

"METAL ION COMPLEXATION BY IONIZABLE CROWN ETHERS"

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FINAL REPORT

FOR THE PERIOD OF  
JANUARY 1, 1988 - JUNE 30, 1994

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UNDER GRANT NUMBER DE-FG05-88ER13832

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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  $\text{Hg}^{2+}$  has been discovered.

Complexation of alkali metal cations by proton-ionizable crown ethers in homogeneous media has been probed by  $^1\text{H}$  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



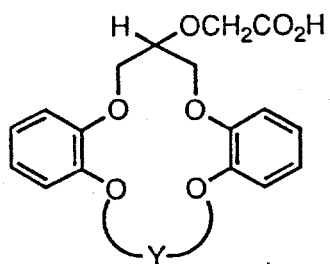
media by nuclear magnetic resonance spectroscopy or by titration calorimetry, such lipophilic groups are not necessary.

### 1. Mono-Ionizable Crown Ethers with Pendent Acid Groups

Our first proton-ionizable crown ethers were crown ether carboxylic acids 1-4.<sup>1-3</sup> 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.<sup>4-6</sup>

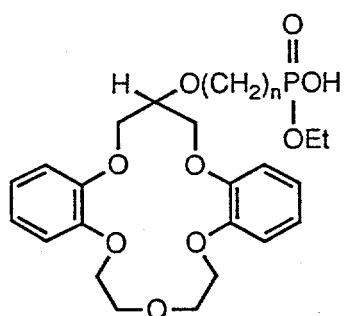
For derivatives of sym-dibenzo-16-crown-5-oxyacetic acid (3), the highest Na<sup>+</sup> selectivity in competitive solvent extraction of alkali metal cations from aqueous solution into chloroform was observed when an eight-carbon lipophilic group was attached to the center carbon of the three-carbon 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.<sup>5,6</sup> It was proposed that the enhanced Na<sup>+</sup> 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

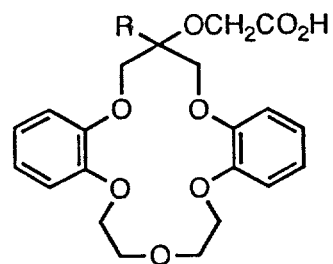


Y

- |          |   |
|----------|---|
| <u>1</u> | -CH <sub>2</sub> CH <sub>2</sub> -  |
| <u>2</u> | -CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -                                  |
| <u>3</u> | -CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>2</sub> -                 |
| <u>4</u> | -CH <sub>2</sub> (CH <sub>2</sub> OCH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub> - |

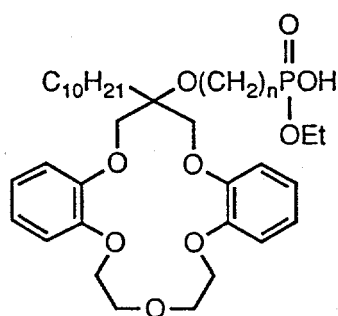


22 (n = 1-4)



R

- |           |  |
|-----------|--|
| <u>5</u>  | -CH <sub>3</sub>   |
| <u>6</u>  | -C <sub>2</sub> H <sub>5</sub>                                       |
| <u>7</u>  | -C <sub>3</sub> H <sub>7</sub>                                       |
| <u>8</u>  | -C <sub>4</sub> H <sub>9</sub>                                       |
| <u>9</u>  | -C <sub>5</sub> H <sub>11</sub>                                      |
| <u>10</u> | -C <sub>6</sub> H <sub>13</sub>                                      |
| <u>11</u> | -C <sub>8</sub> H <sub>17</sub>                                      |
| <u>12</u> | -CH(C <sub>2</sub> H <sub>5</sub> )(C <sub>5</sub> H <sub>11</sub> ) |
| <u>13</u> | -C <sub>10</sub> H <sub>21</sub>                                     |
| <u>14</u> | -C <sub>12</sub> H <sub>23</sub>                                     |
| <u>15</u> | -C <sub>14</sub> H <sub>29</sub>                                     |
| <u>16</u> | -C <sub>16</sub> H <sub>33</sub>                                     |
| <u>17</u> | -C <sub>18</sub> H <sub>37</sub>                                     |
| <u>18</u> | -C <sub>20</sub> H <sub>41</sub>                                     |
| <u>19</u> | -C <sub>3</sub> F <sub>7</sub>                                       |
| <u>20</u> | -C <sub>6</sub> F <sub>13</sub>                                      |
| <u>21</u> | -C <sub>8</sub> F <sub>17</sub>                                      |



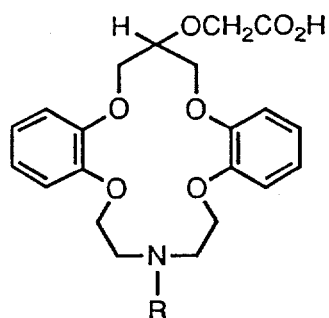
23 (n = 1-4)

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.<sup>7</sup> 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.

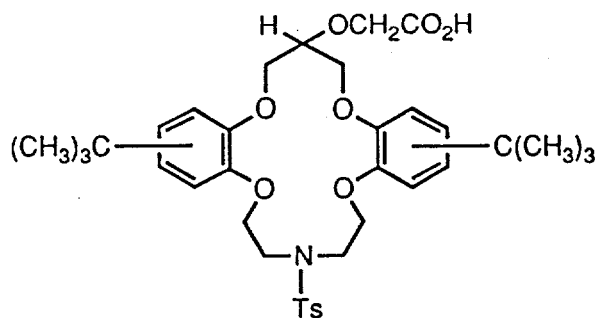
The proton-ionizable dibenzocrown ethers 1-23 all have attachment of the sidearm to the polyether ring through an oxygen atom of the sidearm. To determine the effect of the structural variation in which this linkage is through a carbon atom, two new series of dibenzocrown ether carboxylic acids were 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



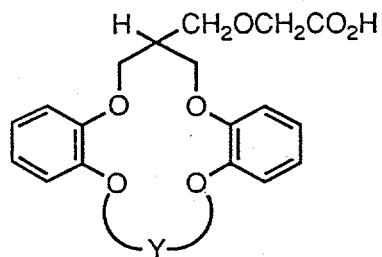
R

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25

-Ts  
-C<sub>10</sub>H<sub>21</sub>



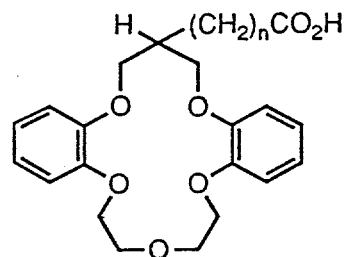
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28  
29

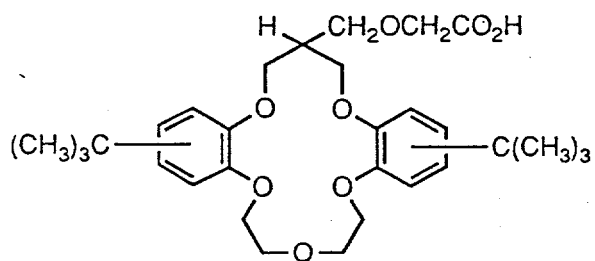
-CH<sub>2</sub>CH<sub>2</sub>-  
-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-  
-CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>-



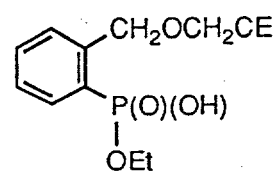
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32

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1  
2



33



CE

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35

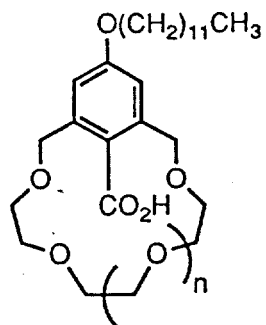
15-Crown-5  
18-Crown-6

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  $^1\text{H}$  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  $^1\text{H}$  NMR absorption pattern.

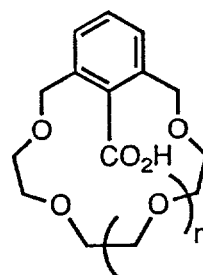
## 2. Mono-Ionizable Crown Ethers with Inward-Facing Acid Groups

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<sup>8</sup> and 40-43 by Reinhoudt and coworkers.<sup>9,10</sup> By adaptation of the procedure of Reinhoudt and coworkers,<sup>9,10</sup> 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.



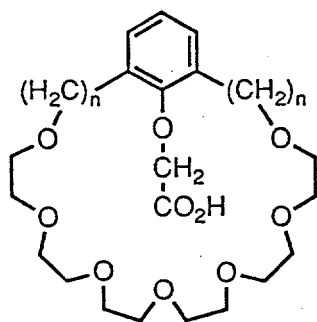
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<u>36</u>	1
<u>37</u>	2
<u>38</u>	3
<u>39</u>	4



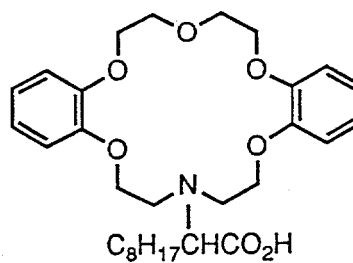
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<u>40</u>	1
<u>41</u>	2
<u>42</u>	3
<u>43</u>	4

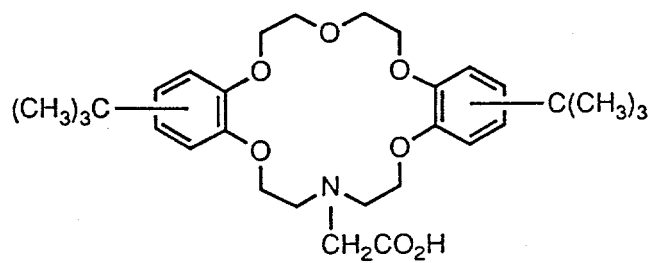


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<u>44</u>	0
<u>45</u>	1



46



47

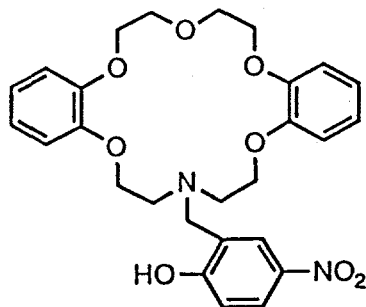
For  $^1\text{H}$  NMR spectroscopic investigations of the corresponding alkali metal carboxylate salts, large ring crown ethers 44 and 45 with inward-facing oxyacetic acid groups were prepared. Ligands 44 and 45 differ in the atoms which connect the polyether portion to the benzene ring change from 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 -

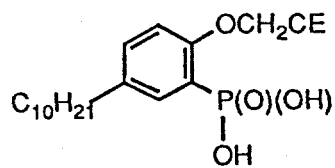
All of the crown ethers with pendent acid groups described above are examples of "C-pivot" lariat ethers in which the sidearm is attached to a carbon atom of the polyether ring. Previously we reported the synthesis of lipophilic crown ether amino acid 46 in which the sidearm is attached to the nitrogen atom of a monoazacrown ether.<sup>11</sup> 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.

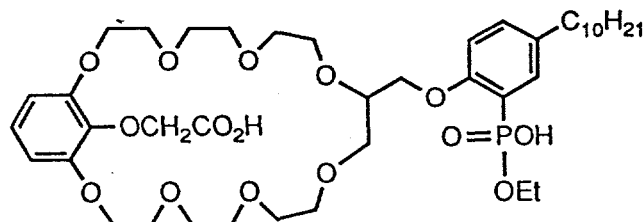


48

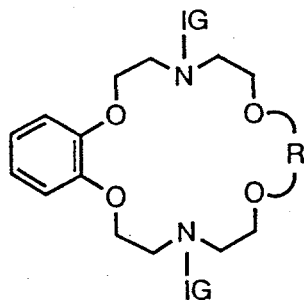


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- |           |            |
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| <u>49</u> | 14-Crown-4 |
| <u>50</u> | 15-Crown-5 |
| <u>51</u> | 18-Crown-6 |
| <u>52</u> | 21-Crown-7 |
| <u>53</u> | 24-Crown-8 |



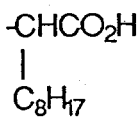
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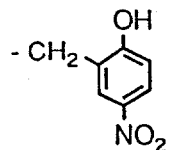
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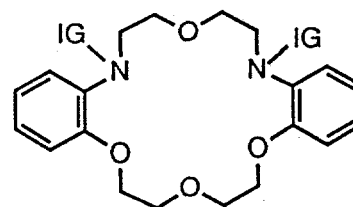
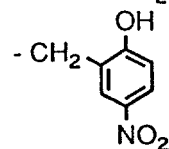
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56

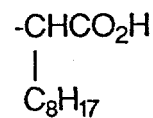


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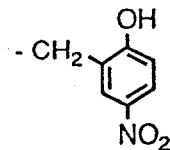


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58



59





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

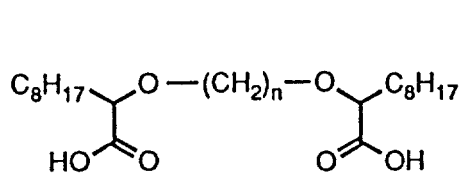
The sophisticated, lipophilic, di-ionizable crown ether 54 was also synthesized. This chelating agent possesses an inward-facing oxyacetic acid group and a pendent phosphonic acid monoethyl ester group. Since the latter is the more acidic of the two proton-ionizable functions, the metal ion complexing 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

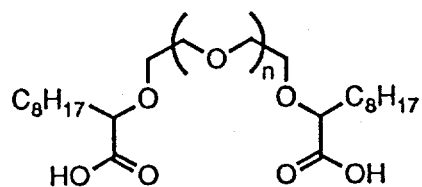
Attachment of acid group-containing sidearms to the nitrogen atoms of a diazacrown ether is an alternative synthetic route to di-ionizable ligands. Such ligands are of the N-pivot type. For evaluation of their metal ion complexation properties, novel di-ionizable crown ethers were prepared from two different 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 bulky 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

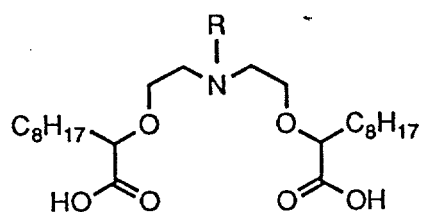
A versatile synthetic route to a variety of lipophilic acyclic polyether dicarboxylic acids was discovered and developed. The lipophilic



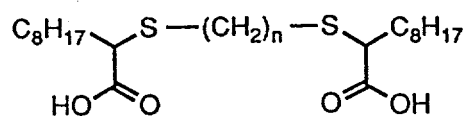
	$n$
<u>60</u>	2
<u>61</u>	3
<u>62</u>	4



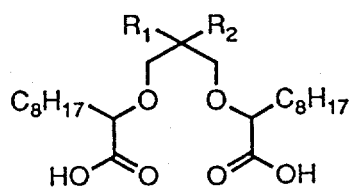
	$n$
<u>63</u>	1
<u>64</u>	2



	$R$
<u>65</u>	-Ts
<u>66</u>	-C <sub>6</sub> H <sub>5</sub>



	$n$
<u>67</u>	2
<u>68</u>	3



	$R_1$	$R_2$
<u>69</u>	-H	-CH <sub>3</sub>
<u>70</u>	-H	-CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>
<u>71</u>	-H	-C <sub>6</sub> H <sub>5</sub>
<u>72</u>	-H	-C(C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub>
<u>73</u>	-H	-C <sub>10</sub> H <sub>33</sub>
<u>74</u>	-CH <sub>3</sub>	-CH <sub>3</sub>
<u>75</u>		-CH <sub>2</sub> CH <sub>2</sub> -
<u>76</u>		-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -

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.

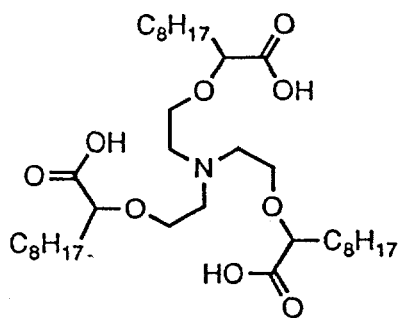
For the series of lipophilic acyclic diether carboxylic acids 61,69-76, the substituents on the center carbon of the three-carbon bridge are varied widely. Such changes will alter the possible conformations of the acyclic di-ionizable polyether ligands.

#### 8. A Lipophilic Tri-Ionizable Acyclic Polyether

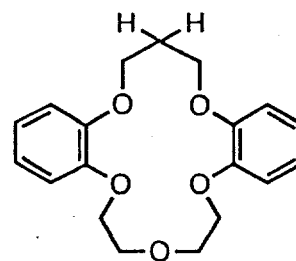
Extension of the new synthetic method allowed the novel lipophilic acyclic polyether tricarboxylic acid 77 to be prepared. Examination of CPK space filling models suggests that 77 will be an efficient chelator for trivalent metal ions.

##### B. Acidities of Lipophilic Proton-Ionizable Crown Ethers

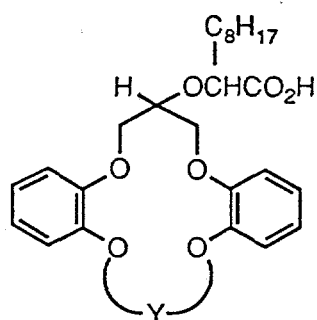
Since proton-ionizable crown ethers are effective metal ion complexing agents only in the dissociated form, knowledge of the  $pK_a$  values for such ligands is important for their application in separation processes. Unfortunately, the high lipophilicity of the proton-ionizable crown ethers



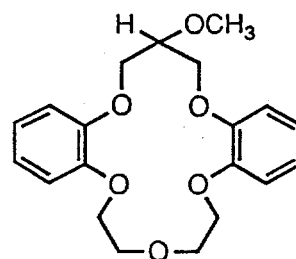
77



78

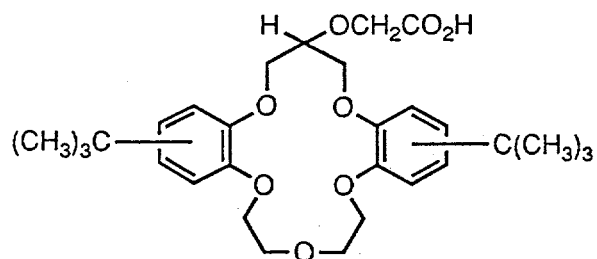


Y

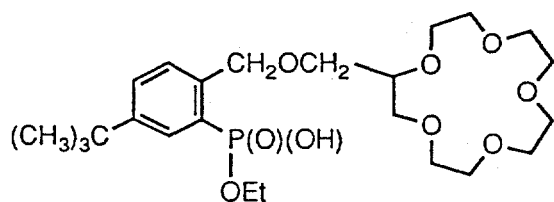


79

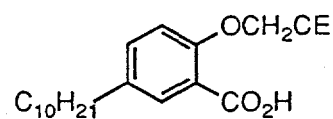
- 80    -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-  
81    -CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>-  
82    -CH<sub>2</sub>(CH<sub>2</sub>OCH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>-



83



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.<sup>12</sup> 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.<sup>13</sup> For six of the compounds, the dissociation behavior was also studied at 35.0 °C in 70% dioxane-water and the thermodynamic functions,  $\Delta G^\circ$ ,  $\Delta H^\circ$  and  $\Delta S^\circ$ , for ionization were calculated.<sup>13</sup> 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  $25.00 \pm 0.02$  °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 tetra-

methylammonium 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  $\log K$ ,  $\Delta G$ ,  $\Delta H$  and  $T\Delta S$ .<sup>14</sup> The values of  $\log K$  and  $\Delta H$  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.<sup>15</sup>

Using this method, values of  $\log K$ ,  $\Delta G$ ,  $\Delta H$  and  $\Delta S$  have been and continue to be determined for complexation of  $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Rb}^+$  and  $\text{Cs}^+$  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  $\text{Na}^+$  as would be predicted for the dibenzo-16-crown-5 ring size. The change to somewhat stronger binding of  $\text{K}^+$  than  $\text{Na}^+$  by 79 suggests a perching complex in which the  $\text{K}^+$ , 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  $\text{Na}^+$  and a 0.9 log unit enhancement in  $\text{K}^+$  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  $\text{Na}^+$  by 11. Since 11 also exhibits the highest  $\text{Na}^+$  selectivity of the three structural isomers in competitive alkali metal cation solvent extraction into chloroform,<sup>5,6</sup> 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  $\text{Na}^+$  to  $\text{Na}^+=\text{K}^+$  to  $\text{K}^+$ , 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

Crown Ether	log K				
	Li <sup>+</sup>	Na <sup>+</sup>	K <sup>+</sup>	Rb <sup>+</sup>	Cs <sup>+</sup>
<u>78</u>	ND <sup>a</sup>	2.61	2.19	ND <sup>a</sup>	ND <sup>a</sup>
<u>79</u>	1.18	2.07	2.35	1.28	IN <sup>b</sup>
<u>3</u>	IN <sup>b</sup>	3.69	3.27	2.63	2.43

<sup>a</sup>ND = Not determined. <sup>b</sup>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.

Crown Ether	log K				
	Li <sup>+</sup>	Na <sup>+</sup>	K <sup>+</sup>	Rb <sup>+</sup>	Cs <sup>+</sup>
<u>81</u>	IN <sup>a</sup>	3.56	3.53	2.30	UA <sup>b</sup>
<u>83</u>	IN <sup>a</sup>	3.67	3.50	3.10	UA <sup>b</sup>
<u>11</u>	IN <sup>a</sup>	4.40	3.42	2.87	2.34

<sup>a</sup>IN = Insufficient heat change for reliable calculation. <sup>b</sup>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.

Crown Ether	log K				
	Li <sup>+</sup>	Na <sup>+</sup>	K <sup>+</sup>	Rb <sup>+</sup>	Cs <sup>+</sup>
<u>80</u>	IN <sup>a</sup>	3.82	3.57	2.85	1.96
<u>81</u>	IN <sup>a</sup>	3.56	3.53	2.30	UA <sup>b</sup>
<u>82</u>	IN <sup>a</sup>	3.37	3.88	3.70	3.18

<sup>a</sup>IN = Insufficient heat change for reliable calculation. <sup>b</sup>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  $\text{Na}^+$  selective in solvent extraction.<sup>5</sup>

Through a comparison of the changes in  $\Delta H$  and  $\Delta S$  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  $\text{CDCl}_3$ .<sup>16</sup> 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.<sup>16</sup>

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  $^1\text{H}$  NMR absorption for the benzylic protons was a singlet in  $\text{CDCl}_3$ . 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  $^1\text{H}$  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  $^1\text{H}$  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.<sup>17,18</sup> 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  $\text{Li}^+$ . 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.<sup>17</sup>

## 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  $\text{Hg}^{2+}$  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.<sup>5</sup> In addition the extraction selectivities and efficiencies have been examined in detail for a series of nine lipophilic dibenzocrown ether carboxylic acids<sup>6</sup> and a series of 14 lipophilic salicylic acid crown compounds<sup>85,19</sup> 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  $\text{Na}^+$  selectivity in competitive alkali metal cation extraction into chloroform. For the analogous 14-crown-4 and 19-crown-6 compounds, good extraction selectivity for  $\text{Li}^+$  and  $\text{K}^+$  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  $\text{Li}^+$  and good selectivities for  $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{Cs}^+$  were obtained.<sup>5,19</sup>

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  $\text{Na}^+$  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  $\text{Na}^+/\text{K}^+$  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  $\text{Na}^+/\text{Li}^+$  selectivity ( $\text{Li}^+$  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  $\text{Na}^+$  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  $\text{Na}^+$  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:  $\text{Li}^+ > \text{Na}^+ > \text{K}^+ > \text{Rb}^+ \sim \text{Cs}^+$  for 36;  $\text{Li}^+ > \text{K}^+ > \text{Na}^+ > \text{Rb}^+ > \text{Cs}^+$  for 37;  $\text{Cs}^+ > \text{Rb}^+ > \text{K}^+ > \text{Na}^+ > \text{Li}^+$  for 38 and  $\text{Cs}^+ > \text{Rb}^+ \sim \text{K}^+ > \text{Li}^+ \sim \text{Na}^+$  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.<sup>5,6</sup> 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  $\text{Na}^+ >> \text{K}^+ > \text{Li}^+$  with no detectable  $\text{Rb}^+$  or  $\text{Cs}^+$ . With 23 ( $n=1$ ), the maximum organic phase loading was 93% and the extraction selectivity order was  $\text{Na}^+ > \text{K}^+ > \text{Rb}^+ > \text{Cs}^+ > \text{Li}^+$ . 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  $\text{pH}=4$ , 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  $\text{Na}^+$  which surpasses even the very high  $\text{Na}^+$  extraction selectivity ( $\text{Na}^+ \gg \text{Li}^+, \text{K}^+, \text{Rb}^+, \text{Cs}^+$ ) 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  $\text{Li}^+ > \text{Na}^+ > \text{K}^+ > \text{Rb}^+, \text{Cs}^+$  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  $\text{Li}^+$ .

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  $\text{Na}^+ > \text{K}^+ > \text{Li}^+, \text{Rb}^+, \text{Cs}^+$ . The extraction selectivity for  $\text{Na}^+$  is surprising since selectivity for  $\text{K}^+$  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-dichloroethane, 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,  $\text{Na}^+$  selectivity was observed, as would be predicted for the ring size of crown carboxylic acid 13. Very high selectivities for  $\text{Na}^+$  over  $\text{K}^+$  (the second best extracted cation) were noted when the extraction solvents were dichloromethane, chloroform and 1,2-dichloroethane. For the other solvents,  $\text{Li}^+$  was the second best extracted cation and  $\text{Na}^+/\text{Li}^+$  ratios were 2.9-5.7. Very good correlation between extraction selectivity and  $E_T$  (Dimroth's empirical 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  $\text{Cs}^+ > \text{Rb}^+ > \text{Li}^+ > \text{K}^+ > \text{Na}^+$  which is just the opposite of the competitive extraction selectivity.<sup>5,6</sup> 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  $\text{Na}^+ > \text{K}^+ > \text{Li}^+ > \text{Rb}^+ > \text{Cs}^+$  at pH 6-8 and  $\text{Li}^+ > \text{K}^+ > \text{Na}^+ > \text{Rb}^+ > \text{Cs}^+$  at pH 9-12. The high extractability of  $\text{Li}^+$  by 55 at alkaline pH suggests cooperative complexation of  $\text{Li}^+$  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  $\text{M}^{2+}(\text{A}^-)_2$ , where  $\text{A}^-$  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  $\text{Ba}^{2+} > \text{Ca}^{2+} > \text{Sr}^{2+} > \text{Mg}^{2+}$ ; whereas for 23 ( $n=1$ ) the selectivity order was  $\text{Mg}^{2+} > \text{Ca}^{2+}$  with no detectable  $\text{Sr}^{2+}$  or  $\text{Ba}^{2+}$  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  $\text{Ca}^{2+} > \text{Mg}^{2+}, \text{Ba}^{2+} > \text{Sr}^{2+}$ . 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	pH 8-10
<u>49</u>	14C4	$\text{Ca}^{2+} > \text{Mg}^{2+}, \text{Ba}^{2+} > \text{Sr}^{2+}$	$\text{Ca}^{2+} > \text{Mg}^{2+}, \text{Ba}^{2+} > \text{Sr}^{2+}$
<u>50</u>	15C5	$\text{Ba}^{2+} \gg \text{Ca}^{2+}, \text{Sr}^{2+} > \text{Mg}^{2+}$	$\text{Ca}^{2+} > \text{Sr}^{2+} > \text{Ba}^{2+} > \text{Mg}^{2+}$
<u>51</u>	18C6	$\text{Ba}^{2+} > \text{Sr}^{2+} > \text{Ca}^{2+} > \text{Mg}^{2+}$	$\text{Ca}^{2+} > \text{Ba}^{2+} > \text{Sr}^{2+} > \text{Mg}^{2+}$
<u>52</u>	21C7	$\text{Ba}^{2+} > \text{Ca}^{2+} > \text{Sr}^{2+} > \text{Mg}^{2+}$	$\text{Ca}^{2+} > \text{Ba}^{2+} > \text{Sr}^{2+} > \text{Mg}^{2+}$
<u>53</u>	24C8	$\text{Ba}^{2+} > \text{Ca}^{2+} > \text{Sr}^{2+} > \text{Mg}^{2+}$	$\text{Ca}^{2+} > \text{Ba}^{2+} > \text{Sr}^{2+} > \text{Mg}^{2+}$

Lipophilic crown ether phosphonic acid 49 exhibits selectivity for  $\text{Ca}^{2+}$  which is too large to be accommodated within the crown ether cavity. For 50-53, greater or lesser selectivity for  $\text{Ba}^{2+}$  is noted at acidic pH and greater or lesser selectivity for  $\text{Ca}^{2+}$  at basic pH. Presumably, the  $\text{Ba}^{2+}$  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  $\text{Ca}^{2+}$  selectivity at alkaline pH for all five crown

phosphonic acids strongly suggest primary coordination of the metal ion outside the polyether ring.

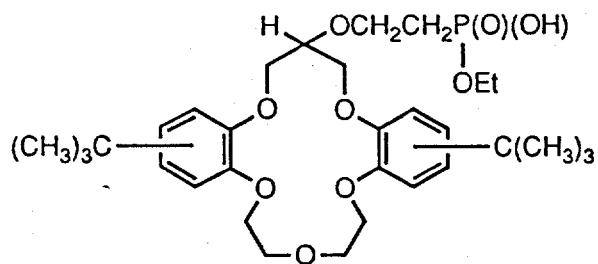
### 3. Mixed Alkali Metal and Alkaline Earth Cations

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.

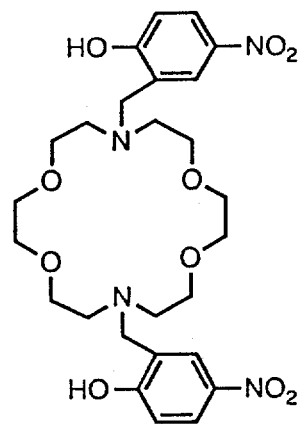
Table 5. Competitive Solvent Extraction of Alkali Metal and Alkaline Earth Cations into Chloroform by Lipophilic Mono-Ionizable Crown Ethers

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

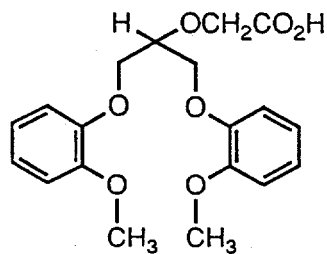
Dibenzo-16-crown-5 carboxylic acids 13, 81 and 83 have very similar structures except for the positioning of the lipophilic group(s). However their selectivities in competitive alkali metal and alkaline earth cation extractions into chloroform are very different. Thus when the lipophilic group is attached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



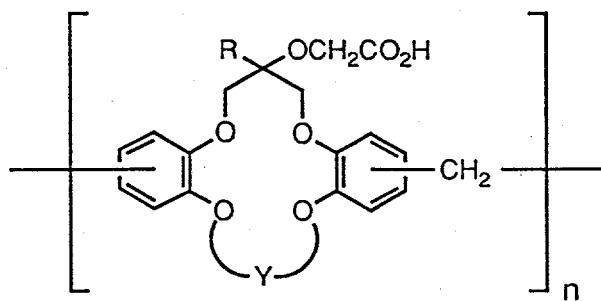
86



87



88



R

Y

89

-H

-CH<sub>3</sub>

CH<sub>3</sub>-

90

-H

-CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>-

91

-C<sub>3</sub>H<sub>7</sub>

-CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>-

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  $\text{Na}^+$  extraction, there is a marked difference in extraction of other metal ions such as  $\text{Ba}^{2+}$  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  $\text{pH}=7.0$  was  $\text{K}^+ > \text{Rb}^+ > \text{Na}^+ > \text{Li}^+, \text{Cs}^+$ . Although the metals loading increased smoothly as the  $\text{pH}$  of the aqueous phase was increased from 3.5 to 7.0, at higher  $\text{pH}$  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  $\text{Ca}^{2+} > \text{Ba}^{2+} > \text{Sr}^{2+} > \text{Mg}^{2+}$  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  $\text{Ca}^{2+} \gg \text{Ba}^{2+} > \text{Sr}^{2+} \gg \text{Mg}^{+}, \text{K}^{+}, \text{Rb}^{+}, \text{Na}^{+}, \text{Li}^{+}, \text{Cs}^{+}$  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  $\text{Ba}^{2+}, \text{Ca}^{2+}, \text{Cd}^{2+}, \text{Cu}^{2+}, \text{Hg}^{2+}, \text{Pb}^{2+}$  and  $\text{Sr}^{2+}$  into 1,2-dichloroethane by 56 were conducted using the method reported<sup>20</sup> 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  $\text{Hg}^{2+}$ . This demonstrates the importance of oxygen basicity upon extraction efficiency. In sharp contrast,  $\text{Hg}^{2+}$  was extracted five orders of magnitude better by 56 than 87. The extraction selectivity order for 56 was  $\text{Hg}^{2+} \gg \text{Pb}^{2+} > \text{Cu}^{2+} > \text{Cd}^{2+} \gg \text{Ca}^{2+} > \text{Sr}^{2+} > \text{Ba}^{2+}$ . The calculated extraction selectivity for  $\text{Hg}^{2+}$  over  $\text{Pb}^{2+}$  was  $10^7$  and for  $\text{Hg}^{2+}$  over  $\text{Ca}^{2+}$  was  $10^{15}$ ! Hence the new chromogenic di-ionizable crown ether 56 possesses an amazing selectivity for  $\text{Hg}^{2+}$  and may have potential application in lead removal from biological systems (i.e. treatment of lead poisoning) where high  $\text{Hg}^{2+}/\text{Ca}^{2+}$  selectivity is required.

Due to the extremely high extraction selectivity for  $\text{Hg}^{2+}$  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  $\text{Hg}^{2+}$  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  $\text{Ca}^{2+} \gg \text{Sr}^{2+}$ ,  $\text{Ba}^{2+} \gg \text{Mg}^{2+}$ , the maximal metals loading for compound 62 was only 9% and only slight selectivity for extraction of  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  selectivity. For 63 the metals loading decreased to 90% and the selectivity order was  $\text{Ca}^{2+} \gg \text{Ba}^{2+} \gg \text{Sr}^{2+}$  with no detectable  $\text{Mg}^{2+}$  extraction. With 64 the metals loading remained at 90% and the selectivity order was  $\text{Ca}^{2+}, \text{Ba}^{2+} \gg \text{Sr}^{2+} \gg \text{Mg}^{2+}$ . Thus the selectivity for  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  selectivity of the former was replaced by a selectivity order of  $\text{Ba}^{2+} > \text{Ca}^{2+} > \text{Sr}^{2+} > \text{Mg}^{2+}$  for the sulfur analog 67. For 68 the metals loading increased from 2% at  $\text{pH}=4.2$  to 91% at  $\text{pH}=6.7$  with a selectivity order of  $\text{Ca}^{2+} > \text{Ba}^{2+} > \text{Sr}^{2+} > \text{Mg}^{2+}$  at  $\text{pH}=6.7$ . However as the aqueous phase  $\text{pH}$  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- $\text{C}_6\text{H}_5$  in 66. For replacement of the ether oxygen with N- $\text{C}_6\text{H}_5$ , the metals loading increased by a few percent to become nearly quantitative and the extraction selectivity order was  $\text{Ca}^{2+} > \text{Ba}^{2+} > \text{Sr}^{2+} > \text{Mg}^{2+}$ . 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  $\text{Ca}^{2+} \gg \text{Mg}^{2+}$ ,  $\text{Sr}^{2+}$ ,  $\text{Ba}^{2+}$ . Thus the  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  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<sup>21</sup> 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  $\text{Na}^+$  was observed with barely detectable amounts of  $\text{K}^+$  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  $\text{Na}^+$  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  $\text{Co}^{2+}$  and  $\text{Ni}^{2+}$  transport through bulk toluene membranes, it was found that lipophilic crown carboxylic acids provide efficient and selective transport of  $\text{Co}^{2+}$ .<sup>22</sup>

## 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  $\text{Na}^+$  transport was achieved with  $\text{Na}^+/\text{K}^+$  and  $\text{Na}^+/\text{Li}^+$  transport selectivity ratios exceeding 50. The  $\text{Na}^+/\text{Rb}^+$  selectivity ratio could not be determined since no  $\text{Rb}^+$  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  $\text{Na}^+$  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  $\text{Li}^+$  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  $\text{Na}^+$  sorption selectivity. Since the cyclic polyether ring size is most appropriate for  $\text{Na}^+$  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  $\text{Na}^+$  selectivity in competitive alkali metal cation sorption was markedly enhanced. As in solvent extraction<sup>5</sup> 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.

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- (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.
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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.
- (12) "Ion Extraction and Transport by Proton-Ionizable Crown Ethers," P. R. Brown and R. A. Bartsch in "Inclusion Aspects of Membrane Chemistry," T. Osa and J. L. Atwood (Eds.), Kluwer Academic Publishers, in press.
- (13) "Effect of Structural Variations within Lipophilic Dibenzo-crown 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.

## I. ABSTRACT

During the report period a variety of new cyclic and acyclic polyether compounds with pendent carboxylic acid, phosphonic acid monoethyl ester, sulfonic acid, phosphinic acid and hydroxamic acid groups have been synthesized. In some cases, the proton-ionizable polyether compounds possess lipophilic groups which allow them to be utilized as extractants in solvent extraction of metal ions or as carriers in metal ion transport across liquid membranes. In other cases, proton-ionizable polyether compounds without lipophilic groups were prepared to study how structural variations within the ligand influence metal ion complexation in homogeneous media as assessed by titration calorimetry and NMR spectroscopy.

Two types of lipophilic di-ionizable lariat ethers for complexation of divalent metal ions have been prepared. The first type has a single, pendent, di-ionizable group. The second variety contains two pendent, mono-ionizable groups.

Conformations of proton-ionizable lariat ethers have been probed by solid state structure determinations using X-ray diffraction and in solution by NMR spectroscopy. Dissociation constants in water as determined by a new micro method have also been utilized to probe the conformational relationship between the pendent proton-ionizable group and the crown ether ring in solution.

A detailed investigation of the influence of experimental variables upon competitive alkali metal cation transport by sym-(decyl)dibenzo-16-crown-5-oxyacetic acid in polymer-supported liquid membranes was conducted. In addition the influence of structural variation upon the selectivity and efficiency of competitive alkali metal cation transport across polymer-supported liquid membranes by a series of lipophilic proton-ionizable, dibenzo lariat ethers under standardized experimental conditions were

assessed.

Thermodynamic parameters for complexation of alkali-metal cations with ionized lariat ethers have been determined in 90% methanol-10% water by titration calorimetry. The influence of structural variation within the ionophore upon  $\log K$ ,  $\Delta H$  and  $\Delta S$  values in homogeneous solution provides insight into the selectivity and efficiency of metal ion separations using the proton-ionizable lariat ethers in multi-phase systems.

Condensation polymerization of cyclic and acyclic dibenzo polyethers containing pendent mono-ionizable groups with formaldehyde produces novel ion-exchange resins which possess not only ion-exchange sites for metal ion complexation, but also polyether binding sites for metal ion recognition. Rapid alkali metal cation sorption and stripping with these new crown ether polymers allow them to be utilized in batch sorption and concentrator column separations. The influence of structural variation within the proton-ionizable dibenzo polyether monomer units upon the selectivity and efficiency of competitive alkali metal cation sorption selectivity and efficiency has been probed. Resins prepared from lariat ether dibenzo phosphonic acid monoethyl esters also exhibit strong sorption of divalent heavy metal cations with selectivity for  $Pb^{2+}$ .

## II. RESULTS AND DISCUSSION

### A. Synthesis of Proton-Ionizable Cyclic and Acyclic

#### Polyether Ligands

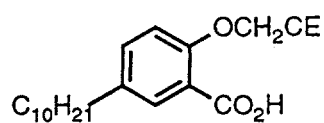
To probe the effects of structural variation within the complexing agent upon metal ion complexation by proton-ionizable polyethers, a variety of new cyclic and acyclic ligands has been prepared. The common features of these ligands include the presence of one or more ionizable group (carboxylic acid, phosphonic acid monoethyl ester, phosphonic acid) and at least two

ethereal oxygen atoms. Ligands which are to be utilized in multiphase separations, such as 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 titration calorimetry and by NMR spectroscopy, such lipophilic groups are not necessary.

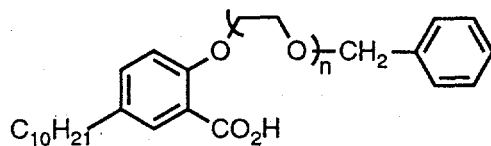
### 1. Mono-Ionizable Cyclic and Acyclic Polyethers with Pendent Carboxylic Acid Groups

Previously we have investigated competitive solvent extractions of alkali-metal cations into chloroform by lipophilic lariat ether carboxylic acids 1 (with CE = 12C4, 13C4, 14C4, 15C4, 15C5, 16C5, 18C6, 19C6, 21C7, 24C8, 27C9 and 30C10)<sup>1</sup> and by lipophilic acyclic polyether carboxylic acids 2 (with  $n = 0-4$ )<sup>2</sup>. To allow for comparison of the solvent extraction results with association constants for interactions of the alkali metal cations by analogous ionized lariat ethers in homogeneous media (90% methanol-10% water), the non-lipophilic analogues 3 (with CE = 12C4, 13C4, 14C4, 15C5, 18C6 and 21C7) and 4 (with  $n = 0-2$ ) have been prepared.

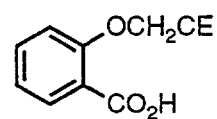
In earlier work, we synthesized lariat ether phosphonic acid monoethyl esters 5 (CE = 12C4, 15C5 and 18C6) for examination of ligand conformations in homogeneous solution by <sup>1</sup>H NMR spectroscopy.<sup>3</sup> The benzylic protons in 5 are diastereotopic. When the ionized side arm is conformationally restricted by interaction with a crown ether complexed metal ion, the benzylic protons become magnetically non-equivalent and give an AB pattern in the <sup>1</sup>H NMR spectrum. We are probing the potential for use of the weighted average chemical shift difference<sup>4</sup> for the benzylic protons as a measure of side arm restriction in the ionized crown ether metal ion complex. To expand this NMR study and include a different proton-ionizable group, lariat ether carboxylic



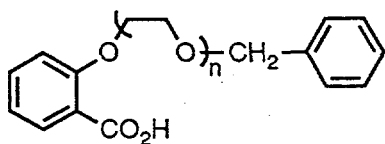
1



2



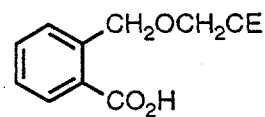
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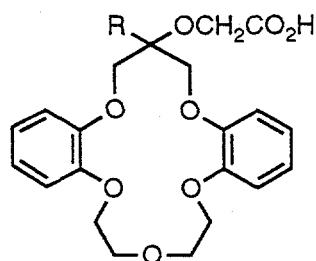
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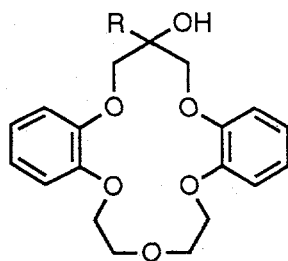
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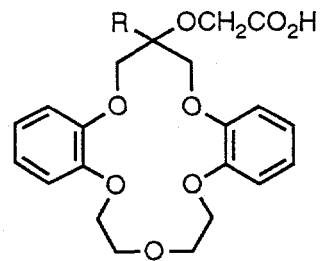
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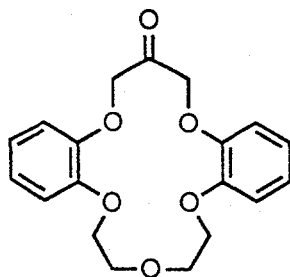
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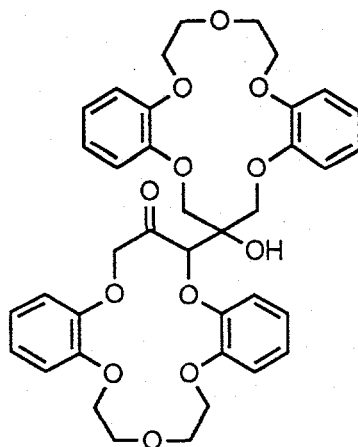
8



- R
- 9 CH<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>
  - 10 CH(CH<sub>3</sub>)<sub>2</sub>
  - 11 CH=C(CH<sub>3</sub>)<sub>2</sub>
  - 12 C<sub>6</sub>H<sub>5</sub>
  - 13 C≡CC<sub>4</sub>H<sub>9</sub>
  - 14 C≡CC<sub>6</sub>H<sub>13</sub>
  - 15 C≡CC<sub>8</sub>H<sub>17</sub>



16



17

acids **6** (with CE = 12C4, 15C5 and 18C6) have been prepared. Also comparison of association constants for ionized **6** (with CE = 12C4, 15C5 and 18C6) determined by titration calorimetry in aqueous methanol with values for ionized **3** will allow the influence of side arm length on the strength of metal ion complexation to be assessed for this type of lariat ether carboxylic acid.

In earlier investigations, we have utilized sym-(R)dibenzo-16-crown-5-oxyacetic acids (**7** with R = normal alkyl, normal perfluoroalkyl and 2-ethylhexyl) to study the influence of this structural variation upon the selectivity and efficiency of alkali-metal cation solvent extraction<sup>5</sup> and transport across liquid membranes.<sup>6</sup> Lariat ether carboxylic acids **7** had been prepared by reaction of the analogous alcohols **8** with sodium hydride in tetrahydrofuran followed by addition of bromoacetic acid. During the current grant period, we have found that the use of potassium hydride instead of sodium hydride significantly enhanced the yield for this coupling reaction to 82-93%. It is postulated that the crown ether alkoxide ion is less nucleophilic when the counterion is sodium ion which is well-accommodated within the crown ether cavity and interacts with the alkoxide oxygen atom to diminish its electron density. On the other hand, potassium ion is too large to fit within the polyether cavity and the electron density on the alkoxide oxygen is higher which provides greater nucleophilicity.

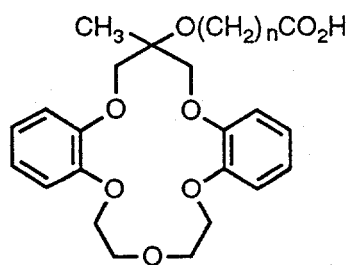
In the lariat ether carboxylic acids **7** examined to date, the geminal alkyl group has always been attached with a primary carbon atom. To further probe the influence of structural variation of the geminal group to i) a sterically hindered primary alkyl group, ii) a secondary alkyl group, iii) alkenyl and phenyl groups with sp<sup>2</sup>-hybridized first atoms, and iv) alkynyl groups with sp-hybridized first atoms, a new series of lariat ethers **9-15** was prepared. For the synthesis of **9-12**, appropriate alkyl, alkenyl and phenyl bromides were converted into the corresponding Grignard reagents by reaction

with magnesium in tetrahydrofuran followed by the addition of sym-keto-dibenzo-16-crown-5 (**16**) to produce the corresponding lariat ether alcohols **8**. The alcohols **8** were then converted into lariat ether carboxylic acids by reaction with potassium hydride and bromoacetic acid in tetrahydrofuran. Interestingly the reaction of crown ether ketone **16** with tert-butylmagnesium bromide did not provide the desired lariat ether alcohol **8** with R = tert-butyl. Instead the dimeric product **17** was isolated. Apparently nucleophilic attack by the sterically hindered Grignard reagent on the carboxyl carbon of the crown ether ketone was retarded resulting in removal of an  $\alpha$ -hydrogen to form an enolate anion which coupled with another molecule of the crown ether ketone. For attachment of geminal alkynyl groups, terminal alkynes were added to solutions of ethylmagnesium bromide in tetrahydrofuran to form the 1-alkynyl-magnesium bromides.

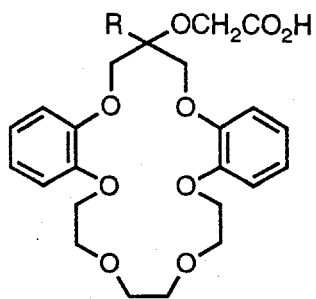
To probe the influence of varying the side arm which joins the proton-ionizable group and the macrocyclic polyether ring, lariat ether carboxylic acids **18** with  $n = 1-3$  were synthesized.

To investigate the effect of crown ether ring size variation upon metal ion complexation selectivity, a series of dibenzo-19-crown-6-oxyacetic acids (**19** with R = H, methyl, ethyl, propyl and butyl) was prepared from the corresponding lariat ether alcohols **20** with sodium hydride and bromoacetic acid in tetrahydrofuran. Once again a mismatch of the alkali-metal cation of the metal hydride and the crown ether ring size gave higher yields in the coupling reaction. Thus sodium hydride rather than potassium hydride gave higher yields for alkylation of the dibenzo-19-crown-6 alcohols **20**. (Recall that a change from sodium hydride to potassium hydride in the alkylation of dibenzo-16-crown-5 alcohols **8** enhanced the coupling yield.)

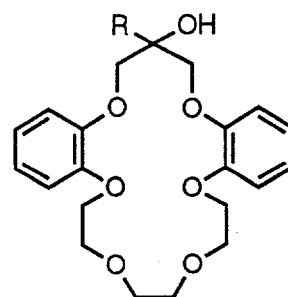
For use as model compounds the series of dibenzo acyclic polyether carboxylic acids **21-30** was prepared.



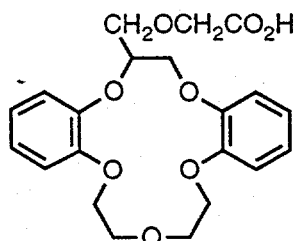
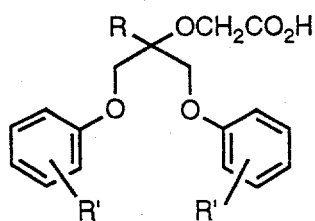
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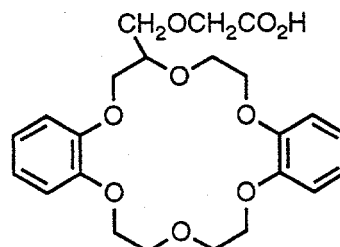
19



20

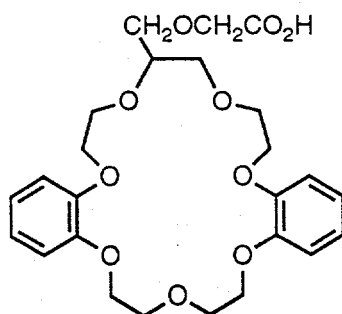


31

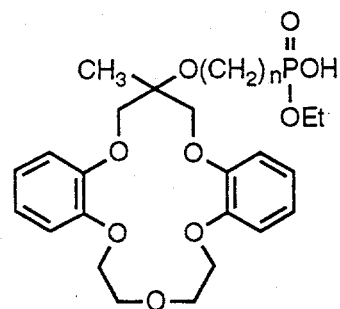


32

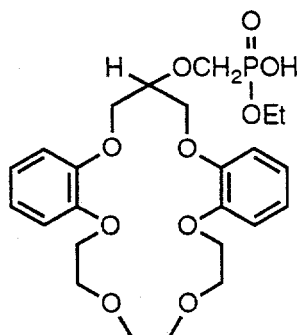
	R	R'
21	H	H
22	C <sub>3</sub> H <sub>7</sub>	H
23	H	<i>o</i> -CH <sub>3</sub>
24	C <sub>3</sub> H <sub>7</sub>	<i>o</i> -CH <sub>3</sub>
25	H	<i>o</i> -OCH <sub>3</sub>
26	C <sub>3</sub> H <sub>7</sub>	<i>o</i> -OCH <sub>3</sub>
27	C <sub>10</sub> H <sub>21</sub>	<i>o</i> -OCH <sub>3</sub>
28	H	<i>p</i> -OCH <sub>3</sub>
29	C <sub>3</sub> H <sub>7</sub>	<i>p</i> -OCH <sub>3</sub>
30	C <sub>10</sub> H <sub>21</sub>	<i>p</i> -OCH <sub>3</sub>



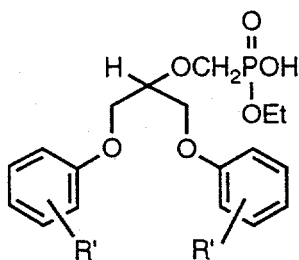
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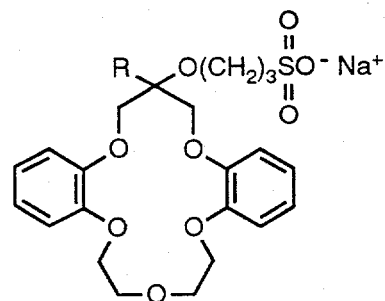
34



35



	R'
36	<i>o</i> -OCH <sub>3</sub>
37	<i>p</i> -OCH <sub>3</sub>



	R
38	H
39	C <sub>3</sub> H <sub>7</sub>



Lariat ether carboxylic acids **7** and **19** contain a three-carbon bridge in the polyether ring. For comparison of metal ion recognition by dibenzolariat ether carboxylic acids which contain only two carbon bridges in the macrocyclic polyether units, the dibenzo-15-crown-5, -18-crown-6 and -21-crown-7 carboxylic acids **30-32**, respectively, have been synthesized.

## **2. Mono-Ionizable Cyclic and Acyclic Polyethers with Pendent Phosphonic Acid Monoethyl Ester Groups**

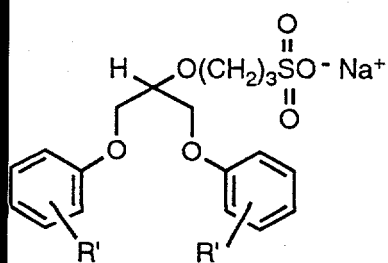
Phosphonic acid monoethyl ester functions are mono-ionizable groups with higher acidity than carboxylic acid groups. For comparison with analogous lariat ether carboxylic acids, the new lariat ether phosphonic acid monoethyl esters **34** with  $n = 0-3$  and **35** were prepared. Also acyclic polyether phosphonic acid monoethyl esters **36** and **37** were synthesized.

## **3. Mono-Ionizable Cyclic and Acyclic Polyethers with Pendent Sulfonic Acid Groups**

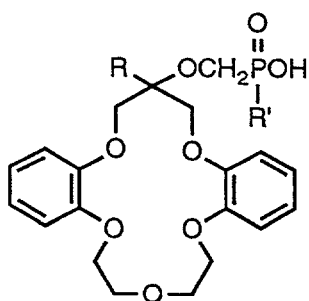
Even more acidic mono-ionizable functions are sulfonic acid groups. Lariat ether sulfonates **38** and **39** and acyclic polyether sulfonates **40** and **41** were prepared by reaction of the appropriate alcohol with sodium hydride and 1,3-propanesultone in tetrahydrofuran.

## **4. Mono-Ionizable Lariat Ethers with Pendent Phosphinic Acid and Hydroxamic Acid Groups**

To better understand the effect of varying the acidic function in lariat ethers with mono-ionizable groups, lariat ethers phosphinic acids **42** and **43** were prepared. Use of the route which provided good yields of **42** was unsuccessful for the synthesis of **44**, a structural analogue with a geminal alkyl group. Lariat ether hydroxamic acids **45** and **46** were also prepared. These compounds share a common ring structure and side arm length with lariat ether carboxylic acids **7** and analogous phosphonic acid monoethyl esters.

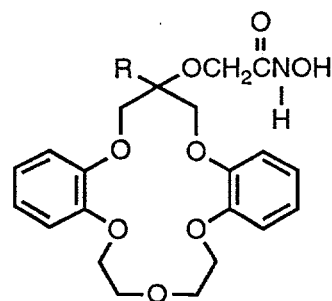


40  $\alpha$ -OCH<sub>3</sub>  
41  $p$ -OCH<sub>3</sub>



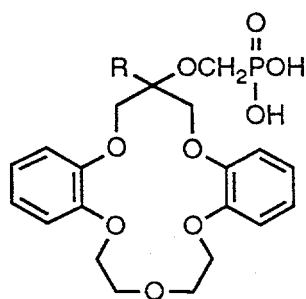
42 H  
43 H  
44 C<sub>3</sub>H<sub>7</sub>

$R'$   
CH<sub>3</sub>  
C<sub>4</sub>H<sub>9</sub>  
alkyl

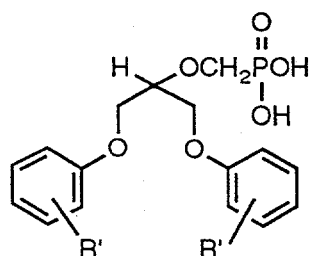


45 H  
46 C<sub>3</sub>H<sub>7</sub>

$R$

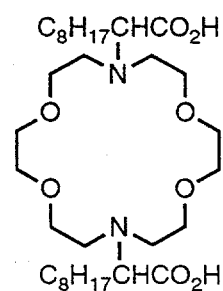


47

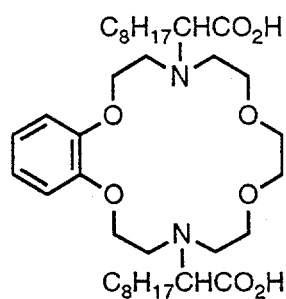


48  $\alpha$ -OCH<sub>3</sub>  
49  $p$ -OCH<sub>3</sub>

$R'$

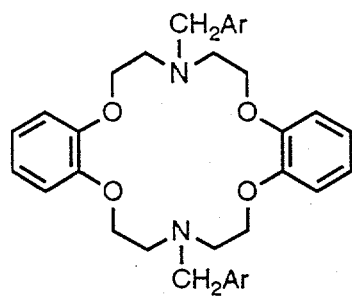


50



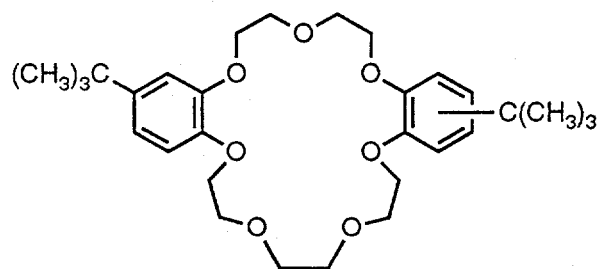
51 0  
52 1

$\bar{n}$

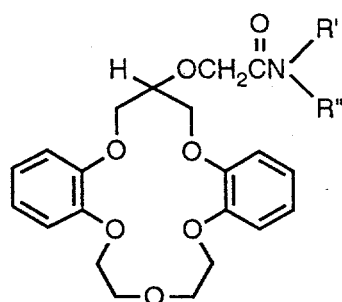


53

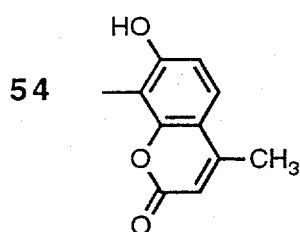
Ar  
HO-NO<sub>2</sub>



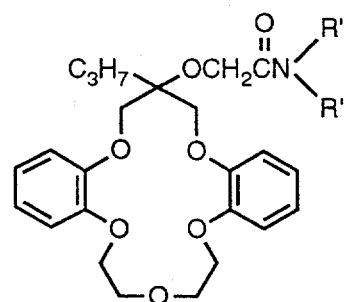
55



56



54



57

## 5. Di-Ionizable Cyclic and Acyclic Polyethers with Pendent Phosphonic Acid Groups

Cyclic or acyclic polyethers with pendent phosphonic acid groups possess di-ionizable functionality for formation of electroneutral complexes with divalent metal ions. New lariat ether phosphonic acids 47 with R = H, methyl, ethyl and propyl were synthesized. Also the acyclic polyether phosphonic acids 48 and 49 were prepared.

## 6. Diazacrown Ethers with Two Pendent Mono-Ionizable Groups

For studies of divalent metal ion extraction and transport across liquid membranes, diazacrown ethers substituted on both nitrogens with lipophilic, carboxylic acid containing sidearms were realized. For lipophilic macrocyclic diamino acids 50 and 52, the structural variation is the presence or absence of a benzo groups substituent on the 1,10-diaza-18-crown-6 ring. For 51 and 52 the diazacrown ether ring size is varied from 15-crown-5 to 18-crown-6.

In earlier work, we discovered that chromogenic di-ionizable macrocyclic ligand 53 possesses extremely high  $\text{Hg}^{2+}$  selectivity for solvent extraction into 1,2-dichloroethane.<sup>7</sup> To determine if a structurally related compound with proton-ionizable fluorogenic groups would also exhibit high selectivity for  $\text{Hg}^{2+}$ , compound 54 was designed and synthesized.

### B. Synthesis of Non-Ionizable Crown Ethers and Lariat Ethers

For application in the solvent extraction of cesium ions, a viable synthetic route to bis(tert-butylbenzo)-21-crown-7 (55) was developed.<sup>8</sup>

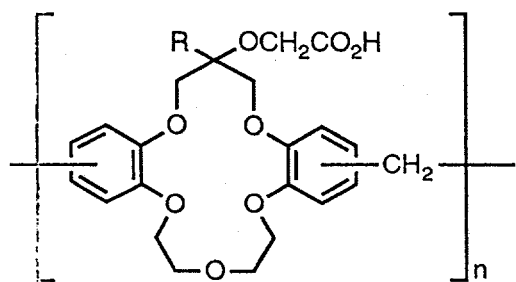
Through research conducted in the current and previous funding period considerable insight has been gained into the influence of structural variation within proton-ionizable dibenzo-16-crown-5 lariat ethers upon the

selectivity and efficiency of alkali-metal cation complexation. To compare these alkali metal cation complexation propensities with those for analogous lariat ethers which have non-ionizable chelating groups on the side arm, two series of N-substituted dibenzo-16-crown-5-oxyacetamides **56** and **57** with  $R' = H$ , alkyl and  $R'' = H$ , alkyl have been prepared.<sup>9</sup> For both series of compounds there was systematic structural variation in the  $R'$  and  $R''$  groups to alter the electron density at the carboxyl oxygen and the steric properties of the amide groups. The compounds of series **57** possess a geminal propyl group to orient the amide group containing side arm over the polyether cavity and preorganize the binding site.

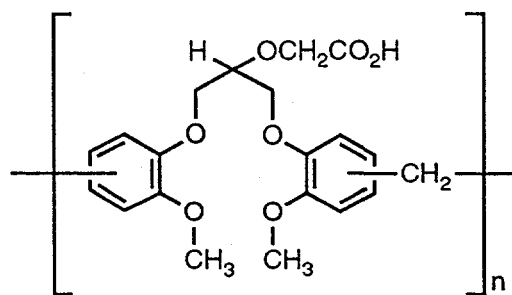
### C. Synthesis of Proton-Ionizable Cyclic and Acyclic Polyether Resins

As we have reported previously,<sup>10</sup> condensation polymerization of dibenzo-16-crown-5-oxyacetic acid and sym-(propyl)dibenzo-16-crown-5-oxyacetic acid with formaldehyde in formic acid produces polymers **58** and **59**, respectively.<sup>10</sup> These polymers are a new type of ion-exchange resin with both ion-exchange and cyclic polyether binding sites for metal ion complexation. Since some degree of crosslinking is anticipated in such polymers, the structural representations shown in **58** and **59** are oversimplifications.

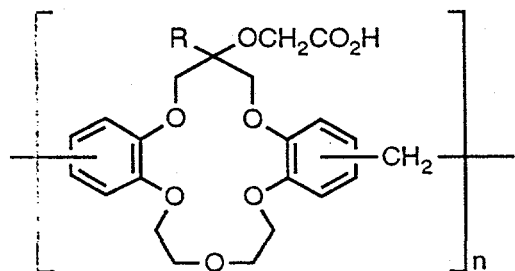
It was demonstrated that alkali-metal cation sorption by cyclic polyether carboxylic acid resins **58** and **59** and acyclic polyether carboxylic acid resin **60** and stripping by treatment with aqueous hydrochloric acid were rapid.<sup>10</sup> Furthermore it was found that the selectivity for  $Na^+$  in competitive alkali-metal cation sorption increases in the order  $60 < 58 < 59$ . Thus the presence of a dibenzo-16-crown-5 ring in resins **58** and **59** enhanced sorption of  $Na^+$  over that observed with the structurally related acyclic polyether carboxylic acid resin **60**. The greater  $Na^+$  sorption selectivity of



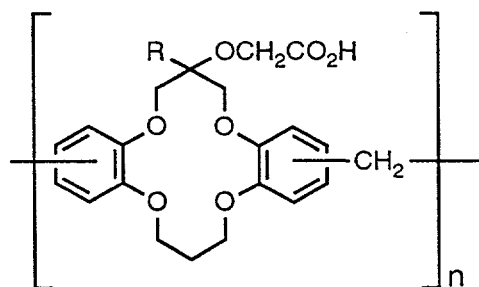
58  $\begin{matrix} R \\ H \end{matrix}$   
59  $\begin{matrix} C_3H_7 \end{matrix}$



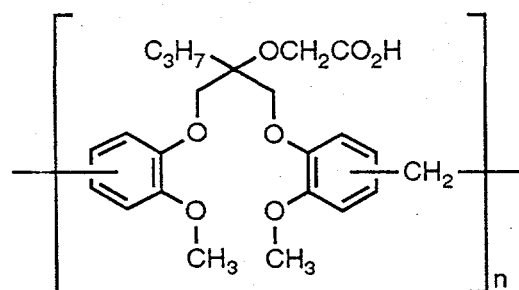
60



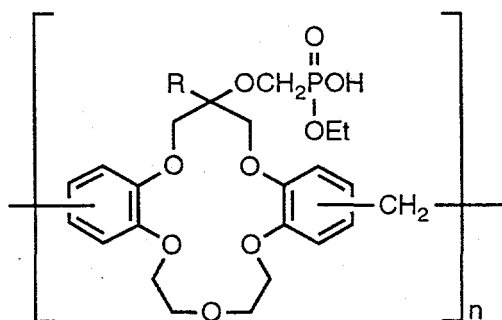
61  $\begin{matrix} R \\ CH_3 \end{matrix}$   
62  $\begin{matrix} C_2H_5 \end{matrix}$   
63  $\begin{matrix} C_4H_9 \end{matrix}$   
64  $\begin{matrix} C_6H_{13} \end{matrix}$   
65  $\begin{matrix} C_{10}H_{21} \end{matrix}$



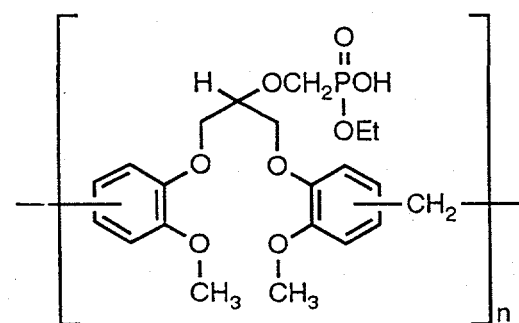
66  $\begin{matrix} R \\ H \end{matrix}$   
67  $\begin{matrix} C_3H_7 \end{matrix}$



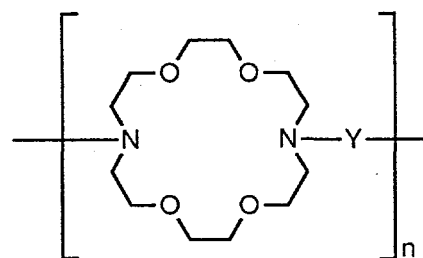
68



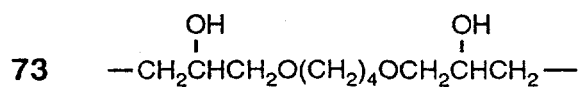
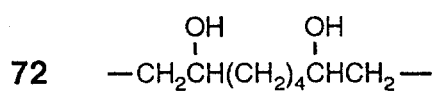
69  $\begin{matrix} R \\ H \end{matrix}$   
70  $\begin{matrix} CH_3 \end{matrix}$



71



Y



resin 59 than 58 is attributed to the geminal propyl group in the former which orients the proton-ionizable group over the crown ether cavity to pre-organize the binding site.

To further probe the influence of structural modification within the dibenzo polyether carboxylic acid monomer upon the selectivity and efficiency of competitive metal ion sorption, additional proton-ionizable dibenzo polyether resins have been synthesized. To examine the effect of varying the geminal alkyl group, the series of lariat ether carboxylic acid resins 61-65 was prepared.<sup>11</sup> For the series of polymers 58, 61, 62, 59, 63-65, there is systematic structural variation of the geminal group from hydrogen to methyl to ethyl to propyl to butyl to hexyl to decyl.

In lariat ether carboxylic acid resins 66 and 67, the crown ether ring has been changed to dibenzo-14-crown-4. The resin pairs of 66 and 60 and of 67 and 68 are very similar in structure except for the variation from a cyclic polyether unit to an acyclic polyether linkage with the same number of oxygens.

Another important structural variation is the identity of the pendent proton-ionizable group. Lariat ether resins 69 and 70 are identical with 58 and 61 with the exception that the proton-ionizable group is a phosphonic acid monoethyl ester in the former pair and a carboxylic acid in the latter pair. Proton-ionizable acyclic polyether resins 71 and 60 are related similarly.

#### D. Synthesis of Water-Soluble Polymers with Diazacrown Ether Units in the Backbone

For evaluation of their performance in homogeneous, aqueous-phase separation of metal ions by liquid-phase, polymer-based retention (LPR), polymers 72 and 73 were prepared by condensation polymerization of 1,10-diaza-18-crown-6 with 1,2,7,8-diepoxyoctane and 1,4-butanediol diglycidyl

ether. In water-soluble polymers 72 and 73, the metal ion chelating diaza-crown ether unit is incorporated into the polymer backbone.

## E. Proton-Ionizable Lariat Ethers in Homogeneous Media

### 1. Acidity in Aqueous Solution

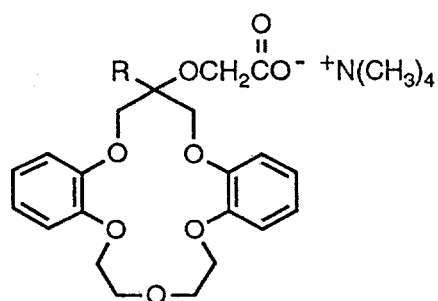
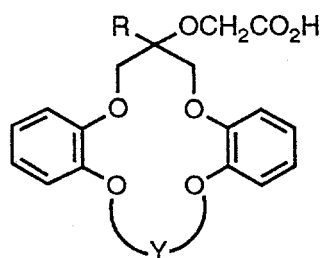
For the application of proton-ionizable lariat ethers in separation processes, the acidity of the ionizable group is a very important factor. Previously we have determined dissociation constants for proton-ionizable lariat ethers in aqueous dioxane.<sup>12,13</sup> A mixed aqueous-organic solvent system was utilized due to the very low solubilities of lipophilic proton-ionizable lariat ethers in water.

Recently Dasgupta and Nara reported a novel micro method for determination of acid dissociation constants of weak acids in water by cation exchange and conductance.<sup>14</sup> A distinct advantage of this method is that only a very small quantity (ca. 10 milligrams) of the sodium salt of the acid is required.

Using this method, the determination of acidity constants for non-lipophilic lariat ether carboxylic acids in water has been undertaken. Some of the initial results are presented in Table 1.

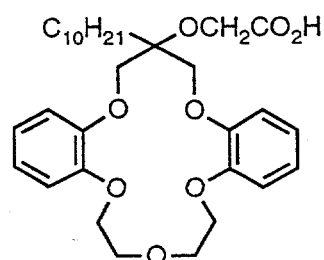
Table 1. Acidity Constants for Dibenzo Lariat Ether Carboxylic Acids in Water at 25.0 °C.

Compound	Ring Size	pK <sub>a</sub>
74	13-crown-4	3.949 ± 0.002
75	14-crown-4	4.018 ± 0.004
76	16-crown-5	4.585 ± 0.007
77	19-crown-6	4.268 ± 0.003
78	16-crown-5	4.761 ± 0.005

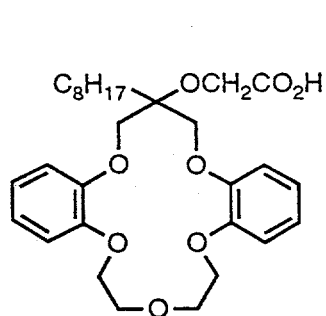


79

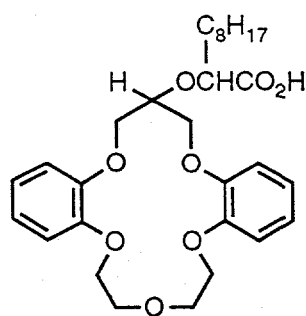
	<u>R</u>	<u>Y</u>
74	H	CH <sub>2</sub> CH <sub>2</sub>
75	H	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>
76	H	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>2</sub>
77	H	CH <sub>2</sub> (CH <sub>2</sub> OCH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub>
78	CH <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>2</sub>



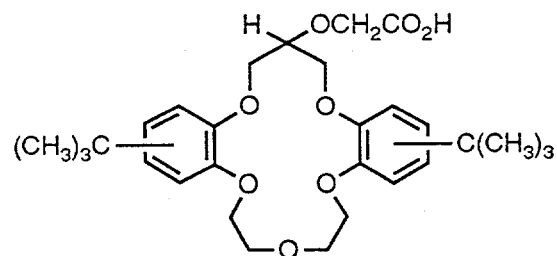
80



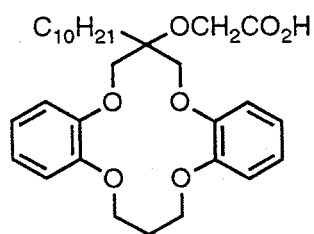
81



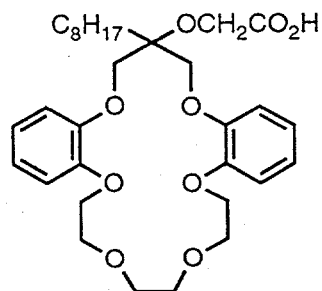
82



83



84



85



Thus for the series of dibenzocrown ether oxyacetic acids 74-77 which differ only by variation of ring size from 13-crown-4 to 14-crown-4 to 16-crown-5 to 19-crown-6, the acidity is found to first decrease then increase. From examination of CPK space-filling models, it appears that intramolecular hydrogen bonding of the pendent carboxylic acid group with the dialkyl ether oxygen of the crown ether ring in dibenzo-16-crown-5 compound 76 is responsible for the lowest acidity within the series. Attachment of a geminal methyl group in 78, which is postulated to orient the carboxylic acid group containing side arm over the macrocyclic cavity, should accentuate the acid-weakening, intramolecular hydrogen bonding. In agreement, sym-(methyl)-dibenzo-16-crown-5-oxyacetic acid (78) is found to be less acidic than sym-dibenzo-16-crown-5-oxyacetic acid (76). These results demonstrate that the precise acidity constants determined by this method can provide valuable insight into conformations of proton-ionizable lariat ethers in solution.

## 2. Alkali-Metal Cation Complexation 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 lariat 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  $25.00 \pm 0.02$  °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 lariat ether and tetramethylammonium hydroxide are analyzed by a least squares method to obtain  $\log K$ ,  $\Delta H$  and  $T\Delta S$ .<sup>15</sup> The values of  $\log K$  and  $\Delta H$  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.<sup>16</sup>

By this method, values of  $\log K$ ,  $\Delta H$  and  $\Delta S$  have been and continue to be determined for complexation of  $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Rb}^+$  and  $\text{Cs}^+$  by the ionized forms of proton-ionizable lariat ethers. An example of the type of data which has been obtained appears in Table 2. In this investigation, the effect of geminal alkyl groups on the complexation of alkali-metal cations by sym-(R)-dibenzo-16-crown-5-oxyacetates is assessed.<sup>17</sup>

For **79** with R = hydrogen, the association constant for  $\text{Na}^+$  is largest, as would be predicted for the 16-crown-5 ring size. When a methyl group is introduced on the ring carbon geminal to the carboxylate containing side arm, the association constants for  $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{Rb}^+$  increase, while that for  $\text{Cs}^+$  remains unchanged. The increase in  $\log K$  is much larger for  $\text{Na}^+$  than for  $\text{K}^+$  and  $\text{Rb}^+$ . Thus the methyl group not only gives overall binding enhancement for appropriately sized alkali-metal cations, but also increases the  $\text{Na}^+$  selectivity. Replacement of R = methyl with ethyl causes only minor alteration in the association constants and for the series of **79** with R = ethyl, butyl, hexyl, octyl, and decyl, the association constants are essentially the same. Thus the enhanced  $\text{Na}^+$  selectivity of sym-(alkyl)-dibenzo-16-crown-5-oxyacetic acids relative to sym-dibenzo-16-crown-5-

Table 2. Association Constants for Complexation of Alkali Metal Cations by Tetramethylammonium sym-(R)dibenzo-16-crown-5-oxyacetates (79) in 90% methanol-10% water.<sup>a</sup>

R	log K			
	Na <sup>+</sup>	K <sup>+</sup>	Rb <sup>+</sup>	Cs <sup>+</sup>
hydrogen	3.69 ± 0.15	3.27 ± 0.14	2.63 ± 0.07	2.43 ± 0.09
methyl	4.69 ± 0.07	3.56 ± 0.07	3.22 ± 0.24	2.35 ± 0.08
ethyl	4.47 ± 0.08	3.60 ± 0.10	2.92 ± 0.12	2.18 ± 0.10
butyl	4.46 ± 0.06	3.43 ± 0.06	2.85 ± 0.14	2.11 ± 0.12
hexyl	4.50 ± 0.01	3.47 ± 0.06	2.73 ± 0.08	2.01 ± 0.03
octyl	4.40 ± 0.06	3.42 ± 0.04	2.87 ± 0.15	2.34 ± 0.21
decyl	4.41 ± 0.01	3.31 ± 0.03	2.90 ± 0.25	2.32 ± 0.01

<sup>a</sup>In all cases insufficient heat was generated with lithium ion for calculation of the association constant.

oxyacetic acid occurs for both small and extended normal alkyl groups.

In similar fashion the influence of crown ether ring size and lipophilic group attachment site upon the complexation of alkali-metal cations by dibenzo lariat crown carboxylic acids has been probed.

### 3. Conformational Studies by Proton NMR Spectroscopy

In the <sup>1</sup>H NMR spectrum of sym-dibenzo-16-crown-5-oxyacetic acid (76) the absorption for the methylene protons on the three-carbon bridge appears as a singlet at 4.29 ppm in deuteriochloroform. For sym-(methyl)dibenzo-16-crown-5-oxyacetic acid (78), the absorption for the methylene protons on the three-carbon bridge is changed to a widely spaced AB pattern with a chemical shift difference (calculated as the weighted average chemical shift difference<sup>4</sup>) of 197 Hz and a geminal coupling constant of 10 Hz.<sup>17</sup> Such non-equivalence of the diastereotopic methylene protons in the <sup>1</sup>H NMR

spectrum of 78 demonstrates that their interconversion by flipping of the three-carbon bridge is slow on the NMR time scale. Thus the introduction of a geminal methyl group causes a marked change in conformational flexibility. (It should be recalled that Na<sup>+</sup> selectivity as assessed by titration calorimetry in 90% methanol-10% water is substantially enhanced by the introduction of a geminal methyl group.)

The effect of solvent upon the chemical shift difference was assessed for sym-(decyl)-dibenzo-16-crown-5-oxyacetic acid (80). The results which are recorded in Table 3 reveal a very substantial influence of the NMR solvent upon the chemical shift difference for the diastereotopic methylene group hydrogens. This result is rationalized on the basis of intramolecular versus intramolecular hydrogen bonding for the lariat ether carboxylic acid. Benzene is neither a hydrogen bond donor nor a hydrogen bond acceptor.

Table 3. Influence of Solvent upon the Chemical Shift Difference for the Methylene Hydrogens of the Three-Carbon Bridge of sym-(Decyl)-dibenzo-16-crown-5-oxyacetic Acid (80)

Solvent	Chemical Shift Difference, Hz
Benzene-d <sub>6</sub>	244
Deuteriochloroform	205
Acetone-d <sub>6</sub>	134
Acetonitrile-d <sub>3</sub>	127
Dimethyl Sulfoxide-d <sub>6</sub>	87

Therefore in benzene intramolecular hydrogen bonding of the pendent carboxylic acid group with a crown ether oxygen is maximized which provides the greatest restriction to flipping of the three-carbon bridge and the

largest chemical shift difference. On the other hand, dimethyl sulfoxide is a hydrogen bond acceptor which should markedly reduce the level of intra-molecular hydrogen bonding. In agreement, the chemical shift difference is diminished to approximately one third of the value observed in benzene.

Thus it appears that the chemical shift difference for the diastereotopic methylene protons in the three-carbon bridge of sym-(alkyl)-dibenzo-16-crown-5 oxyacetic acids may be a useful probe of conformational rigidity in solution.

#### 4. Solid State Structures

To provide further insight into the conformational changes produced by attachment of a geminal alkyl group in sym-dibenzo-16-crown-5-oxyacetic acid (76), solid state structures for 76 and the analogous compound with a geminal decyl group 80 have been determined in collaboration with Professor N. K. Dalley of Brigham Young University.<sup>17</sup> In the crystal structure of 76, the carboxylic acid containing side arm is directed away from the crown ether ring; whereas in 80, the oxyacetic acid side arm is oriented over the polyether cavity.

#### F. Proton-Ionizable Lariat Ethers and Their Polymers in Heterogeneous Metal Ion Complexation Systems

Lariat ether carboxylic acids were utilized as carriers for transport of alkali-metal and alkaline-earth cations across polymer-supported liquid membranes. Novel proton-ionizable lariat ether resins were employed in separations of alkali-metal cations and of heavy metal cations.

##### 1. Alkali-Metal and Alkaline-Earth Cation Transport across Polymer-Supported Liquid Membranes by Proton-Ionizable Lariat Ethers

Considerable effort was expended in the investigation of competitive, proton-coupled transport of alkali-metal cations across polymer-supported

liquid membranes by sym-(decyl)dibenzo-16-crown-5-oxyacetic acid (80). In this system, the source phase was an aqueous solution of lithium, sodium, potassium, and rubidium chlorides. (Contact with cesium chloride was found to degrade the membrane.) The receiving phase was aqueous hydrochloric acid. 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 80 in an alkyl 2-nitrophenyl ether. This type of liquid membrane solvent was chosen due to the combination of good polarity and low water solubility. In earlier work, we established that among a number of alkyl 2-nitrophenyl ethers evaluated pentyl 2-nitrophenyl ether gave the best combination of flux and  $\text{Na}^+$  selectivity.<sup>18</sup> It should be noted that this membrane system exhibits very high selectivity for  $\text{Na}^+$  transport. The  $\text{Na}^+/\text{Li}^+$  and  $\text{Na}^+/\text{K}^+$  transport selectivities are near 50. Since no  $\text{Rb}^+$  could be detected in the receiving phase, the  $\text{Na}^+/\text{Rb}^+$  transport selectivity is even higher.

A variety of experimental variables were investigated to determine their influence upon the metal ion flux and  $\text{Na}^+$  selectivity. These included:

- a) The technique for loading the solution of 80 in pentyl 2-nitrophenyl ether into the porous polypropylene sheet;
- b) The influence of the carrier concentration in the pentyl 2-nitrophenyl ether membrane solvent;
- c) The effect of temperature;
- d) The effect of pH of the aqueous source phase;
- e) The effect of the hydrochloric acid concentration in the aqueous receiving phase;
- f) The effect of the alkali-metal cation concentrations in the aqueous source phase; and
- g) The ability of the system to selectively remove  $\text{Na}^+$  from an aqueous

source phase in which the  $K^+$  concentration is several times larger than  $Na^+$ .

In another experiment, competitive transport from an aqueous source phase containing four alkali-metal cation species and the four alkaline-earth cations was performed. At the final sampling, no  $Li^+$ ,  $Rb^+$  or  $Sr^{2+}$  were detected in the receiving phase and the  $Na^+/K^+$ ,  $Na^+/Mg^{2+}$ ,  $Na^+/Ca^{2+}$  and  $Na^+/Ba^{2+}$  transport selectivity ratios were 30, 87, 28 and 47, respectively. Thus this polymer-supported liquid membrane system provides highly selective separation of  $Na^+$  from alkaline-earth cations as well as other alkali metal cations.

The study was then expanded to examine the effectiveness and selectivities of other lipophilic lariat ether carboxylic acid carriers for alkali metal cations. Under standardized conditions, the lipophilic dibenzo-16-crown-5-oxyacetic acid series of 81-83 was examined. These compounds are structural isomers which differ in the attachment sites for the lipophilic groups(s). Of the three, the  $Na^+$  flux was the highest with 81, as well as the  $Na^+/Li^+$  and  $Na^+/K^+$  transport selectivities. In 81 presence of the geminal octyl group is postulated to orient the carboxylic acid group over the crown ether cavity and pre-organize the binding site which enhances the  $Na^+$  selectivity.

It was determined that the fit of the alkali-metal cation within the crown ether cavity determines the predominant cation transported. Thus sym-(decyl)dibenzo-14-crown-4-oxyacetic acid (84) and sym-(octyl)dibenzo-19-crown-6-oxyacetic acid (85) exhibited transport selectivities for  $Li^+$  and  $K^+$ , respectively.

## 2. Metal Ion Sorption by Proton-Ionizable Lariat

### Ether Polymers

In earlier work,<sup>10</sup> condensation polymerization of dibenzo polyether carboxylic acids with formaldehyde in formic acid provided novel ion-exchange

resins 58-60. These resins possess both ion-exchange and polyether binding sites for metal ion complexation. Therefore this new class of ion-exchange resins is expected to exhibit metal ion sorption selectivities which are unavailable with common, commercially available ion-exchange resins.

It was demonstrated that alkali-metal cation sorption from aqueous solutions by resin 58 was rapid (> 85% complete after shaking for five minutes).<sup>10</sup> This contrasts sharply with the slow sorption of alkali-metal salts from aqueous solutions by condensation polymers of dibenzocrown ethers and formic acid as reported by Blasius et al.<sup>19</sup> Furthermore, sorbed alkali-metal cations can be readily stripped from resin 2 by shaking with aqueous hydrochloric acid.<sup>10</sup>

The enhanced  $\text{Na}^+$  sorption selectivity for resin 59 compared with 58 was attributed to the presence of the geminal propyl group in the former which positions the carboxylic acid group over the crown ether cavity and pre-organizes the binding site.<sup>10</sup> To more thoroughly explore the influence of the geminal alkyl group, resins 61-65 were prepared and their behavior in competitive alkali-metal cation sorption examined.<sup>11</sup> In these resins the geminal alkyl group was varied to include methyl, ethyl, butyl, hexyl and decyl. The highest efficiency (loading) and  $\text{Na}^+$  sorption selectivity were obtained when the geminal alkyl group was methyl, ethyl or propyl. The longer alkyl groups were found to be detrimental to both sorption efficiency and selectivity.<sup>11</sup>

The influence of medium polarity upon competitive sorption of alkali-metal cations from aqueous and aqueous methanolic solutions by lariat ether carboxylic acid resins 58, 61, 62, 59, 64 and 65 and acyclic polyether carboxylic acid resin 60 was assessed.<sup>20</sup> Enhancement of metal ion-crown ether interactions as the percentage of methanol in the medium was increased accentuates the  $\text{Na}^+$  sorption selectivity for the lariat ether carboxylic acid



resins. The highest  $\text{Na}^+$  sorption selectivity was obtained when the geminal alkyl group was ethyl or propyl in 80% methanol-20% water.

Column concentration of alkali-metal cations from dilute aqueous solutions by lariat ether carboxylic acid resins 58 and 59 was investigated.<sup>21</sup> Selective column concentration of alkali-metal cations was attained with resin 59. Due to the strong interaction of  $\text{Na}^+$  with resin 59, the elution peak for  $\text{Na}^+$  in the stripping solution was retarded with respect to the other alkali-metal cations. With gradient stripping, the maximum concentration factor for  $\text{Na}^+$  from aqueous sample solution which was  $6.0 \times 10^{-5}$  M in each of the five alkali-metal cations reached 1030 with an 84% purity.

Selective sorption and column concentration of alkali-metal cations by carboxylic acid resins 66 and 67 with dibenzo-14-crown-4 units and their acyclic analogues 60 and 68 were also studied.<sup>22</sup> The lariat ether carboxylic acids exhibited enhanced sorption selectivity over the acyclic polyether resins. Good sorption selectivity for  $\text{Li}^+$  and  $\text{Na}^+$  was obtained with resin 67 which has a geminal propyl group. For column concentration of alkali metal cations from dilute aqueous solutions, gradient elution of the sorbed metal ions from resin 67 gave selective column concentration of  $\text{Li}^+$  and  $\text{Na}^+$ .

Competition sorption of alkali-metal cations by lariat ether phosphonic acid monoethyl ester resins 69 and 70 and the acyclic analogue 71 was also examined.

Assessment of potential applications from proton-ionizable lariat ether resins in the separations of heavy metal ions has been initiated. It has been found that lariat ether phosphonic acid monoethyl ester resins are much more effective at sorbing  $\text{Pb}^{2+}$  and  $\text{Zn}^{2+}$  from acidic aqueous solutions than are lariat ether carboxylic acid resins or acyclic polyether phosphonic acid monoethyl ester or carboxylic acid resins. Lariat ether phosphonic acid monoethyl resins 69 exhibits good selectivity for sorption of  $\text{Pb}^{2+}$  over  $\text{Cd}^{2+}$ ,

Co<sup>2+</sup>, Cu<sup>2+</sup>, Hg<sup>2+</sup>, Ni<sup>2+</sup> and Zn<sup>2+</sup>.

### G. Non-Ionizable Crown Ethers and Lariat Ethers and Their Polymers in Heterogeneous Metal Ion Complexation Systems

Although most of the research conducted during the report period involved proton-ionizable lariat ethers and acyclic analogues and their polymers, some very interesting results were also obtained with non-ionizable lariat ethers and crown ethers and their polymers.

#### 1. Alkali-Metal Cation Extraction by a Lipophilic Crown Ether and by Lariat Ether Amides

In a collaborative project with W. J. McDowell at Oak Ridge National Laboratory,<sup>8</sup> the selective extraction of Cs<sup>+</sup> from acidic nitrate solutions by didodecyl-naphthalenesulfonic acid (HDDNS) synergized with bis-(tert-butylbenzo)-21-crown-7 (55) was achieved. Under non-loading condition, the distribution coefficient for Cs<sup>+</sup> between a toluene solution 0.025 M in HDDNS and crown ether 55 and an aqueous solution 0.1 M in nitric acid is 100 with separation factors of 1.2 from Rb<sup>+</sup>, 5.6 from K<sup>+</sup> and 294 from Na<sup>+</sup>. Under loading and competitive extraction conditions, the distribution coefficients were lower (5 for Cs<sup>+</sup>), but the separation factors remained in the same order and of useful magnitude, 1.5 from Rb<sup>+</sup>, 6.4 from K<sup>+</sup> and 192 from Na<sup>+</sup>.

The alkali-metal cation extracting ability of lariat ether amides 56 and 57 with R' and R'' = H and alkyl was examined by the picrate extraction method using chloroform as the organic solvent. For 56 the Na<sup>+</sup> extraction selectivity and efficiency were found to be higher for dialkyl (ethyl, propyl, butyl, pentyl, hexyl) tertiary amides than for the unsubstituted amide (R' = R'' = H) or a monoalkyl substituted amide (R' = H, R'' = pentyl). For 57, the presence of the geminal propyl group enhanced both the Na<sup>+</sup> extraction efficiency and selectivity compared with 56. The highest Na<sup>+</sup>

extraction selectivity was obtained for 57 and  $R' = R'' = \text{pentyl}$ .

## 2. Alkali-Metal Complexation by Lariat Ether

### Amides in Polymeric Membrane Electrodes

Alkali-metal cation selectivities of the lariat ether amides 56 and 57 have been determined in solvent polymeric membrane electrodes. Using the fixed interference method in membrane electrodes composed of poly(vinyl chloride), *o*-nitrophenyl octyl ether and 57 with  $R' = R'' = \text{pentyl}$  as the ionophore, excellent  $\text{Na}^+/\text{K}^+$  and  $\text{Na}^+/\text{Li}^+$  selectivities of 145 and 810, respectively, have been obtained.

## 3. Heavy Metal Complexation by Water-Soluble

### Diazacrown Ether Polymers

Polymers 72 and 73 possess 1,10-diaza-18-crown-6 ether units in the polymer backbone. These polymers are water-soluble and were designed and synthesized for use in homogeneous, aqueous phase separation of toxic, heavy metal ions from dilute aqueous solutions. The objective is to complex the heavy metal ion species on the chelating polymer and thereby prevent its passage through an ultrafiltration membrane which is permeable to uncomplexed metal ion species. In this liquid-phase, polymer-based retention (LPR) method, polymers 72 and 73 exhibited high propensity (>90%) from complexation of  $\text{Hg}^{2+}$  and  $\text{Pb}^{2+}$  in dilute aqueous solutions. Unfortunately, it has been found that the higher molecular weight components of the polymers are absorbed on the hydrophobic surface of the ultrafiltration membrane.

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IV. PROJECT SUPPORTED PRESENTATIONS SINCE SUBMISSION OF THE LAST PROGRESS REPORT IN JUNE OF 1990.

1. "Proton-Coupled Transport of Alkali-Metal Cations across Polymer-Supported Liquid Membranes by Lipophilic Crown Ether Carboxylic Acids," R. A. Bartsch and J. Strzelbicki, 201st National Meeting of the American Chemical Society, Atlanta, Georgia, April, 1991. (Invited paper in the Symposium on Macrocycles in Separation Science sponsored by the Separation Science and Technology Subdivision of the Division of Industrial and Engineering Chemistry.)
2. "Synthesis and Alkali-Metal Cation Sorption of Ion Exchange Resins Formed from Proton-Ionizable Crown Ethers," T. Hayashita and R. A. Bartsch, 201st National Meeting of the American Chemical Society, Atlanta, Georgia, April 1991. (Invited paper in the Symposium on Macrocycles in Separation Science sponsored by the Separation Science and Technology Subdivision of the Division of Industrial and Engineering Chemistry.)



3. "Influence of Structural Variation within Lipophilic, Proton-Ionizable Crown Ether Carriers upon Proton-Coupled Transport of Alkali-Metal Cations across Polymer-Supported Liquid Membranes," R. A. Bartsch, J. Strzelbicki and B. Strzelbicka, 201st National Meeting of the American Chemical Society, Atlanta, Georgia, April, 1991. (Invited paper in the Symposium on Membrane Technology for New Applications sponsored by the Separation Science and Technology Subdivision of the Division of Industrial and Engineering Chemistry.)
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