Metal ion extraction by lariat ethers with 'tunable' proton-ionizable groups

Richard A. Bartsch,* Sheryl N. Ivy, Jianping Lu, Vincent J. Huber, Vladimir S. Talanov, Wladyslaw Walkowiak,‡ Chunkyung Park and Bijan Amiri-Eliasi

Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409-1061, USA.
‡Permanent address: Institute of Inorganic Chemistry and Metallurgy of Rare Elements,
Technical University of Wroclaw, 50-730 Wroclaw, Poland

Abstract: Compared with crown ethers and lariat ethers with neutral side arms, proton-ionizable lariat ethers have an important advantage for metal ion separations. Due to ion-exchange of the metal ion and a proton from the pendent acidic function, transfer of an aqueous phase anion into the organic medium is avoided. A new type of proton-ionizable group, the N-(X)sulfonyl carbamoyl function, has now been incorporated into lariat ethers. For competitive solvent extraction of alkali metal cations from aqueous solutions into chloroform, variation of the X group is found to change the acidity without concomitant steric effects. A series of N-(X)sulfonyl *sym*-(decyl)dibenzo-16-crown-5-oxyacetamides exhibits very high Na$^+$ selectivity. The effect of varying the crown ether ring size on alkali metal cation extraction is explored with dibenzo-14-crown-4 and dibenzo-19-crown-6 analogs.

Introduction

In comparison with ordinary crown ether extractants, a crown ether with a proton-ionizable group has the advantage that metal ion transport into the organic phase does not require concomitant transport of an ion (or ions) from the aqueous phase (Fig. 1) (refs. 1-3). This feature is of immense importance to potential practical applications of crown ether-type extractants in which the hard aqueous phase anions of chloride, nitrate, and sulfate would be involved. An additional

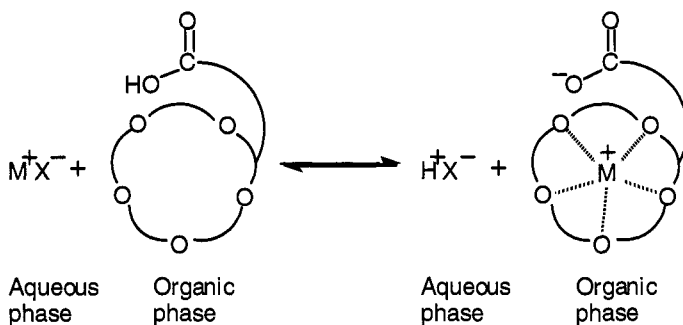| Aqueous | Organic | Aqueous | Organic |
| phase | phase | phase | phase |

Fig. 1. Metal Ion Extraction by a Proton-Ionizable Crown Ether.

advantage of proton-ionizable crown ethers is that a mechanism for cation release has been incorporated (Fig. 2). Following the extraction step, shaking of the separated organic phase with aqueous hydrochloric acid strips the extracted metal ions into an aqueous phase and regenerates the neutral form of the extractant.

The three primary strategies which have evolved for the incorporation of proton-ionizable groups into macrocyclic ligands are illustrated in Fig. 3 (ref. 2). These are: i) attachment of a pendent side arm which includes or is terminated by an acidic entity (*e.g.*, **1**) (ref. 1); ii) inclusion within the
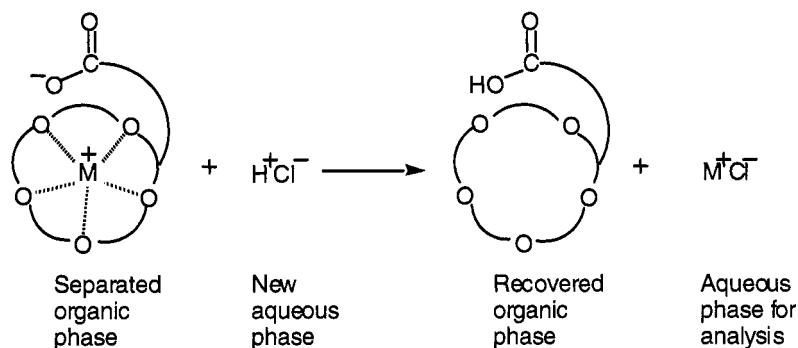
Fig. 2. Metal Ion Stripping from an Ionized Crown Ether-Metal Ion Complex.

crown ether framework of a subunit which projects an acidic entity so that both the proton and the atom which bears it are within the cavity (e.g., 2) (ref. 4); and iii) inclusion as part of the crown ether framework of a unit which places a heteroatom in a ligating position, with an attached proton projecting into the ring cavity (e.g., 3) (ref. 5). The studies in our laboratories have involved mostly ligands, such as 1, in which a side arm bearing a terminal acidic group is attached to a crown ether ring.
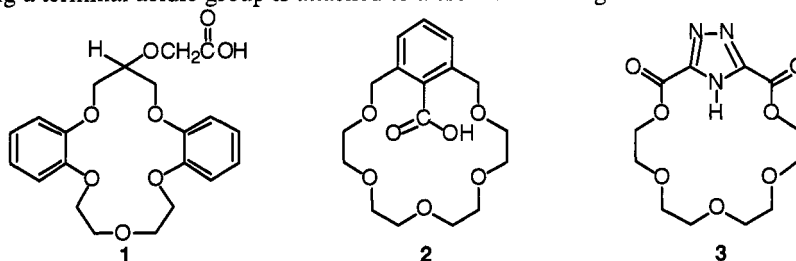

Fig. 3. Three Types of Proton-Ionizable Macrocyclic Polyether Ligands.

Attachment of one or more side arms with potential metal ion coordination sites to a crown ether framework produces complexing agents known as 'lariat ethers' (ref. 6). Therefore, ligand 1 is a proton-ionizable lariat ether (ref. 3). More specifically, ligand 1 is a lariat ether carboxylic acid.

Many of our proton-ionizable lariat ether extractants are based upon a dibenzo-16-crown-5 ring system (e.g., in 1) due to the ease with which the synthetic precursor sym-(hydroxy)dibenzo-16-crown-5 (ref. 7) can be prepared on a large scale. For the three-carbon bridge in such ligands, there are two limiting conformations as shown in Fig. 4. When R = H, the side arm is pseudo-equatorial and points away from the polyether ring. On the other hand, when R is a geminal alkyl group, the functional side arm is pseudo-axial and the proton-ionizable group is oriented over the crown ether cavity. Support for this contention is provided by solid-state structures and NMR investigations in solution (ref. 3). Orientation of the functional side arm over the crown ether cavity

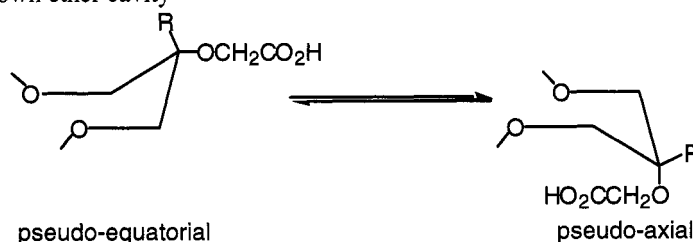pseudo-equatorial   pseudo-axial

Fig. 4. Limiting Conformations of the Three-Carbon Bridge.
preorganizes the binding site (ref. 8) and enhances selectivity.

Our previous studies of proton-ionizable lariat ethers as metal ion extractants (refs. 1-3) have involved lariat ether carboxylic acids (4), phosphonic acid monoethyl esters (5), and phosphonic acids (6). Because

of their propensity to form emulsions in aqueous-organic extraction systems, lariat ether sulfonic acids have received much less attention.

PIG			X
4	CO_2H	**7**	CH_3
5	$P(O)(OEt)OH$	**8**	C_6H_5
6	$P(O)(OH)_2$	**9**	$4\text{-}NO_2C_6H_5$
		10	CF_3
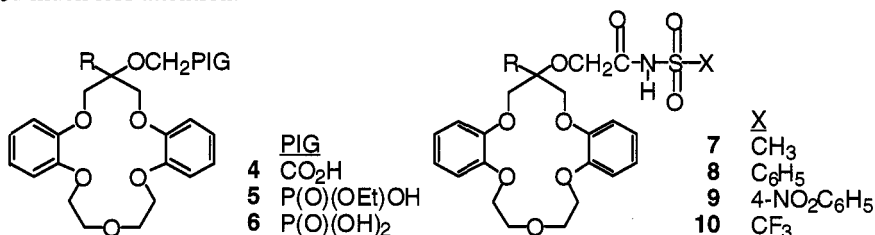
In these earlier investigations, we were unable to determine the effect of varying the acidity of the proton-ionizable group, since a change from one type of acidic function to another involves other factors than just the acidity. Recently, we have been investigating a novel type of proton-ionizable lariat ether in which the acidity of the pendent function is 'tunable'. In the N-(alkyl)- or N-(aryl)sulfonyl carbamoyl lariat ethers **7-10**, variation of the X group influences the acidity of the proton-ionizable group.

Synthesis of N-(X)sulfonyl Carboxamide Lariat Ethers

The preparative method for the new N-(X)sulfonyl carboxamide lariat ethers is outlined in Fig. 5. Thus a lariat ether alcohol is converted into the corresponding lariat ether carboxylic acid and then into the acid chloride. Coupling of the lariat ether acid chloride with the potassium salt of a commercially available sulfonamide produces the N-(X)sulfonyl oxyacetamide lariat ether (ref. 9).
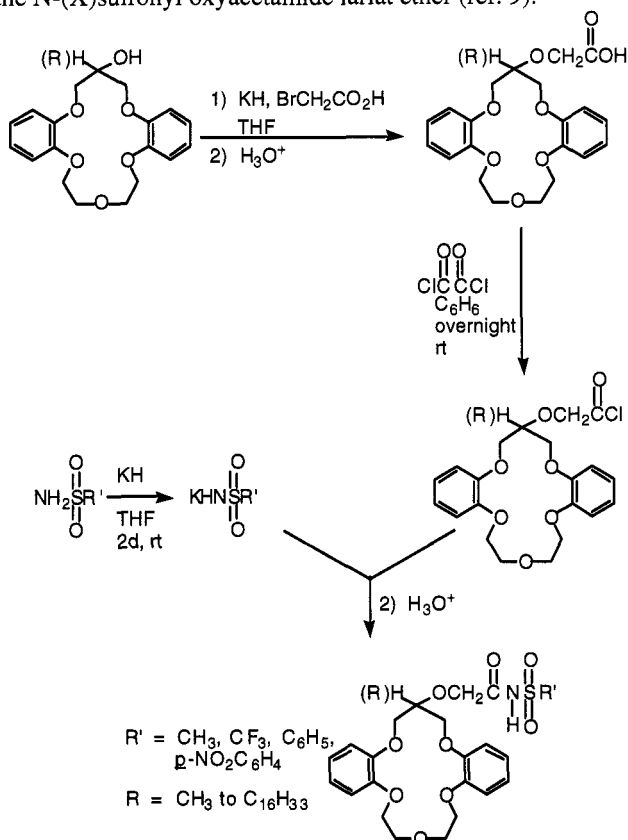

Fig. 5. Synthesis of N-(X)sulfonyl *sym*-(R)dibenzo-16-crown-5-oxyacetamides.

Competitive Solvent Extraction of Alkali Metal Cations

The metal ion-complexing properties of the new proton-ionizable lariat ethers are being evaluated by competitive solvent extraction of alkali metal cations from aqueous solutions into chloroform. An aqueous

phase which was 20 mM in NaCl, KCl, RbCl and CsCl and 20 mM in LiCl + LiOH is extracted with an equal volume of a 5.0 mM solution of the proton-ionizable lariat ether in chloroform. Subsequently, a portion of the organic phase is separated and shaken with 0.1 M HCl to strip the extracted metal ions into an aqueous solution for analysis by ion chromatography.

Results for competitive solvent extractions of alkali metal cations from aqueous solutions into chloroform by the N-(X)sulfonyl *sym*-(decyl)dibenzo-16-crown-5-oxyacetamides **11-14** are shown in Fig. 6 (ref. 9). For these extractions, K^+, Rb^+, and Cs^+ were undetectable in the aqueous strippant. Of the Na^+ (O) and K^+ (□) which are extracted into the chloroform phase, Na^+ is strongly preferred. For an aqueous phase equilibrium pH of 11, the alkali metal cation loadings for ligands **11-14** as calculated for formation of 1:1 ionized lariat ether-metal ion complexes are 96-100% and the Na^+/K^+ extraction selectivities are 47-49. Thus, ligands **11-14** are efficient and highly selective extractants for Na^+.

The very similar selectivities for the four extractants indicates that changing X does not exert an appreciable steric effect. However, the variation of X does significantly influence the side arm acidity. As judged from the extraction profiles, the acidities of these proton-ionizable lariat ethers decrease in the order: **11 > 12 > 13 > 14**. This ordering reflects the electron-withdrawing ability

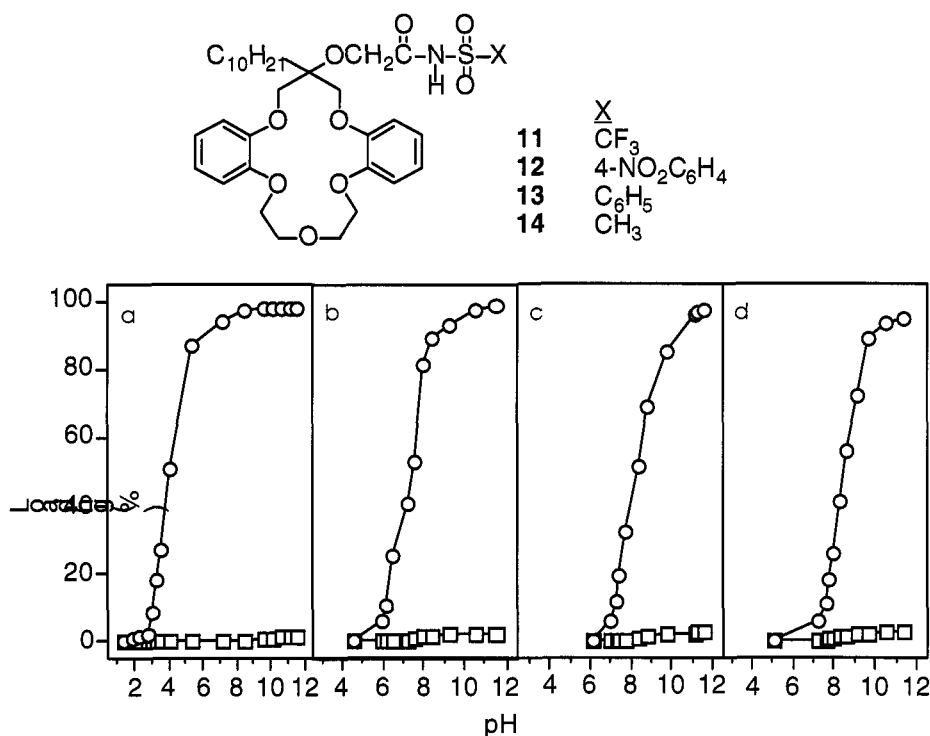|	X
11	CF_3
12	$4\text{-}NO_2C_6H_4$
13	C_6H_5
14	CH_3

Fig. 6. Metal Loadings of the Organic Phase *vs.* the pH of the Aqueous Phase for Competitive Solvent Extractions of 20 mM (Each) Solutions of Alkali Metal Cations with 5.0 mM Chloroform Solutions of a) **11**, b) **12**, c) **13** and d) **14** with O = Na^+ and □ = K^+.

of X upon the acidity of the proton-ionizable group. The efficiency with which **11** extracts Na^+ from acidic aqueous solutions is noteworthy.

To probe the influence of varying R, the geminal alkyl group, upon the extraction efficiency and selectivity, competitive solvent extractions of alkali metal cations were conducted with a series of N-(methyl)sulfonyl *sym*-(R)dibenzo-16-crown-5-oxyacetamides (**7**) with R variation from hydrogen to alkyl groups with variable chain lengths of 1-18 carbon atoms. The extraction efficiency and selectivity results are presented in Figs. 7 and 8, respectively.
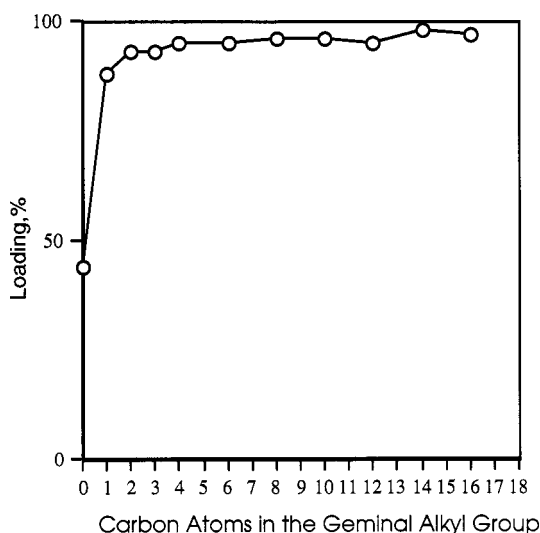
Fig. 7. Influence of the Geminal Alkyl Group upon the Total Metal Ion Loading for Competitive Solvent Extraction of Alkali Metal Cations into Chloroform by N-(Methyl)sulfonyl *sym*-(R)dibenzo-16-crown-5-oxyacetamides (7).

Fig. 8. Influence of the Geminal Alkyl Group upon the Na^+/K^+ Selectivity for Competitive Solvent Extraction of Alkali Metal Cations into Chloroform by N-(Methyl)sulfonyl *sym*-(R)dibenzo-16-crown-5-oxyacetamides (7).
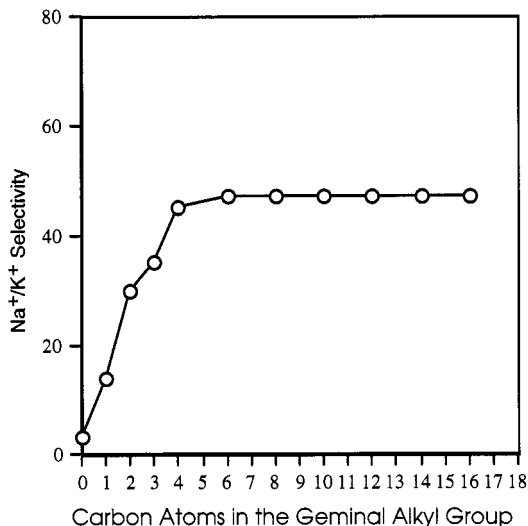
The metal ion loading (Fig. 7) increases sharply in going from a geminal hydrogen atom to a geminal methyl group. An additional, but much smaller enhancement, in extraction efficiency is noted when the geminal methyl group is replaced with ethyl. Essentially quantitative metal ion loading is observed when the alkyl group is systematically varied by one-carbon units from ethyl to butyl and then by two-carbon units from butyl to hexadecyl.

The data in Fig. 8 show that the low Na^+/K^+ selectivity obtained with R = H systematically increases when the geminal group is changed to methyl, from methyl to ethyl, from ethyl to propyl, from propyl to butyl, and from butyl to hexyl. When the alkyl group is hexyl or larger, the Na^+/K^+ selectivity remains constant near 50. We interpret these changes as resulting from an influence of the geminal alkyl group on the conformational positioning of the functional side arm as shown in Fig. 4.

Influence of Changing the Polyether Ring Size

To evaluate the effect of expanding the basic ring system from dibenzo-16-crown-5 to dibenzo-19-crown-6, the new proton-ionizable lariat ether series **15-18** was prepared by a route analogous to that shown in Fig. 5. Results from the competitive solvent extraction of alkali metal cations from aqueous solutions into chloroform by ligands **15-18** are given in Table 1.

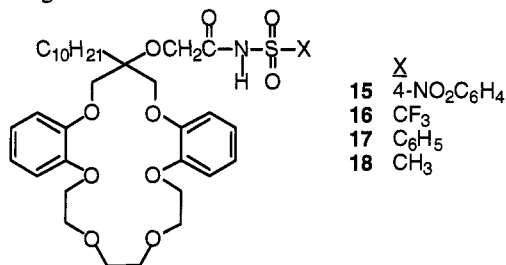|	X
15	$4\text{-}NO_2C_6H_4$
16	CF_3
17	C_6H_5
18	CH_3

Table 1. Efficiency and Selectivity for Competitive Solvent Extraction of Aqueous Solutions Containing Alkali Metal Cations (20 mM in Each) with 5.0 mM Chloroform Solutions of N-(X)sulfonyl *sym*-(Decyl)dibenzo-19-crown-6-oxyacetamides **15-18**.

Compound	Maximal Metal Ion Loading, %	Selectivity and Selectivity Ratio[a]						
15	99	K^+ >	Na^+ >	Rb^+ >	Li^+,Cs^+		
			4.8	11.3	>100		
16	99	K^+ >	Na^+ >	Rb^+ >	Li^+,Cs^+		
			4.9	9.1	>100		
17	99	K^+ >	Na^+ >	Rb^+ >	Li^+ >	Cs^+	
			5.1	8.8	87	99	
18	95	K^+ >	Na^+ >	Rb^+ >	Cs^+ >	Li^+	
			6.4	7.1	76	>100	

[a]Selectivity ratio = $[K^+]$ in the strippant/$[M^+]$ in the strippant.

The selectivity order for all four extractants is $K^+ > Na^+ > Rb^+ >> Cs^+ \approx Li^+$. Thus, this family of proton-ionizable lariat ethers exhibits modest selectivity for K^+ (the alkali metal cation which should best fit the dibenzo-19-crown-6 cavity) over Na^+ and Rb^+ and high selectivity for K^+ over Cs^+ and Li^+.

The 'selectivity ratio' is defined as the concentration in the strippant of the best extracted cation divided by that of another alkali metal cation. As can be seen from the data in Table 1, the selectivity ratios for K^+/Na^+ increase in the order: **15 < 16 < 17 < 18**; whereas the selectivity ratios for K^+/Rb^+ decrease in the order: **15 > 16 > 17 > 18**. The opposite influences of X group variation upon the magnitude of the selectivity ratios for K^+/Na^+ and K^+/Rb^+ selectivities may be rationalized as arising from the formation of nesting (ref. 10) complexes by Na^+ and K^+, but perching (ref. 10) complexes with Rb^+. Thus for K^+ and Na^+ the competition is between formation of two nesting complexes; whereas for K^+ and Rb^+ the competition involves formation of a nesting complex for the former and a perching complex for the latter. Thus for the K^+/Rb^+ selectivity a decrease in the acidity of the pendant proton-ionizable group diminishes the relative proportion of extracted K^+. This arises from enhanced side arm participation in the complexation of Rb^+ as the ionized side arm becomes more basic.

To evaluate the effect of contracting the basic ring system from dibenzo-16-crown-5 to dibenzo-14-crown-4, the new proton-ionizable lariat ether series **19-22** was synthesized by a route analogous to that shown in Fig. 5. Results from the competitive solvent extraction of alkali metal cations from aqueous solutions into chloroform by ligands **19-22** are given in Table 2.

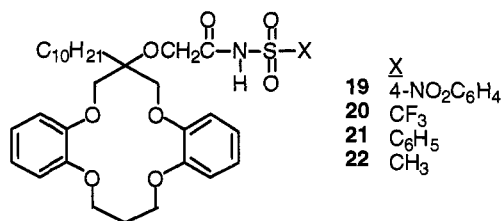|	X
19	4-NO$_2$C$_6$H$_4$
20	CF$_3$
21	C$_6$H$_5$
22	CH$_3$

Table 2. Efficiency and Selectivity for Competitive Solvent Extractions of Aqueous Solutions Containing Alkali Metal Cations (20 mM in Each) with 5.0 mM Chloroform Solutions of N-(X)sulfonyl *sym*-(Decyl)dibenzo-14-crown-4-oxyacetamides **19-22.**

Compound	Maximal Metal Ion Loading, %	Selectivity and Selectivity Ratio[a]			
19	90	Li$^+$ >	Na$^+$ >	K$^+$ >	Rb$^+$,Cs$^+$
			2.6	37	ND[b]
20	94	Na$^+$ >	Li$^+$ >	K$^+$ >	Rb$^+$,Cs$^+$
			1.7	7.8	ND
21	98	Na$^+$ >	Li$^+$ >	K$^+$ >	Rb$^+$,Cs$^+$
			2.2	7.8	ND
22	90	Na$^+$ >	Li$^+$ >	K$^+$ >	Rb$^+$,Cs$^+$
			22	27	ND

[a]Selectivity ratio = [best extracted cation] in the strippant/[M$^+$] in the strippant. [b]Not determined, since neither Rb$^+$ nor Cs$^+$ were detectable in the strippant.

For none of the ligands **19-22** was extraction of Rb$^+$ or Cs$^+$ detectable. Ligand **22** exhibits a selectivity order of Na$^+$ >> Li$^+$ > K$^+$. Although compounds **20** and **21** also favor extraction of Na$^+$, their Na$^+$/Li$^+$ selectivities are much lower than that for **22**. For **19**, the most acidic of the proton-ionizable lariat ether ligands in this series, the extraction selectivity order changes to Li$^+$ > Na$^+$ > K$^+$.

The Na$^+$/Li$^+$ selectivity decreases in the order: **22** (22) > **21** (2.2) > **20** (1.7) > **19** (0.39). Thus, variation of the X group in the N(X)sulfonyl *sym*-(decyl)dibenzo-14-crown-4-oxyacetamide ligand series can cause a change in the selectivity order, as well as the selectivities between the competing alkali metal cations.

Of the alkali metal cations, only Li$^+$ is expected to form a nesting complex with perching complexes for the other alkali metal cations. Thus, formation of a perching complex with Na$^+$ is preferred for all of the ligands, except **19** which has the most acidic proton-ionizable group. When ionized, the functional side arm of **19** is the least basic of the series. This decreases the importance of metal ion-side arm interactions in the complex, which enhances the relative importance of the metal ion-crown ether interactions and allows the innate Li$^+$ selectivity of the dibenzo-14-crown-4 ring to be expressed.

Summary and Future Directions

The N-(X)sulfonyl carbamoyl function, a new type of proton-ionizable group, has been incorporated into lariat ethers. For competitive solvent extraction of alkali metal cations, it is shown that variation of the X group changes the acidity of the side arm without concomitant steric effects. Thus, variation of the X group may be used to 'tune' the acidity of the side arm in proton-ionizable lariat ethers. This will provide new insight into the roles of the crown ether unit and the acidic function of the side arm in metal ion complexation by proton-ionizable lariat ethers.

In expansion of this work, we are utilizing calix[4]arene as a platform for the attachment of one-four N-(X)sulfonyl carbamoyl functions. Extractants with high selectivities for Pb(II) (ref. 11) and for Hg(II) (ref. 12) have been obtained when two of 'tunable' proton-ionizable groups are attached.

Acknowledgment

Zeneca Pharmaceuticals for the suggestion that N-alkyl- and N-arylsulfonyl carbamoyl groups could be incorporated into proton-ionizable lariat ethers.

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