behaved and exhibited high extractability of Hg^{2+} into 1,2-dichloroethane compared to other divalent metal ions.

G. Metal Ion Complexation by Lipophilic Di-Ionizable Acyclic Polyethers Assessed by Solvent Extraction

Competitive solvent extraction of alkaline earth cations into chloroform by lipophilic acyclic dicarboxylic acids with two or more ether oxygen binding sites is under investigation.

Extractants **60-62** are the same except for variation of the number of methylene groups between the two ether oxygens. Although ligands **60** and **61** both gave quantitative metals loadings and selectivity orders of $Ca^{2+}>>Sr^{2+}$, $Ba^{2+}>Mg^{2+}$, the maximal metals loading for compound **62** was only 9% and only slight selectivity for extraction of Ca^{2+} was observed.

Compounds **60,63,64** form a series in which the number of ethyleneoxy units between the two ether oxygens is systematically varied from 0-2. As mentioned above, ligand **60** gave quantitative metals loading and high Ca^{2+} selectivity. For **63** the metals loading decreased to 90% and the selectivity order was $Ca^{2+}>Ba^{2+}>Sr^{2+}$ with no detectable Mg^{2+} extraction. With **64** the metals loading remained at 90% and the selectivity order was $Ca^{2+},Ba^{2+}>Sr^{2+}>Mg^{2+}$. Thus the selectivity for Ca^{2+} was found to decrease as the number of ethyleneoxy units was increased.

Attention was then focused upon the replacement of one or more ether oxygens with sulfur or nitrogen atoms. Ligands **67** and **68** are the same as **60** and **61**, respectively, except for the replacement of the two ether oxygens in the latter pair with sulfide sulfurs in the former pair. This structural modification had a pronounced influence upon the extraction selectivity and efficiency. Although both **60** and **67** showed quantitative metals loading, the Ca^{2+} selectivity of the former was replaced by a selectivity order of $Ba^{2+}>Ca^{2+}>Sr^{2+}>Mg^{2+}$ for the sulfur analog **67**. For **68** the metals loading increased from 2% at pH=4.2 to 91% at pH=6.7 with a selectivity order of $Ca^{2+}>Ba^{2+}>Sr^{2+}>Mg^{2+}$ at pH=6.7. However as the aqueous phase pH was increased to 8.0 the metals loading plummeted to 6% indicating loss of the extractant from the organic phase.

Chelating agents **65** and **66** are derived from **63** by replacement of the central ether oxygen with N-tosyl in **65** and with N-C_6H_5 in **66**. For replacement of the ether oxygen with N-C_6H_5, the metals loading increased by a few percent to become nearly quantitative and the extraction selectivity order was $Ca^{2+}>Ba^{2+}>Sr^{2+}>Mg^{2+}$. Thus this structural modification had a relatively minor influence on the extraction behavior. However, replacement of the ether oxygen with N-tosyl had a larger influence. The maximal metals loading remained near quantitative for **65** and the selectivity order was $Ca^{2+}>>Mg^{2+}, Sr^{2+}, Ba^{2+}$. Thus the Ca^{2+} selectivity of **65** was markedly better than that observed for **63**. Since the strongly electron withdrawing tosyl group diminishes the electron density on nitrogen, these results indicate that maximal extraction selectivity for Ca^{2+} will be obtained when there are only two ether oxygen ligation sites available.

H. Transport of Metal Ions Across Liquid Membranes by Lipophilic Proton-Ionizable Crown Ethers

During the report period, the factors which influence proton-coupled transport of alkali metal cations across liquid membranes by lipophilic proton-ionizable crown ethers received considerable attention. The investigations utilized both bulk liquid and polymer-supported liquid membrane systems.

1. Bulk Liquid Membranes

An extensive investigation of experimental variables upon the proton-coupled transport[21] of alkali metal cations across bulk chloroform membranes by lipophilic proton-ionizable crown ethers was conducted. For these studies, a special transport cell was devised in which the membrane phase as well as the source and receiving aqueous phases could be sampled periodically. Thus alkali metal cation concentrations in the source, membrane, and receiving phases could be monitored during the transport experiment. For the competitive alkali metal cation transport across bulk chloroform membranes by lipophilic proton-ionizable crown ethers **13** and **23** (n=1), the influence of varying the source phase basicity and receiving phase acidity (i.e. the pH gradient for transport), the carrier concentration in the membrane phase, and the identity of the ionizable group upon the transport efficiency and selectivity were assessed.

The effect of changing the organic membrane solvent upon the rates and selectivity of competitive alkali metal cation transport across bulk liquid membranes by lipophilic crown ether carboxylic acid **13** was investigated. The solvents included dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, 1,1,1-trichloroethane, ortho-dichlorobenzene, toluene and para-xylene. For **13** in dichloromethane, chloroform and 1,2-dichloroethane, highly selective transport of Na^+ was observed with barely detectable amounts of K^+ appearing in the receiving phase.

For the lipophilic dibenzo-16-crown-5 phosphonic acid monoethyl esters **23** (n=1-4) the influence of sidearm length variation upon the efficiency and selectivity of proton-coupled competitive transport of alkali metal cations across a chloroform membrane was assessed. The rate of metal ion transport decreased with changes of n in the order 1,2>3>4. The high Na^+ transport selectivity observed for **23** with n=1,2 diminished when n=3. With n=4 the transport was almost unselective. Examination of CPK space filling models suggests that for **23** with n=1,2 the sidearm is of appropriate length to position the ionizable group directly over the polyether cavity and pre-organize the binding site.

For competitive transport of Co^{2+} and Ni^{2+} transport through bulk toluene membranes, it was found that lipophilic crown carboxylic acids provide efficient and selective transport of Co^{2+}.[22]

2. Polymer-Supported Liquid Membranes

Considerable effort was expended in the investigation of competitive proton-coupled transport of alkali metal cations across polymer-supported liquid membranes by proton-ionizable crown ether **13**. In these systems, the source phase was a basic aqueous solution of lithium, sodium, potassium and rubidium chlorides and the receiving phase is 1.0 M aqueous hydrochloric acid. (Contact with cesium chloride was found to degrade the membrane.) The liquid membrane was supported by Accurel® 0.2 porous polypropylene sheet. Within the vacant spaces in this porous material (70% voids) was absorbed a solution of **13** in an alkyl 2-nitrophenyl ether. This type of liquid membrane solvent was chosen due to the combination of polarity and low water solubility.

To determine which membrane solvents gave the best combination of membrane stability, cation flux, and cation selectivity, a series of alkyl 2-nitrophenyl ethers with differing alkyl groups was prepared. This included compounds with ethyl, propyl, butyl, pentyl, hexyl, heptyl, isopropyl and isopentyl groups. Methyl and octyl 2-nitrophenyl ethers were available commercially. Membranes prepared with the different alkyl 2-nitrophenyl ethers were found to have widely varying stabilities and cation transport properties. The membrane behavior was also found to depend upon the procedure by which the solution of **13** in an alkyl 2-nitrophenyl ether was loaded into the porous polypropylene. With pentyl and octyl 2-nitrophenyl ethers as the membrane solvent and appropriate loading of the Accurel® 0.2 porous polypropylene with the alkyl 2-nitrophenyl ether solution of **13**, highly selective Na^+ transport was achieved with Na^+/K^+ and Na^+/Li^+ transport selectivity ratios exceeding 50. The Na^+/Rb^+ selectivity ratio could not be determined since no Rb^+ was detected in the receiving phase.

Following the preliminary studies in which various parameters for membrane constitution and preparation and operational factors were optimized with flat membrane configurations, this metal ion separation technology has now been transferred to hollow fiber membranes. Due to their much higher surface areas, hollow fiber membranes possess a much higher potential for commercial development than do flat membranes. Once again a variety of operational parameters (e.g. flow rates and concentrations of the source and receiving solutions which flow through the hollow fiber membrane module) had to be evaluated and optimized. An efficient system for the separation of Na^+ from aqueous alkali metal cation solutions using polymer-supported liquid membranes of lipophilic crown ether carboxylic acid **13** in pentyl or octyl 2-nitrophenyl ether has been developed.

I. Sorption of Metal Ions by Acyclic and Cyclic Polyether Carboxylic Acid Resins

Novel weak acid ion exchange resins with integral cyclic polyether coordination sites were prepared by condensation polymerization of dibenzo-16-crown-5 carboxylic acids **3** and **7** with formaldehyde in formic acid. To provide an acyclic polyether carboxylic acid resin for comparison, compound **88** was converted similarly into a resin. The polyether carboxylic acids **89-91** were characterized by elemental analysis and infrared spectroscopy.

(Representations **89-91** are oversimplifications since some crosslinking is anticipated.)

Competitive alkali metal cation sorption by the polyether carboxylic acid resins was studied by shaking the water-insoluble resin with an aqueous solution of the alkali metal cations, filtration through a sintered glass funnel, and rinsing of the filtered resin with de-ionized water. After drying a portion of the resin was shaken with aqueous HCl to strip the sorbed metal ions from the resin into the aqueous solution for analysis by ion chromatography. In control experiments, it was shown that both the alkali metal cation sorption and the stripping steps take place in a few minutes.

The acyclic polyether carboxylic acid resin **89** exhibited sorption selectivity for Li^+ as would be expected if electrostatic metal ion-carboxylate interactions control the propensity for sorption. On the other hand, crown ether carboxylic acid resin **90** showed weak Na^+ sorption selectivity. Since the cyclic polyether ring size is most appropriate for Na^+ complexation, the change in sorption selectivity provides convincing evidence for association of the sorbed alkali metal cations with the crown ether units as well as the carboxylic acid groups. For crown ether carboxylic acid resin **91**, the Na^+ selectivity in competitive alkali metal cation sorption was markedly enhanced. As in solvent extraction[5] it is proposed that the propyl groups in **91** extend away from the polar polyether rings which orients the pendent carboxylic acid groups over the crown ether cavities and pre-organizes the binding site. To our knowledge this is the first instance in which conformations with an ion exchange resin have been demonstrated to influence the selectivity of metal ion sorption.

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III. RESEARCH PUBLICATIONS RESULTING FROM THIS PROJECT WHICH HAVE APPEARED OR BEEN ACCEPTED SINCE SUBMISSION OF THE LAST FORMAL PROGRESS REPORT IN JUNE OF 1987.

(1) "Proton-Coupled Transport of Alkali Metal Cations Across Liquid Membranes by Ionizable Crown Ethers," R. A. Bartsch, W. A. Charewicz, S. I. Kang and W. Walkowiak in "Liquid Membranes: Theory and Applications," ACS Symposium Series No. 347, R. D. Noble and J. D. Way (Eds.), American Chemical Society, Washington, D.C., 1987, pp 86-97.

(2) "Selective Separation of Alkali Metal Cations by Bulk Chloroform Membranes Containing Crown Phosphonic Acid Monoethyl Esters," W. Walkowiak, P. R. Brown, J. P. Shukla and R. A. Bartsch, *Journal of Membrane Science*, 1987, 32, 59-68.

(3) "Synthesis and Complexing Properties of Diazacrown and Cryptand Ligands with Inward-Facing Phenolic Groups," A. Czech, B. P. Czech, R. A. Bartsch, C. A. Chang and W. O. Ochaya, Journal of Organic Chemistry, 1988, 53, 5-9.

(4) "Extraction of Co(II) and Ni(II) Ammine Cations from Aqueous Solutions into Chloroform by Highly Lipophilic Crown Carboxylic Acids," J. Strzelbicki, W. A. Charewicz and R. A. Bartsch, Journal of Inclusion Phenomena, 1988, 6, 57-64.

(5) "Thermodynamic Acid Dissociation Constants for Proton-Ionizable Crown Compounds in Aqueous Dioxane," J. P. Shukla, E.-G. Jeon, B. E. Knudsen, M. J. Pugia, J. S. Bradshaw and R. A. Bartsch, Thermochimica Acta, 1988, 130, 103-113.

(6) "Flow Injection Analysis Potentiometric Selectivity Study of Alkali Metal and Alkaline Earth Cation Complexation by 1,3-Bis-(tropone-2'-oxy)propane," A. S. Attiyat, G. D. Christian, M. J. Pugia and R. A. Bartsch, Microchemical Journal, 1988, 38, 246-250.

(7) "Comparative Evaluation of Neutral and Proton-Ionizable Crown Ether Compounds as Lithium Ionophores in Ion-Selective Electrodes and in Solvent Extraction," A. S. Attiyat, G. D. Christian, R. Y. Xie, X. Wen and R. A. Bartsch, Analytical Chemistry, 1988, 60, 2561-2564.

(8) "A Comparative Study of the Effect of o-Nitrophenyl Octyl Ether and o-Nitrophenyl Pentyl Ether as Plasticizers on the Response and Selectivity of Carrier-Based Liquid Membrane Ion-Selective Electrodes," A. S. Attiyat, G. D. Christian, J. L. Hallman and R. A. Bartsch, Talanta, 1988, 35, 789-794.

(9) "Potentiometric Selectivity Study of Crown Ethers Containing Four Ring Oxygen Atoms and Benzoxymethyl or Carboxylic Acid Side Chains

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(10) "Solvent Extraction and Bulk Liquid Membrane Transport of Co(II) and Ni(II) Ammine Cations by Proton-Ionizable Crown Ethers," J. Strzelbicki, W. A. Charewicz and R. A. Bartsch, Journal of Inclusion Phenomena and Molecular Recognition in Chemistry, 1989, 7, 349-361.

(11) "Effects of Structural Variation within Proton-Ionizable Crown Ethers upon the Selectivity and Efficiency of Solvent Extraction of Alkali Metal and Alkaline Earth Cations," R. A. Bartsch, Solvent Extraction and Ion Exchange, 1989, 7, 829-854.

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(13) "Effect of Structural Variations within Lipophilic Dibenzocrown Ether Carboxylic Acids on the Selectivity and Efficiency of Competitive Alkali Metal Cation Solvent Extraction into Chloroform," W. Walkowiak, W. A. Charewicz, S. I. Kang, I.-W. Yang, M. J. Pugia and R. A. Bartsch, Analytical Chemistry, in press.

(14) "Effect of Ring Size Variation within Lipophilic Crown Ether Carboxylic Acids on the Selectivity and Efficiency of Competitive Alkali Metal Cation Solvent Extraction into Chloroform," W. Walkowiak, S. I. Kang, L. E. Stewart, G. Ndip and R. A. Bartsch, Analytical Chemistry, in press.

(15) "Competitive, Proton-Coupled, Alkali Metal Cation Transport across Polymer-Supported Liquid Membranes Containing sym-(Decyl)-dibenzo-

16-crown-5-oxyacetic Acid: Variation of the Alkyl 2-Nitrophenyl Ether Membrane Solvent," P. R. Brown, J. L. Hallman, L. W. Whaley, D. K. Desai, M. J. Pugia and R. A. Bartsch, Journal of Membrane Science, in press.

IV. PROJECT-SUPPORTED PRESENTATIONS SINCE SUBMISSION OF THE LAST FORMAL PROGRESS REPORT IN JUNE OF 1987.

(1) "Metal Ion Transport Across Liquid Membranes by Ionizable Crown Ethers," R. A. Bartsch, P. R. Brown and J. Strzelbicki, Asian Chemical Congress '87 Seoul, Seoul, Korea, June 1987 (Invited lecture).

(2) "Proton-Coupled Transport of Sodium Ions Across a Polymer-Supported Liquid Membrane by a Lipophilic Crown Ether Carboxylic Acid," R. A. Bartsch, P. R. Brown and J. Strzelbicki, The 12th International Symposium on Macrocyclic Chemistry, Hiroshima, Japan, July 1987 (Invited presentation).

(3) "Recognition in Solvent Extraction and Liquid Membrane Transport of Metal Ions by Proton-Ionizable Crown Ethers," R. A. Bartsch, Symposium on Molecular Recognition and Selectivity in Separations, Division of Industrial and Engineering Chemistry, The Third Chemical Congress of North America, Toronto, Canada, June 1988 (Invited lecture).

(4) "A New Chromogenic Crown Ether with Very High Selectivity for Mercury (II)," J. L. Hallman, B. Strzelbicka and R. A. Bartsch, Fifth International Symposium on Inclusion Phenomena and Molecular Recognition, Orange Beach, Alabama, September 1988.

(5) "Influence of Lipophilic Group Attachment Site and Polyether Ring Size on Complexation of Alkali Metal Cations by Lipophilic Crown Carboxylates in Aqueous Methanol," J. Strzelbicki and R. A.

Bartsch, Fifth International Symposium on Inclusion Phenomena and Molecular Recognition, Orange Beach, Alabama, September 1988.

(6) "Thermodynamics of Alkali Metal Cation Complexation by Dibenzo-16-crown-5 Compounds in Aqueous Methanol," J. Strzelbicki and R. A. Bartsch, Fifth International Symposium on Inclusion Phenomena and Molecular Recognition, Orange Beach, Alabama, September 1988.

(7) "Synthesis of Di-*tert*-butyldibenzo-21-crown-7 and Its Alkali Metal Cation Complexation," J. A. McDonough, B. Strzelbicka and R. A. Bartsch, Fifth International Symposium on Inclusion Phenomena and Molecular Recognition, Orange Beach, Alabama, September 1988.

(8) "Effects of Structural Variation within Proton-Ionizable Crown Ethers upon the Selectivity and Efficiency of Solvent Extraction of Alkali Metal and Alkaline Earth Cations," R. A. Bartsch, Invited lecture in Symposium on Recent Initiatives in the Synthesis of Organic Extractants, Division of Industrial and Engineering Chemistry, 197th National Meeting of the American Chemical Society, Dallas, Texas, April 1989.

V. GRANT COMPLIANCE

It is estimated that by the termination of the present grant period on December 31, 1990, all funds allocated by the U.S. Department of Energy will have been expended or encumbered. During the grant period, Dr. Richard A. Bartsch, the Principal Investigator, has devoted 15 percent of his time and effort during the academic year and 35 percent of his time during the summer to the project. All items of the Supplemental Agreement for the current grant period have met with compliance.