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Kristin A. Arnold[a]; Jeanette C. Hernandez[a]; Chensheng Li[a]; Jesus V. Mallen[a]; Akio Nakano[ab]; Otto F. Schall[ac]; John E. Trafton[a]; Mara Tsesarskaja[a]; Banita D. White[a]; George W. Gokel[c]
[a] Department of Chemistry, University of Miami, Coral Gables, FL [b] Faculty of Engineering, Toa University, Shimonoseki, Yamaguchi, Japan [c] Department of Molecular Biology & Pharmacology, Washington University School of Medicine, MO, U.S.A.

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Analysis of sodium, potassium, calcium, and ammonium cation binding and selectivity in one- and two-armed nitrogen-pivot lariat ethers†

KRISTIN A. ARNOLD[a], JEANETTE C. HERNANDEZ[a], CHENSHENG LI[a], JESUS V. MALLEN[a], AKIO NAKANO[a,b], OTTO F. SCHALL[a,c], JOHN E. TRAFTON[a], MARA TSESARSKAJA[a], BANITA D. WHITE[a] and GEORGE W. GOKEL[c,*]

[a]*Department of Chemistry, University of Miami, Coral Gables, FL 33124,* [b]*Faculty of Engineering, Toa University, Ichinomiya-Yakuencho 2-1; Shimonoseki; Yamaguchi 751; Japan and Bioorganic Chemistry Program and* [c]*Department of Molecular Biology & Pharmacology, Washington University School of Medicine, 660 S. Euclid Ave., Campus Box 8020, St. Louis, MO 63110 U.S.A.*

†*Dedicated to Professor Donald J. Cram on the occasion of his 75th birthday.*

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Complexation of sodium, potassium, calcium, and ammonium cations by one- and two-armed (bibracchial) lariat ethers is surveyed and analyzed. A comprehensive list of binding data determined at 25.0±0.1 °C in anhydrous methanol is presented. More than 100 new, experimentally determined (K_s) and calculated (selectivity) values especially for calcium and ammonium are presented. Both cation binding strength and selectivity are evaluated in terms of ring size, sidearm length, number and type of donor groups and other factors. Hitherto unreported divalent calcium cation binding selectivities for bibracchial lariat ethers in aqueous solution rival the cation selectivities of some cryptands. N,N'-bis(Ethoxycarbonylmethyl)-4,13-diaza-18-crown-6 exhibits a Ca^{2+}/K^+ selectivity equal to that of [2.2.1]-cryptand and a Ca^{2+}/Na^+ selectivity better than that of any cryptand. Two bibracchial systems having $>NCH_2CONHCHRCOOCH_2CH_3$ sidearms (R=H, *s*-butyl), have shown Ca^{2+} over Na^+ selectivity in water of $\geq 10^3$. Cation binding constants determined by extraction and ISE methods are also compared with transport rates determined in bulk organic membranes and by dynamic ^{23}Na-NMR methods.

INTRODUCTION

An important goal of our lariat ether program has been to understand the factors that affect binding strengths and selectivities. Although the K^+-selective ionophore valinomycin[1] gave considerable impetus to our program, we have long been interested in the problem of Ca^{2+}-selectivity. We have reported, in a number of previous papers, the syntheses, cation binding properties, solid-state structural properties, and some thermodynamic data for the class of compounds we have called "lariat ethers."[2] In this paper, we add Ca^{2+} and NH_4^+ binding constants for a large number of these previously known structures and data for several previously unreported structures. We analyze the binding and selectivity for the broad family of one- and two-armed (bibracchial) lariat ethers. We attempt to bring forth some general rules concerning binding strengths, binding selectivities, and to offer some observations on ring sizes, donor groups, and complexation geometries. We discuss the relationship between cation binding strengths as assessed by extraction procedures and ISE methods and their relationship to transport in bulk organic membranes and bilayers. Finally, we demonstrate extremely high Ca^{2+} cation binding strengths and selectivities in aqueous solution for certain dipeptide-substituted BiBLEs.

RESULTS AND DISCUSSION

Equilibrium and kinetic components of the binding constant. The complexation phenomenon, when determined for a homogeneous system, is represented by the equation

$$\text{cation} + \text{ligand} \rightleftarrows \text{complex}$$

*To whom correspondence should be addressed.

The position of the equilibrium (K_{eq}) is expressed for the solvent and temperature used and is usually called K_s (for stability constant). The magnitude of the equilibrium constant is substantially affected by solvent. For example, when the ligand is 18-crown-6 and the cation is Na^+, K_s is about 6 in water[3] and about 23,000 in absolute methanol.[4] Note that these equilibrium constants are usually expressed as their decadic logarithms (0.8 and 4.36, respectively) because the range known for cation binding constants is so large. In this paper, binding is expressed throughout as $\log_{10} K_s$. The trend observed here is general and well-known:[5] the less polar the solvent, the greater the magnitude of K_s. The same trend holds for the cryptands. Thus, for example, [2.2.1]-cryptand binds Na^+ with log K_s = 5.4 in water[6] and *ca.* 9.3 in methanol.[7] 18-Crown-6 binds Ca^{2+} with log K_s = 1.8 in water and 3.90 in methanol solution.[4d]

The equilibrium constant can be expressed as the ratio of forward and reverse rate constants: $K_s = k_{complex}/k_{release}$. Binding rates ($k_{complex}$) are now well known to be rapid for flexible binders such as crown ethers and slower for less flexible (or more rigid) systems such as cryptands. In aqueous solution, K_s for the reaction of K^+ with 18-crown-6 is 115 M^{-1} (log K_s 2.06). The rates for this system are reported to be $k_{complex} = 4.3\times10^8$ $M^{-1}s^{-1}$ and $k_{release} = 3.7\times10^6 s^{-1}$. In the same solvent, the binding rates for K^+ by [2.2.2]-cryptand are reported to be $k_{complex} = 7.5\times10^6$ $M^{-1}s^{-1}$ and $k_{release}$ = 38 s^{-1}.[9] The value of K_s is thus 2.0×10^5 M^{-1} (log K_s = 5.3).[9] In absolute methanol solvent, the rates for [2.2.2]-cryptand are reported to be $k_{complex} = 4.7\times10^8$ $M^{-1}s^{-1}$ and $k_{release}$ = 0.018 s^{-1}.[10] The binding constant (log K_s) is thus 10.4[10] It is interesting to note that valinomycin, an ionophore that is flexible but adopts a three-dimensional binding conformation, is found to have the following kinetic and equilibrium constants in methanol: $k_{complex} = 4.0\times10^7$ $M^{-1}s^{-1}$; $k_{release} = 1.3\times10^3$ s^{-1}; $K_s = 3.1\times10^4$ M^{-1}; log K_s = 4.49.[11]

When cation binding is assessed by extraction techniques,[12] the situation is more complicated. In such cases, not only are the rates and equilibrium noted above involved, there are phase transfer processes that must be considered as well. Although extraction techniques have been used extensively from the earliest report of Pedersen,[13] comparisons among different solvent and salt systems are problematic. It is in part because of this latter difficulty that all of the data reported here are for homogeneous complexation reactions, most in absolute methanol at 25.0±0.1 °C.

Cation binding measurements. The equilibrium complexation constants for macrocycles may be obtained using a variety of techniques including calorimetry,[14] spectroscopic methods,[15] and ion selective electrode (ISE) techniques. The ISE approach was described in 1971 by Frensdorff[16] and has proved extremely useful. We have modified the latter technique and used our own variation (see Experimental Section) to obtain the data reported here.[17] Calcium cation binding measurements were made either by the competitive method previously described (for methanol solution) or by using an ion-selective electrode designed for determination of divalent calcium (in water).[18]

Syntheses of nitrogen-pivot lariat ethers. The compounds reported here fall into two distinct groups. The single-armed compounds were prepared by *N*-alkylation of the pre-formed macroring or alkylation of an appropriate fragment (*e.g.*, diethanolamine) followed by cyclization.[19] The two-armed (bibracchial) lariat ethers (BiBLEs) were prepared either by our single-step method[20] or the more conventional two-step approach.[21] In either case, the compounds discussed here have been reported previously or their syntheses and full characterizations may be found in the Experimental Section.

The approaches are shown in Figure 1.

Cation binding by cryptands. Almost no class of synthetic molecules has proved to be of such great interest as the cryptands.[22] Alkali and alkaline earth cation binding by these structures is strong and a "hole" or "cavity-size" relationship is appropriate to account for the cation selectivity. Among the cryptands, only [2.1.1] exhibits substantial Ca^{2+}-selectivity and this is for Ca^{2+}/K^+ = 1350. This selectivity is achieved at the expense of overall binding strength (see Table 1). The best selectivity of Ca^{2+} over Na^+, a more difficult test because both cations are approximately 2Å in diameter, is exhibited by [2.2.1] and is only 3.3. Indeed, the [2.1.1] selectivity ratio for Ca^{2+}/Na^+ is 0.11. The specification of cation selectivities is a somewhat arbitrary affair: the selectivities of the cation relative to each other must be specified. Note also that the values reported as part of the present work are

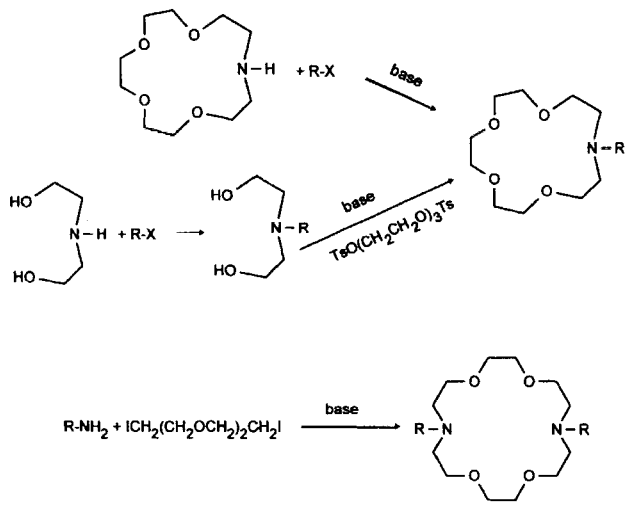


Figure 1 Preparation of one-and two-armed lariat ethers.

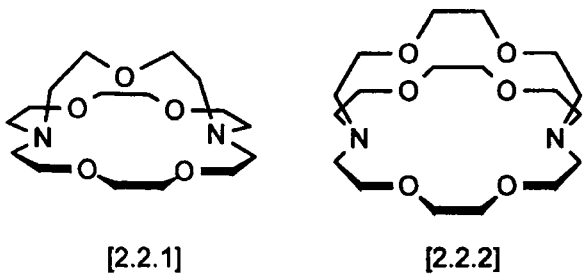


Figure 2 Structures of [2.2.1]-and [2.2.2]-crytands.

for the ratios of binding constants in which each value was determined in the absence of the other (non-competing conditions). The cryptand binding affinities reported in the literature and our calculated cation selectivities are tabulated below.

In the discussion that follows, the questions of binding strength and selectivity are addressed together as these cannot be considered separately.

Cation binding by single-armed, nitrogen-pivot lariat ethers. The family of single-armed, nitrogen-pivot lariat ethers is shown below in Table 2. The previously unreported Ca^{2+} and many NH_4^+ (along with Na^+ and K^+) binding constant values are included. Although some of the Na^+ complexation constants have appeared in various references before, they are included here to aid the overall comparison and to reinforce conclusions.

Aza-12-crown-4 lariat ethers. 12-Crown-4 derivatives lacking sidearms normally form sandwich complexes[24] with such metals as Na^+ and K^+ (see Figure 3). The simplest example noted in this study is aza-12-crown-4 which has no sidearm. Evidence for 2:1 ligand to metal complexation was obtained for aza-12-crown-4 both in solution[24,25] and in the solid state.[26] The sodium binding constants obtained from solution binding studies are log $K_{s1:1}$=1.3±0.1 and log $K_{s2:1}$=2.0±0.1. Examples of other 2:1 complexes of 12-membered rings are 12-crown-4 with Na^+,[26] and Ag^+,[27] and *N*-methylaza-12-crown-4 with Na^+.[24] Further, solid state structural data showed that aza-12-crown-4, forms a sandwich complex with the sodium cation.[25]

Sandwich complex formation[24] permits the cation to be enveloped in a three-dimensional array of donors and also permits the actual number of donor groups to be increased. It is the number of donors rather than their arrangement that is most critical for alkali metal complexation. As additional donor groups are added to the complexing array in the form of a sidearm [*e.g.*<12N>$(CH_2CH_2O)_4CH_3$ ("<YOOY>" indicates ring size ("00") and the presence of non-oxygen atoms ("Y") in the macroring], which has 7 oxygen atoms and one nitrogen, log K_s=3.76] binding strength for Na^+ exceeds that of 15-crown-5 (3.24) and approaches that of 18-crown-6 (4.35).

Flexibility in the molecular ensemble and donor group position are crucial to cation binding strength. For virtually all of the systems described here, the molecular framework is flexible. In a few cases, secondary (non-ring) donor groups are positioned on fairly rigid sidearms. The similarity in Na^+-binding constants observed for compounds <12N>$(CH_2CH_2O)_nR$ (R = CH_3 or allyl) confirms their flexibility and also suggests that only the first three or four sidearm donors in the polyethyleneoxy chain affects cation complexation. The presence of a donor group in the sidearm is a necessary but not a sufficient condition for binding enhancement. *N*-(2-Methoxyphenyl)aza-12-crown-4 binds Na^+ about 25-fold more strongly than does *N*-(4-methoxyphenyl)aza-12-crown-4. In the former, the methoxy group may serve as an additional donor site for the ring-bound cation but the *para*-isomer is sterically prohibited from engaging in such an interaction (Figure 4).

In collaboration with Gandour and Fronczek, we have also been fortunate enough to confirm the sidearm interaction by obtaining the sodium complex of <12N>$CH_2CH_2OCH_3$[28] and the potassium complex of <12N>$(CH_2CH_2O)_3CH_3$.[29] In the latter case, the sidearm so enveloped the cation that no counterion or water molecule was observed in the metal ion's solvation sphere.

It is interesting to consider the Na^+ and K^+ selectivities for aza-12-crown-4 lariat ethers. The small size of the macrocyclic ring might suggest that complexation of smaller cations would be favored. Only when the sidearm on aza-12-crown-4 contains a single oxygen (<12>$CH_2CH_2OCH_3$) is Na^+ favored over K^+ (K^+/Na^+ = 0.3). When the sidearm is extended to $(CH_2CH_2OCH_3)_n$ in which n = 3,5, or 8, the calculated potassium/sodium selectivity ratios are 1,62, 4.07, and 2.69 respectively. As observed for the simple crowns, the

Table 1 Cryptand cation binding affinities and selectivities[a]

Crown or	*Cation Binding Constants*				*Selectivities*			
Cryptand	Na^+	K^+	NH_4^+	Ca^{2+}	*K/Na*	*K/Ca*	*Ca/Na*	*Ca/K*
18-crown-6	4.35	6.08	4.2	3.9	54	151	0.35	<0.01
2.1.1	6.4[b]	2.3	ND[c]	5.43	<0.01	<0.01	0.11	1350
2.2.1	9.4[b]	8.5	ND	9.92	0.12	0.04	3.3	26
2.2.2	8.0	10.6	ND	8.14	398	288	1.3	<0.01
3.2.2	4.8	>7	ND	4.7[d]	158	200	0.8	<0.01

[a] Values expressed as $\log_{10}K_s$ for anhydrous methanol at 25 °C, sometimes with supporting electrolyte added; data from the collection by Izatt *et al.*, reference 23.
[b] Average of two reported values.
[c] *ND means not determined* and not reported in the literature.
[d] Value for 95% methanol. This value should be similar to, but lower than, those observed in anhydrous methanol.

Table 2 Summary of cation binding by single-armed nitrogen-pivot lariat ethers[a]

Cpd	*Cation Binding, log K_s*				*Selectivity*	
No. Sidearm[b]	Na^+	K^+	NH_4^+	Ca^{2+}	*Ca/Na*	*Ca/K*
Derivatives of aza-12-crown-4 lariat ethers						
1 H	—[c]	ND[d]	ND	ND	NA[e]	NA
2 $CH_2CH_2CH_2OH$	2.35	ND	ND	ND	NA	NA
3 $CH_2CH_2OCH_3$[f]	3.25	2.73	3.06	ND	NA	NA
4 $(CH_2CH_2O)_2CH_3$	3.60	ND	ND	ND	NA	NA
5 $(CH_2CH_2O)_3CH_3$	3.64	3.85	3.29	ND	NA	NA
6 $(CH_2CH_2O)_4CH_3$	3.76	ND	ND	ND	NA	NA
7 $(CH_2CH_2O)_5CH_3$	3.73	4.34	3.49	ND	NA	NA
8 $(CH_2CH_2O)_4$allyl	3.97	ND	ND	ND	NA	NA
9 $(CH_2CH_2O)_8CH_3$	3.84	4.27	3.45	ND	NA	NA
10 $CH_2CON(C_5H_{11})_2$	3.32	2.58	ND	ND	NA	NA
11 $CH_2CON(C_{18}H_{37})_2$	3.42	2.64	ND	ND	NA	NA
12 benzyl	2.08	ND	ND	ND	NA	NA
13 2-methoxyphenyl	2.75	ND	ND	ND	NA	NA
14 4-methoxyphenyl	1.38	ND	ND	ND	NA	NA
15 2-methoxybenzyl	2.49	ND	ND	ND	NA	NA
16 2-nitrobenzyl	1.77	ND	ND	ND	NA	NA
Derivatives of aza-15-crown-5 lariat ethers						
17 H	1.70	1.60	2.99	ND	NA	NA
18 CH_3	3.39	3.07	3.22	3.50	1.3	2.7
19 CH_2COOH	2.31	2.02	ND	ND	NA	NA
20 allyl	3.14	2.97	ND	2.73	0.4	0.6
21 $CH_2CH_2OCH_3$	3.88	3.95	3.14	3.75	0.7	0.63
22 $CH_2CH_2SCH_3$	3.18	3.04	ND	ND	NA	NA
23 $CH_2CH_2SOCH_3$	3.06	2.75	ND	ND	NA	NA
24 *n*-butyl	3.02	2.90	ND	2.86	0.7	0.9
25 *t*-butyl	2.15	2.41	ND	ND	NA	NA
26 $(CH_2CH_2O)^2CH_3$	4.54	4.68	3.19	4.06	0.3	0.2
27 CH_2COOEt	4.10	4.03	2.48	4.36	1.8	2.1
28 CH_2COO-*t*-butyl	4.20	4.06	2.51	4.60	2.5	3.5
29 $(CH_2CH_2O)_3CH_3$	4.32	4.91	3.38	3.84	0.3	0.08
30 $CH_2CONHC_5H_{11}$	3.09	3.20	ND	ND	NA	NA
31 $CH_2CON(C_5H_{11})_2$	4.20	3.84	ND	ND	NA	NA
32 $CH_2COOC_6H_{13}$	4.10	3.97	ND	4.36	1.8	2.45
33 $CH_2COOC_{10}H_{21}$	3.95	3.95	ND	ND	NA	NA
34 $CH_2CONHC_{10}H_{21}$	3.04	2.61	ND	ND	NA	NA
35 $CH_2CON(C_{10}H_{21})_2$	4.35	3.77	ND	ND	NA	NA
36 $CH_2COOC_{12}H_{25}$	4.07	3.95	ND	4.34	1.9	2.4
37 $CH_2COOC_{16}H_{33}$	4.11	3.99	ND	4.41	2.0	2.6
38 $CH_2CON(C_{18}H_{37})_2$	4.10	3.51	ND	ND	NA	NA
39 $(CH_2CH_2O)_4CH_3$	4.15	5.28	3.48	3.78	0.4	0.03
40 $(CH_2CH_2O)_5CH_3$	4.19	4.91	3.49	3.80	0.4	0.08
41 $(CH_2CH_2O)_8CH_3$	4.18g	4.15	ND	ND	NA	NA
42 2-methoxyphenyl	3.86	3.46	ND	2.46	0.04	0.1
43 4-methoxyphenyl	2.12	2.13	ND	ND	NA	NA
44 CH_2CH_2SPh	3.08	2.93	ND	ND	NA	NA
45 benzyl	2.77	2.61	ND	2.45	0.5	0.7
46 2-methoxybenzyl	3.54	3.21	ND	2.93	0.2	0.52
47 2-nitrobenzyl	2.40	ND	ND	ND	NA	NA
48 4-nitrobenzyl	2.30	ND	ND	ND	NA	NA
49 COOcholesteryl	<1.5	<1.5	ND	ND	NA	NA
50 CH_2COOcholesteryl	4.10	4.03	ND	ND	NA	NA
51 CH_2COOcholestanyl	4.12	4.03	ND	ND	NA	NA
52 CH_2CH_2OPh	3.57	ND	ND	ND	NA	NA
53 $CH_2CH_2OCH_2Ph$	3.83	ND	ND	ND	NA	NA
Derivatives of aza-18-crown-6 lariat ethers						
54 H	2.69	3.98	ND	3.96	18.6	1
55 CH_3	3.93	5.33	4.08	ND	NA	NA
56 *n*-propyl	3.50	4.92	ND	3.49	1	0.04
57 allyl	3.58	5.02	ND	3.65	1.2	0.04
58 $CH_2CH_2OCH_3$	4.58	5.67	4.21	4.34	0.6	0.05
59 CH_2COOEt	4.67	5.92	ND	ND	NA	NA
60 $CH_2COOC_{10}H_{21}$	4.48	5.74	ND	ND	NA	NA
61 $CH_2COOC_{18}H_{37}$	4.61	5.82	ND	ND	NA	NA
62 $CH_2CON(C_5H_{11})_2$	4.61	5.47	ND	ND	NA	NA
63 $CH_2NHC_{10}H_{21}$	3.63	4.70	ND	ND	NA	NA
64 $CH_2CON(C_{10}H_{21})_2$	4.71	5.58	ND	ND	NA	NA
65 $CH_2COOC_{18}H_{37}$	4.61	5.82	ND	ND	NA	NA
66 $CH_2CONHC_{18}H_{37}$	3.64	4.77	ND	ND	NA	NA
67 $CH_2CON(C_{18}H_{37})_2$	4.58	5.12	ND	ND	NA	NA
68 $(CH_2CH_2O)2CH_3$	4.33	6.07	4.75	4.23	0.8	0.01
69 $CH_2CONHCH_2COOCH_3$	3.50	4.53	ND	ND	NA	NA
70 $CH_2CONHCH(i\text{-}Pr)COOCH_3$	4.04	5.03	ND	ND	NA	NA
71 $CH_2CONHCH(s\text{-}Bu)COOCH_3$	4.03	5.10	ND	ND	NA	NA
72 $(CH_2CH_2O)_3CH_3$	4.28	5.81	4.56	4.11	0.7	0.02
73 $(CH_2CH_2O)_4CH_3$	4.27	5.86	4.40	4.13	0.7	0.02
74 $(CH_2CH_2O)_5CH_3$	4.22	ND	4.04	4.11	0.8	NA
75 $(CH_2CH_2O)_8CH_3$	4.80g	6.03	ND	ND	NA	NA
76 2-methoxyphenyl	4.57	6.12	ND	ND	NA	NA
77 benzyl	3.41	4.88	ND	3.10	0.5	0.02

[a] Values determined at 25.0±0.1 °C in anhydrous methanol.
[b] Sidearm attached to nitrogen in the indicated macroring.
[c] Forms 2:1 complex with Na^+ log $K_{s1:1}$ = 1.3 log $K_{s2:1}$ = 2.0
[d] ND means not determined.
[e] NA means not available.
[f] E = CH_2CH_2.
[g] The long chain -$(CH_2CH_2O)_nCH_3$ lariat ether derivatives have proved somewhat unstable (see text).

lariat ethers can thus compete more effectively with the medium for solvation of K^+ than for the solvation of Na^+. Indeed, the hydration numbers reported[30] for these ions: Na^+ 4–5; K^+, 3–4; and Ca^{2+}, 6; reflect this.

A limited number of ammonium (NH_4^+) binding constants for aza-12-crown-4 lariat ethers are shown in Table 2. They are as follows for the indicated sidearms: $CH_2CH_2OCH_3$, 3.06; $(CH_2CH_2O)_3CH_3$, 3.29;

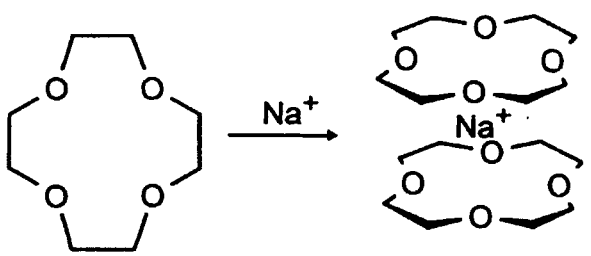
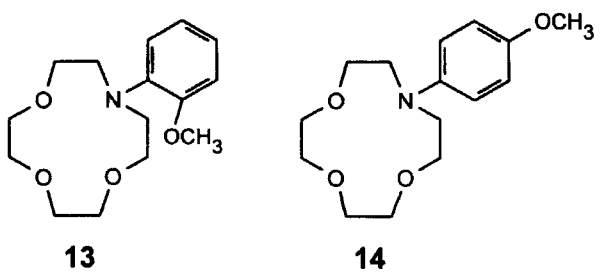


Figure 3 "Sandwich" Complex between.



13 **14**

Figure 4 *ortho* and *para*-methoxyphenylaza-12-crown-4 compounds.

$(CH_2CH_2O)_8CH_3$, 3.45. Ammonium ion differs from Na^+ or K^+ in that the latter are spherical but non-directional. Ammonium ion is similar in size to potassium but complexes using tetrahedrally directed N—H bonds. We,[31] and others,[32] have previously demonstrated that stringent steric requirements control ammonium ion binding and 12- or 15-membered rings are simply too small to accommodate the tripod of N—H bonds. We observe that, empirically, each ammonium ion hydrogen bond to a lariat ether is worth about 1.2 (log K_s) units ($K_s \approx 15$, in MeOH at 25.0±0.1 °C). The expectation that either two or three hydrogen bonds could form in the 12-membered ring cases is borne out by the 3.06–3.49 range for log K_s. The larger number of bonds is apparently formed when more donors are present. Regrettably, too few Ca^{2+} binding data are available for this system to comment on calcium selectivity.

Aza-15-crown-5 lariat ethers. Cation binding affinities for Na^+, K^+, NH_4^+, and Ca^{2+} with aza-15-crown-5 lariat ethers having (ethyleneoxy)n monomethyl ether sidearms are shown in Figure 5. Small, but significant, peaks are observed for identically-sized Na^+ and Ca^{2+} cations when two ethyleneoxy units augment the macroring $<15N>(CH_2CH_2O)_2CH_3$. The latter compound possesses six oxygen atoms and a single nitrogen. Note that cation binding strength is greatest for K^+ among all of the compounds studied although only marginally so in some cases. The larger K^+ required 8 oxygen donors for optimal binding in this system. Note that ammonium ion, which complexes by directional hydrogen bond formation shows only weak binding which increases with increasing sidearm length.

When 8 oxygen atoms are present as in $<15N>(CH_2CH_2O)_4CH_3$, the compound can offer the octacoordination K^+ favors[33] the highest K^+/Na^+ (13:1) and K^+/Ca^{2+} (32:1) selectivities in this series are observed. The difference in selectivity ratios between sodium and calcium reflects the latter cation's greater solvation enthalpy.[34] This makes it more difficult for the crown to capture it from the bulk medium. The NH_4^+ binding values are nearly identical to those obtained for the 12-membered ring analogs suggesting that only three hydrogen bonds form in the complex.

Lipophilicity effects on aza-15-crown-5 and aza-18-crown-6 lariats. The Na^+, K^+, and Ca^{2+} binding of six aza-15-crown-5 ethers are compared in Figure 6. They are $<15N>H$, $<15N>CH_3$, $<15N>CH_2CH{=}CH_2$, $<15N>CH_2CH_2CH_2CH_3$, $<15N>C(CH_3)_3$, and $<15N>CH_2C_6H_5$. Very little cation selectivity is observed for any of these compounds. Binding is noticably diminished for $<15N>H$ and slightly reduced for $<15N>C(CH_3)_3$. The former is likely a hydrogen-bonding effect and the latter is due to the bulk of the *t*-butyl group. An examination of CPK molecular models suggests that in the latter case there is steric interference between the sidearm's methyl groups and the ring α-methylenes.

Although a different selection of compounds was surveyed in the aza-18-crown-6 lariat series (see Table 2), the findings were generally similar. The only notable difference is that when six donors are present in the macrocycle (five O and one N), potassium binding is favored over either sodium or calcium complexation. Very little difference in binding strength is observed for Na^+ and Ca^{2+} for the 18-membered ring systems where direct comparisons can be made.

An interesting correlation can be drawn for the aza-crown glycine derivatives (see Figure 7). These compounds were prepared to assess the effects of both hydrophobic groups and a polar donor (amide or ester carbonyl) on cation transport in a bulk liquid membrane[35] and in lipid bilayers.[37,38] The compounds studied fall into three groups: esters, secondary amides, and tertiary amides. In general, amide oxygen is expected to be a stronger donor group than ester oxygen because of the former's more extensive resonance. Superimposed upon

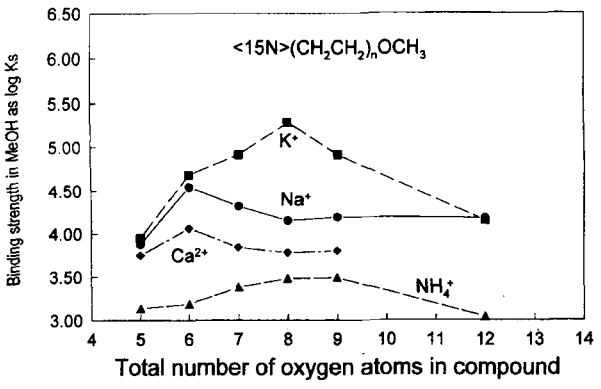


Figure 5 Na^+, K^+, Ca^{2+}, and NH_4^+ cation binding by aza-15-crown-5 derivatives having $(CH_2CH_2O)_nCH_3$ sidearms.

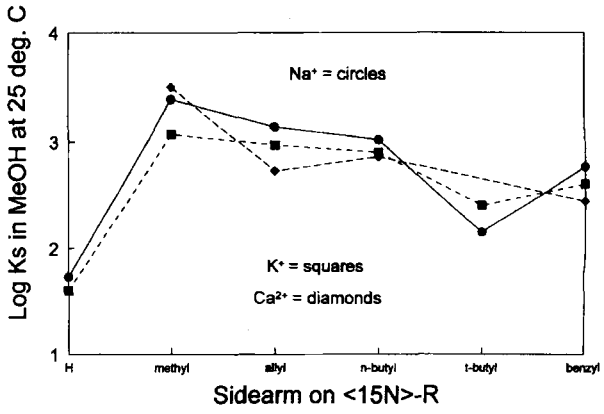


Figure 6 Na^+, K^+, and Ca^{2+} cation binding by aza-15-crown-5 derivatives having hydrocarbon sidearms.

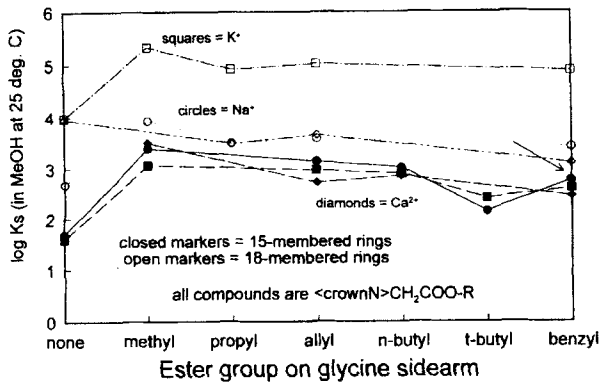


Figure 7 Na^+, K^+, and Ca^{2+} cation binding by aza-15-crown-5 and aza-18-crown-6 derivatives having alkyl groups that form esters on CH_2COOR sidearms. Open markers indicate 18-membered rings and closed markers signify 15-membered rings.

this expectation is what effect can be anticipated from the presence of a hydrogen bond donor in the secondary amide system. Clearly, it could form a hydrogen bond bridge to the macroring which would severely restrict the sidearm's motion. We have recently reported evidence that such an interaction does, in fact, occur.[38]

The Na^+, K^+, and Ca^{2+} binding profiles for the ester series, *i.e.* $<15N>CH_2COOR$ is shown in Figure 7. The effect of the alkyl ester chain is marginal from R = C_1 through C_{16} on the binding of all three cations. Indeed, the binding constants determined for Na^+ and K^+ are nearly superimposable. The higher binding noted for more charge dense divalent calcium is due to the greater polarity of ester carbonyl compared to ether as a donor group. The presence of this additional donor group increases the cation binding constants for Na^+ and K^+ by about a power of ten. This is a greater binding increment than would be expected for addition of an ether residue.

Consider the following group of relatives: $<15N>CH_2CH_2CH_2CH_3$, $<15N>CH_2CH_2OCH_3$, and $<15N>CH_2COOCH_2CH_3$. Their Na^+ binding constants are, respectively: 3.02, 3.88, and 4.10. A comparable but even more dramatic increase is observed for Ca^{2+}, which is the same size as Na^+ but more charge dense and therefore more demanding of a donor group array. The Ca^{2+} complexation constants for these three compounds are, respectively: 2.86, 3.75, and 4.36. The difference in binding due to the presence of an oxygen donor is about a power of ten. The carbonyl makes overall binding of Na^+ less than twice that observed for the ether but in the Ca^{2+} case, the increase in binding is more than four-fold. This effect is noted further below for the dipeptide lariats.

Considering the absence of any significant lipophilicity effect, it is especially interesting to note that cation transport either in a bulk organic membrane or in a vesicular bilayer, is significantly affected. Sodium transport mediated by this series of compounds has been studied in a concentric tube apparatus using $CHCl_3$ as the model membrane. In addition, it was assessed by dynamic ^{23}Na-NMR in large unilamellar vesicles assembled from a mixture of phosphatidyl choline (PC) and phosphatidyl glycerol (PG). The data obtained from these experiments are plotted in Figure 8 against the individually determined[35] cation binding constants (see Table 2). The transport rates determined by each method are recorded in the references indicated and their absolute values have been scaled so they can be compared on the same graph. There is clearly scatter in the data: the R values for the lines are 0.88 ($CHCl_3$ membrane) and 0.82 (bilayer). Even so, the calculated best fit of the data gives two parallel lines suggesting that the two types of data correlate reasonably well. To our knowledge, this is the first time it has been possible to directly compare data obtained by these two different techniques for a series of carriers having systematically varied functional groups and lipophilicities. Our previous finding[35] that transport rates in a bulk organic membranes are predicted equally well by extraction constants and equilibrium binding constants suggests the overall validity of the approaches traditionally used in the macrocycle area.

Lariat ethers having sulfur donors in the sidearm. Much is known about sulfur-containing macrocycles[14,23] especially as transition metal complexing agents but no compound having a sulfur-donor-containing sidearm had appeared prior to our recent report.[38] The compounds of interest (data in Table 2) are shown in Figure 9 along with Na^+ binding constants (additional data are in Table 2). As expected, oxygen as part of an alkyl or aryl ether results in better binding than does sulfur in either case. It is a little surprising that sulfoxide is no more effective than its non-oxidized counterpart. One may speculate about solvation effects but we have no definitive expla-

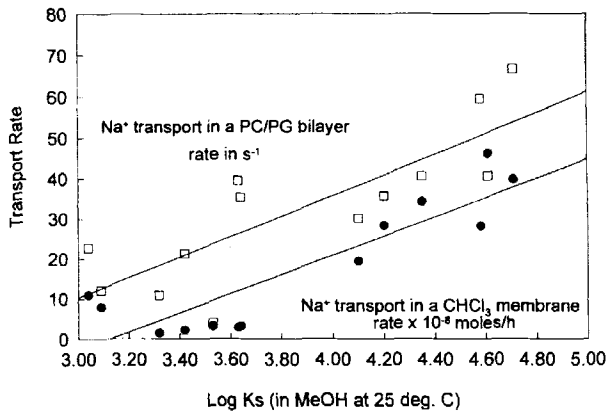


Figure 8 Comparison of sodium transport rates for $<00N>CH_2COY$ derivatives in which <00N> includes 12-, 15-, and 18-membered aza-crown rings. Transport was determined in vesicles by NMR methods or in a bulk chloroform membrane (see text).

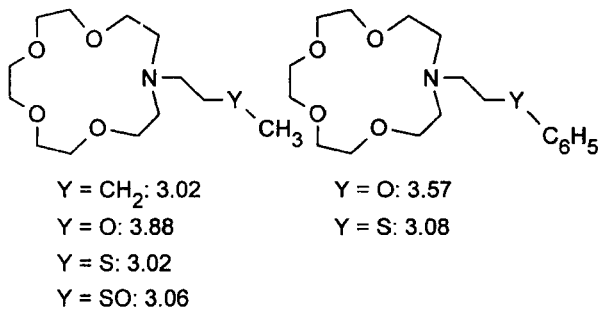


Figure 9 Structures and binding constants (log K_s) for azacrowns.

nation for sulfoxide's remarkable lack of donicity in this case.

Aza-18-crown-6 lariat ethers. Binding data for the series of compounds $<18N>(CH_2CH_2O)_nCH_3$ are shown in Figure 10. Binding constants determined for the aza-18-membered ring lariat ethers are generally stronger than for the corresponding 15-membered ring compounds (see Figure 5). In the 18-membered ring case, binding of K^+ is still favored over the other cations but less dramatically. Overall, binding of Na^+, Ca^{2+}, and NH_4^+ are similar but notably inferior at the 8-oxygen peak observed for K^+. Solvation of K^+ by the 18-membered macroring is more favorable than for other ring sizes due, in part, to the near perfect fit between the macroring and this cation. In addition, the 18-membered ring system is inherently more flexible and less strained (judged from CPK model examination) than either the 12- or 15-membered ring systems. Peak binding was observed for Na^+ and Ca^{2+} when 6 oxygen (7 total) donors were present in the donor group ensemble. Similarly-sized K^+ and NH_4^+ exhibited binding peaks at 8 total donors. An examination of CPK molecular models suggests that when a tripod of N—H bonds attaches to the macrocycle, the fourth N—H of tetrahedral NH_4^+ is bound by the second sidechain oxygen atom. As K^+ is approximately the same size as NH_4^+, optimum com-

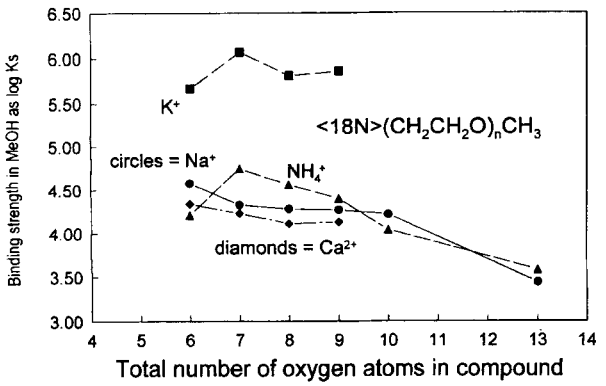


Figure 10 Na^+, K^+, Ca^{2+}, and NH_4^+ cation binding by aza-18-crown-6 derivatives having $(CH_2CH_2O)nCH_3$ sidearms.

plexation of either cation could occur with the same ligand.

Sodium binding strengths were similar in the 15- and 18-membered ring systems when an identical number of donors was present. Potassium cation binding was, however, favored for the 18-membered ring structures over those having 15-membered macrorings in all cases studied. These data show that for flexible systems, the presence of a suitable number of accessible donors is as useful as having them arrayed in a ring that corresponds in size to the cation. The equivalence of sidearm and macroring makes clear that if the molecular ensemble is flexible, there is no inherent advantage to having the donors contained in a macrocyclic ring of "appropriate" size.[18]

The longest-chain $<15N>(CH_2CH_2O)_nCH_3$ (**41**) and $<18N>(CH_2CH_2O)_nCH_3$ (**75**) derivatives pose an interesting question. Our first examination of these compounds suggested that the sidearm hindered cation binding when it became quite long.[19] Additional samples of these long-chain compounds were prepared and the attenuation in binding was no longer apparent. Indeed, our current experimental observation is that the long-chain compounds show an unexpected and unaccountable lack of stability. Thus, the binding measurements are affected by sample freshness. Moreover, the excess of cation present in the solutions under study affects the binding constant with these longest-chained compounds whereas this was not the case for the others. We have thus obtained both unusually high and unusually low values for cation binding by **41** and **75**.[28] The binding constant values reported here for these two compounds should therefore be treated with due caution.

Peptide-sidearmed lariat ethers. The Na^+ and K^+ binding constants for several 18-membered ring azalariats are shown in Table 2. Generally speaking they exhibit surprisingly poor binding for either cation. This group of structures is of interest, however, in the context of two-armed, dipeptide systems where it is discussed further (see below).

18-Membered ring lariats having sidearms lacking donor groups. Binding constants for the aza-18-crown-6 derivatives in which the sidearms contain no donor groups are recorded in Table 2. As in the 15-membered ring series, a bulky sidearm appears to inhibit binding at the apical positions and reduce K_s. In general, if donors are lacking, cation binding strength is indifferent to the length of the sidearm chain.

Generalizations concerning single-armed, nitrogen-pivot lariat ethers. The ring size of the azalariat ether is important in two senses. First, the larger the ring, the greater the number of donors available for complexation. Second, as the ring size increases from 12- to 15- to 18-

membered, strain and congestion within the macroring decrease. In the absence of a sidearm, the 12-membered ring compounds form sandwich complexes with Na^+ (see above) as 15-crown-5 does with K^+.[39] Neither of these factors has to do with "hole-size" the importance of which is inversely proportional to the ligand's rigidity. When a minimum of six oxygen atoms are present, generally strong binding is observed for all of the alkali metals, although K^+ is nearly always favored. Potassium cation selectivity may be overridden by such factors as the presence of an especially polar sidearm (ester or amide) or unusual bulk in the sidearm. Binding strength and selectivity in this series of compounds are still very difficult to predict. Divalent calcium is favored by ligands that are polar and rigid. Potassium is favored by flexible ligands and the best binding is observed when at least six oxygen donors are available to coordinate the cation. The cation need not reside within the macroring hole but will assume the complex geometry that optimizes solvation.

Diaza-bibracchial lariat ethers. The two-armed lariat ethers thus far prepared are known in 12-, 15-, 18-, and 21-membered ring sizes. Although compounds have been prepared by several groups,[40] to our knowledge, no systematic cation binding study was conducted on these structures prior to our own work (see above).

In all previous cases noted herein, consideration was given to the total number and identity (N or O, carbonyl or ether) of the donors as well as to whether they resided in the macroring, sidearm, or both. These variables must also be considered with diaza-BiBLEs but the presence of a second sidearm is also an issue. Solid state structures of diaza-BiBLEs have shown that complexation can occur which does not involve the sidearms or in which the sidearms are on the same or opposite sides of the macroring. These issues are addressed below in individual cases. Comprehensive binding data for these compounds are presented below in Table 3.

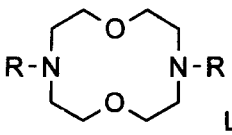
Diaza-12-crown-4 derivatives. No diaza-12-crown-4 derivatives were prepared as part of this study. Parker, Buschmann, and their coworkers[42] have prepared several such compounds and their binding properties are considered briefly here so that the following discussion is in the proper context. The compounds studied in their group are shown in Figure 11. Cation binding constants in anhydrous methanol solution show a strong Ca^{2+} selectivity and binding shows the order $Ca^{2+} > Na^+ > K^+$. The most favorable selectivity ratio they observed was for the 2-hydroxymethyl derivative in which $Ca^{2+}/K^+ = 10^{4.9}$ and $Ca^{2+}/Na^+ = 10^{3.3}$.[42b] The dimethylaminoacetamide derivative is shown to have a binding constant of ">5.5" but it is suggested in a footnote that log K_s could be as high as 8.2. In this case, $Ca^{2+}/Na^+ = 10^{3.5}$. The values reported by Parker, Buschmann, *et al.* were determined calorimetrically in methanol, a solvent in which it is difficult to determine this ion using ISE methods. In aqueous solution, they determined Na^+, K^+, and Ca^{2+} complexation constants for diaza-12-crown-4 derivatives having $CH_2CONHCH_3$ and $CH_2CONHCH_2COOEt$ sidearms. The values for the *N*-methylacetamide derivative was 2.65, 2.70, and 4.74 respectively. The compound having 2 gly-gly-OEt sidearms gave values of 2.48, 2.50, and 4.52 respectively.

Table 3 Summary of cation binding properties for nitrogen-pivot, bibracchial lariat ethers[a]

	Cation Binding, log K_s				*Selectivity*	
Sidearm[b]	*Na^+*	*K^+*	*NH_4^+*	*Ca^{2+}*	*Ca/Na*	*Ca/K*
Derivatives of 4,10-diaza-15-crown-5 lariat ethers						
78 H	<1.5	<1.5	ND	ND	NA	NA
79 $CH_2CH_2OCH_3$	5.09	4.86	ND	4.97	0.8	1.3
80 CH_2COOEt	5.34	4.65	ND	6.04	5.0	25
81 2-furanylemthyl	3.99	3.87	ND	3.45	0.3	0.4
82 benzyl	2.59	2.12	ND	2.34	0.6	0.8
83 2-methoxybenzyl	3.59	3.13	ND	3.04	0.3	0.8
Derivative of 4,10-diaza-18-crown-6-lariat ethers						
84 benzyl	2.88	ND	ND	ND	NA	NA
Derivatives of 4,13-diaza-18-crown-6 lariat ethers						
85 H	1.5	1.8	ND	ND	NA	NA
86 CH_2CH_2OH	4.87	5.08	ND	6.02	15	8.7
87 CH_2CONH_2	3.78	3.75	ND	ND	NA	NA
88 *n*-propyl	2.86	3.77	ND	ND	NA	NA
89 allyl	3.00	4.03	ND	2.84	0.6	0.06
90 propargyl	3.67	5.00	ND	3.52	0.8	0.03
91 cyanomethyl	2.69	3.91	ND	ND	NA	NA
92 $CH_2CH_2OCH_3$	4.75	5.46	ND	4.48	0.5	0.1
93 *n*-butyl	2.84	3.82	ND	2.86	1	0.1
94 CH_2COOEt	5.51	5.78	ND	6.78	19	10
95 $CH_2CON(C_5H_{11})_2$	5.69	5.49	ND	ND	NA	NA
96 $CH_2CONHCH_2COOCH_3$	3.35	3.32	ND	5.36[b]	NA	NA
97 $CH_2CONHCH(Me)COOCH_3$	4.36	4.21	ND	ND	NA	NA
98 $CH_2CONHCH(i\text{-}Pr)COOCH_3$	4.18	4.11	ND	ND	NA	NA
99 $CH_2CONHCH(i\text{-}Bu)COOCH_3$	4.26	4.17	ND	ND	NA	NA
100 $CH_2CONHCH(s\text{-}Bu)COOCH_3$	4.16	4.09	ND	5.86[b]	NA	NA
101 *n*-hexyl	2.89	3.78	ND	ND	NA	NA
102 *n*-nonyl	2.95	3.70	ND	ND	NA	NA
103 *n*-dodecyl	2.99	3.80	ND	ND	NA	NA
104 2-furanylmethyl	3.77	4.98	ND	ND	NA	NA
105 benzyl	2.68	3.38	ND	2.79	1.3	0.3
106 2-methoxybenzyl	3.65	4.94	ND	3.27	0.4	0.02
107 4-methoxybenzyl	2.79	ND	ND	ND	NA	NA
108 2-hydroxybenzyl	2.40	2.59	ND	2.95	3.5	2.3
109 4-chlorobenzyl	2.40	ND	ND	ND	NA	NA
110 4-cyanobenzyl	2.07	ND	ND	ND	NA	NA

[a] Values determined at 25.0±0.1 °C in anhydrous methanol unless otherwise noted.
[b] In water at 25.0±0.1 °C.

Comparison of diaza-15-crown-5 and 4,13-diaza-18-crown-6 derivatives. Sodium and potassium binding constants for diaza-15- and 18-membered ring crowns having the same sidearms are shown in Table 3 and compared graphically in Figure 12. Clearly, appropriate



R	Log K_S Na^+	K^+	Ca^{2+}
CH_2CONMe_2	4.72	3.85	>5,5
$CH_2CH_2CONMe_2$	3.01	3.03	4.10
CH_2CH_2OH	3.6	2.0	6.9

Figure 11 Binding constants for diaza-12-crown-4 derivatives.

placement of donors is of greater import in these cases than the total number of donors.

It is difficult to generalize about the cation binding selectivities of these compounds. The complexation constants are shown for 5 pairs of diaza-BiBLEs in Figure 12. When the sidearms are benzyl, 2-methoxybenzyl, or 2-methoxyethyl, there is little difference in the binding strengths as a function either of ring size or cation. The benzyl- and 2-methoxylbenzyl-sidearmed compounds are poorer binders overall than the pair of 2-methoxyethyl derivatives. In the benzyl case, this is likely due to the absence of a sidearm heteroatom donor (although the π-electron cloud may afford some cation solvation). In the 2-methoxybenzyl case, the methoxy group is removed from the macroring by three non-hydrogen atoms. An example of this situation is illustrated in Figure 11 and binding by the 3-atom chain is decidedly inferior to the 2-atom case.

The only group of compound pairs where trends seem clear involves the carbethoxymethyl derivatives. In all cases the larger ring affords a higher cation binding constant with a given cation. Even so, the differences are small overall and paradoxically, complexation of Ca^{2+} represents both the best and worst cases in this group.

The 2-furanylmethyl derivatives were available in both 15- and 18-membered rings but were not studied

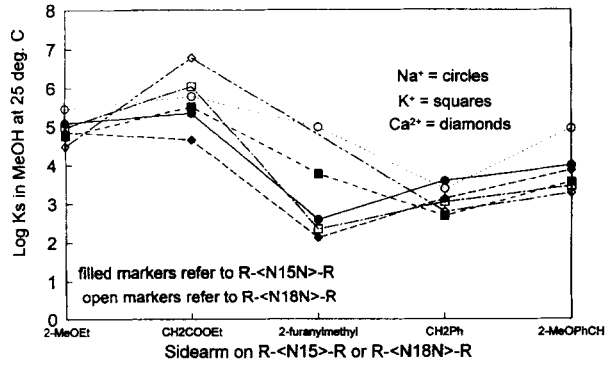


Figure 12 Na^+, K^+, and Ca^{2+} cation binding by diaza-15-crown-5 and diaza-18-crown-6 derivatives having the indicated sidearms.

with all 3 cations. Potassium cation binding by the 18-membered ring system appears to be low, perhaps because of the sidearm's rigidity. This hypothesis is supported by the fact that the 18-membered ring system seems to strongly favor smaller Na^+ which is bound best of all cations studied (binding of Ca^{2+} with <18> was not determined). Another consideration with the furanylmethyl and 2-methoxybenzyl derivatives is that the oxygen donor present in the non-basic, sp^2 hybridized form. Calcium binding strength and selectivity is quite high for both 15- and 18-membered rings having carbethoxymethyl sidearms. Indeed, the Ca^{2+}/K^+ selectivity is nearly identical to that observed for [2.2.1] cryptand, the compound having the correct hole size for Ca^{2+}. The Ca^{2+}/Na^+ selectivity is better for $EtOCOCH_2$ < N15N>CH_2COOEt than for [2.2.1] (5 vs. 3) but the selectivity of $EtOCOCH_2$ <N18N>CH_2COOEt (**94**) shows a higher Ca^{2+}/Na^+ selectivity than any cryptand. Indeed, the Ca^{2+} binding constant for **94** is higher than for [2.1.1], the cryptand showing the highest Ca^{2+}/K^+ selectivity.

Lipophilic diaza-18-crown-6 lariat ethers. The effect of lipophilicity on binding is difficult to predict due to enthalpy-entropy compensation effects.[42] An increase in binding strength with an increase in chain length would suggest a favorable entropy effect due to increasing solvent disorder. A binding decrease would indicate an unfavorable enthalpy effect. The Na^+ binding constants for R <N18N>R derivatives where R= *n*-propyl (**88**), *n*-butyl (**93**), *n*-hexyl (**101**), and *n*-nonyl (**102**) derivatives range from 2.84–2.95. The corresponding range of K^+ binding constants for these compounds is 3.70–3.82. This spread is barely outside of experimental error. It thus appears that enthalpy and entropy effects, if operating as supposed, cancel each other.

Sidearms containing π-systems. It was hoped that *N,N'*-disubstituted lariat ethers having sidearms containing π-systems would show an unprecedented π-donor interaction with an alkali metal cation due to proximity between the ring-bound cation and the sidearm. The Na^+ and K^+ binding constants for R <N18N>R (**88–90**) both increased in the order *n*-propyl<allyl<propargyl. The Na^+ binding constants ranged from 2.69 to 3.61 and the K^+ binding constants ranged from 3.91 to 4.99. If no sidearm interaction occurred, one would expect the binding constants to be similar. Bis(cyanomethyl)BiBLE **91** is isosteric with bis(propargyl)BiBLE **90** but its binding ability is far lower.

An X-ray crystal structure determined for the KSCN complex of the bis(propargyl) derivative, showed that in the solid state the propargyl sidearms did not interact with the ring-bound cation but were turned away from the macroring.[43] The Na^+ binding constants for the 4,13-*N,N'*-disubstituted lariat ethers having *n*-butyl, allyl, and

propargyl sidearms have also been obtained in anhydrous acetonitrile and they are (log K_s): 5.66, 5.70, and 5.65, respectively.[44] Note that acetonitrile has approximately the same dielectric constant as methanol but is a non-hydrogen bonding solvent.

4,13-Diaza-18-crown-6 lariat ethers having benzyl sidearms. Binding constants were obtained for a series of *para*-substituted benzyl derivatives of 4,13-diaza-18-crown-6. The correlation with Taft's s° was excellent. A plot of log K/log K_0 *vs.* -2s° gave a straight line with a correlation coefficient of 0.998 and an r value of 0.45.[43] It is interesting to compare the Na^+ and K^+ binding strengths of *N,N'*-dibenzyldiaza-18-crown-6 and *N,N'*-dihexyldiaza-18-crown-6. Sodium cation binding is slightly but significantly weaker when the sidearms are benzyl (2.68) rather than *n*-hexyl (2.89). The K^+ binding strengths show a similar order: 3.78 for *n*-hexyl and 3.38 for benzyl. It is interesting to note, however, that the enthalpies of cation complexation (ΔH = -4.53 kcal/mol for the reaction Na^+ + crown → complex) determined for sodium binding suggests that this interaction is significantly stronger than when the sidearm is *n*-propyl (ΔH = 2.86 kcal/mol). This suggests a greater inherent donicity of the π-system than for a hydrocarbon chain and this fact may be of special significance in light of the proposal made recently by Kumpf and Dougherty[45] that the aromatic residues present in phenylalanine, tryptophan, and tyrosine mediate the relay of K^+ in peptidic cation-conducting channels.

Peptide sidearms. A series of lariat ethers having peptide sidearms (see structure below) was prepared[46] in the hope that the presence of both ester and amide carbonyl groups would enhance binding strength and Ca^{2+} selectivity. The sidearms complex both Na^+ and K^+ using only one donor in each sidearm and these sidearms appear to be quite rigid. There is thus little selectivity and the binding is not as strong as for simple ether derivatives. These conclusions can be readily confirmed by a perusal of Table 3.

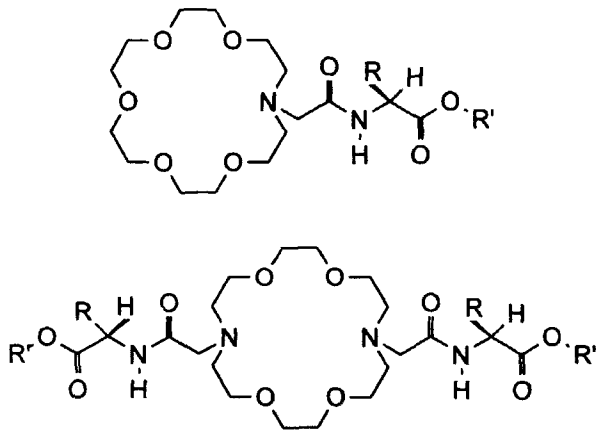


Figure 13 Structures of "peptide lariat ethers".

The dipeptide BiBLEs differ markedly in their behavior from the single-nitrogen analogs, and from the analogs that contain a single sidechain amino acid residue. The aza-18-crown-6 lariat having a glycine sidearm (<18N>CH_2COOEt = <18N>glyOEt = <18N>GOEt) exhibits Na^+ and K^+ binding constants of 4.67 and 5.92 respectively. The dipeptide relative, <18N>glyglyOMe is found to have Na^+ and K^+ binding constants of 3.50 and 4.53 respectively. When two dipeptide sidearms are present (MeOglygly < N18N>glyglyOMe), the K^+/Na^+ selectivity drops to (3.35/3.32) ≈1.

We were unable to determine Ca^{2+} cation binding constants in methanol by our usual competitive method, presumably because this cation was bound much more strongly than either Na^+ or K^+. Binding constants for Ca^{2+} were determined in water where their values could be measured using a commercial electrode designed for the purpose. The following values for log K_s (water) were obtained for Na^+ and Ca^{2+} respectively (A = alanyl, G = glycinyl, L = leucinyl, and V = valinyl): MeOGG <N18N>GGOMe, 2.2, 6.7; MeOAG<N18N>GAOMe, 2.2, 87; MeOVG<N18N>GVOMe, 2.2, 87; MeOLG<N18N>GLOMe, 2.3, 87. The divalent calcium cation binding strengths reported here as ≥7 were originally reported[47] as 7.7–7.8 with the caveat that the ISE electrode method was unreliable when binding was so high. Parker, Buschmann, and their coworkers[48] found Na^+ and Ca^{2+} values for MeOGG<N18N>GGOMe of 2.36 and 5.97 ($Ca^{2+}/Na^+ = 10^{3.61}$). Very recently, Gu, Kenney, and Brown[49] determined Na^+ and Ca^{2+} complexation constants for MeOAG<N18N>GAOMe in methanol using circular dichroism measurements. They reported values of 4.46 and 9.13, respectively. The Ca^{2+}/Na^+ selectivity for this system in methanol is $10^{4.7}$. In water, our calculated selectivity value is $10^{4.8}$.

The extraordinarily strong Ca^{2+} cation binding observed for these systems reflects the demand divalent calcium makes on the relatively polar carbonyl donors groups for solvation. ^{13}C-NMR studies conducted by Parker, Buschmann, *et al.* tentatively suggest that the both carbonyl groups in each chain serve as donor groups for the ring-bound cation. Work of our own in collaboration with Izatt and Chu confirm this notion. X-Ray crystal structure data[29] showed clearly that Na^+ complexes of MeOGG<N18N>GGOMe utilized a single carbonyl donor group in each sidearm. The present binding selectivities strongly suggest that all four carbonyl donor groups are being used in complex formation, although we have been unable to confirm this by solid state structure analysis.

Generalizations concerning bibracchial, nitrogen-pivot lariat ethers. The influence of ring size is general-

ly similar for both the one- and two-armed derivatives. Larger rings afford a macrocycle-bound cation a greater number of donors and, usually, a less strained system. As noted previously, these factors have little to do with "hole-size."[4d] The importance of hole-size increases as the ligand's rigidity increases and is of obvious consequence for cryptand binders. No direct comparison is possible from our own work with the 12-membered ring systems although the work of others suggests parallels to the observations presented here for the larger-ring systems. When a minimum of six oxygen atoms are present, generally strong binding is observed for Na^+ and K^+, although K^+ is nearly always favored in the absence of other factors (sidearm bulk, rigidity, or polarity).

It is still difficult to predict cation binding strength and selectivity for crown and lariat ether compounds. It is clear, however, that (i) lipophilicity has relatively little effect on binding constants; (ii) although π-donors do not appear to be better than simple alkyl donors based on binding constant, their enthalpic contributions are greater; (iii) neither divalent sulfur nor sulfoxide donor groups showed any significant binding enhancement despite "appropriate" placement. In general, if flexibility can be maintained, polar donor groups (ester, amide) on the sidearms will favor more charge dense cations (*e.g.* Ca^{2+}) and disfavor less charge dense species such as K^+. The remarkable cryptands show excellent hole-size selectivity and binding strengths are high when the fit is good and the cation is monovalent. Divalent cations are not accommodated nearly as well whereas the BiBLEs do very well in this case. Of course, sidearms must retain their flexibility in order to utilize the donors effectively.

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EXPERIMENTAL SECTION

General. ^{1}H-NMR were recorded on a Varian EM 360A, Hitachi Perkin-Elmer R-600, JEOL FX90Q, or Varian VXR-400 High Resolution NMR Spectrometer in $CDCl_3$ solvents and are reported in ppm (δ) downfield from internal Me_4Si. ^{13}C-NMR were recorded on a JEOL FX90Q or Varian VXR-400 NMR Spectrometer or as noted above. IR spectra were calibrated against the 1601 cm^{-1} band of polystyrene. Melting points were determined in open capillaries and are uncorrected. TLC analyses were performed on aluminum oxide 60 F-254 neutral (Type E) with a 0.2 mm layer thickness or on silica gel 60 F-254 with a 0.2 mm layer thickness. Preparative chromatography columns were packed with activated aluminum oxide (MCB 80–325 mesh, chromatographic grade, AX 611) or with Kieselgel 60 (70–230 mesh). Chromatotron chromatography was performed on 2 mm circular plates prepared from Kieselgel 60 PF-254. Gas chromatographic analyses (thermal conductivity detector) were conducted on a 5 ft.×0.25 in. column packed with 1.5% OV-101 on 100/120 mesh Chromosorb G. Helium was used as the carrier gas, and the flow rate was *ca.*60 mL/min.

All reactions were conducted under dry N_2 unless otherwise noted. All reagents were the best (non-LC) grade commercially available and were distilled, recrystallized, or used without further purification, as appropriate. Molecular distillation temperatures refer to the oven temperature of a Kugelrohr apparatus. Combustion analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga., and are reported as percents.

Compounds used in the present study. Syntheses for some of the compounds for which new binding data are presented here have been previously described. They are presented in the following sections. If the compound has previously been fully characterized, only the compound number and sidearm followed by the appropriate reference are given.

Derivatives of Aza-12-crown-4 Lariat Ethers. **1**, H;[19] **2**, $CH_2CH_2CH_2$-OH;[19] **3**, $CH_2CH_2OCH_3$,[19] **4**, $(CH_2CH_2O)_2CH_3$;[19] **5**, $(CH_2CH_2O)_3CH_3$;[19] **6**, $(CH_2CH_2O)_4CH_3$;[19] **7**, $(CH_2CH_2O)_5CH_3$;[19] **8**, $(CH_2CH_2O)_4CH_2CH{=}CH_2$;[19] **9**, $(CH_2CH_2O)_8CH_3$;[28] **10**, $CH_2CON(C_5H_{11})_2$; (see below); **11**, $CH_2CON(C_{18}H_{37})_2$;[37] **12**, benzyl;[19] **13**, 2-MeO-Ph;[29] **14**, 4-MeO-Ph;[28] **15**, 2-methoxybenzyl;[19] **16**, 2-nitrobenzyl.[19]

***N*-(*N*,'*N*'-Di-n-pentylamidomethyl)aza-12-crown-4, 11.** *Sidearm precursor*: A solution of di-*n*-pentylamine (2.94 g, 19 mmol) and Et_3N (1.92 g, 19 mmol) in C_6H_6 (30 mL) was slowly added to a stirred (0–8 °C) solution of chloracetyl chloride (2.12 g, 0.019 mol) in C_6H_6 (20 mL). The mixture was stirred for 2 h at ambient temperature and the solvent evaporated. The residue was partitioned between CH_2Cl_2 (50 mL) and brine (30 mL), dried ($MgSO_4$), concentrated *in vacuo*, and the brown oil was then distilled (Kugelrohr apparatus, bp 130 °C at 0.35 torr) to afford the side-arm precursor (3.4 g, 77%) as a colorless oil that was pure as judged by ^{1}H-NMR.

Aza-12-crown-4 (1.3 g, 7.4 mmol), *N,N*-dipentyl chloracetamide (1.73 g, 8.0 mmol) and Na_2CO_3 (1.55 g, 14.8 mmol) were added at once to butyronitrile (50 mL). The resulting mixture was stirred at reflux for 24 h, cooled, filtered, and concentrated *in vacuo* to a heavy yellow oil which was redissolved in CH_2Cl_2 (100 mL), washed with 3N HCl (3×30 mL), 5% Na_2CO_3 (3×30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over alumina [neutral, 0–2%(v/v) MeOH/CH_2Cl_2] to give a pale yellow oil which gave **11** (2.5 g, 75%), after Kugelrohr distillation

[bp 150–152 °C (0.15 torr)]. ^{1}H-NMR: 0.90 (m, 6H); 1.27 (m, 8H); 1.52 (m, 4H); 2.94 (t, 4H, J=4.6 Hz); 3.26 (m, 4H); 3.49 (s, 2H); 3.61 (t, 4H, J=4.6 Hz); 3.68 ppm (m, 8H). IR (neat): 2880 (s), 1620 (s), 1430 (s) cm^{-1}. Anal. calcd for $C_{20}H_{40}N_2O_4$: C, 64.48; H, 10.82%. *Found:* C, 64.23; H, 10.84%.

Derivatives of aza-15-crown-5 lariat ethers. **17**, H;[19] **18**, CH_3; [19] **19**, CH_2COOH (see below); **20**, allyl;[19] **21**, $CH_2CH_2OCH_3$;[19] **22**, $CH_2CH_2SCH_3$;[38] 23; $CH_2CH_2SOCH_3$;[38], **24**, *n*-butyl;[19] **25**, *t*-butyl;[19] **26**, $(CH_2CH_2O)_2CH_3$;[19] **27**, CH_2COOEt (see below); **28**, CH_2COO-t-butyl;[19] **29**, $(CH_2CH_2O)_3CH_3$;[19] **30**, $CH_2CONHC_5H_{11}$; **31**, $CH_2CONH(C_5H_{11})_2$;[37] **32**, $CH_2COOC_6H_{13}$ (see below); **33**, $CH_2COOC_{10}H_{21}$;[37] **34**, $CH_2CONHC_{10}H_{21}$;[37] **35**, $CH_2CON(C_{10}H_{21})_2$;[37] **36**, $CH_2COOC_{12}H_{25}$ (see below); **37**, $CH_2COOC_{16}H_{33}$ (see below); **38**, $CH_2CON(C_{18}H_{37})_2$;[37] **39**, $(CH_2CH_2O)_4CH_3$;[19] **40**, $(CH_2CH_2O)_5CH_3$;[19] **41**, $(CH_2CH_2O)_8CH_3$;[19] **42**, *o*-methoxyphenyl;[19] **43**, *p*-methoxyphenyl;[19] **44**, CH_2CH_2SPh;[19] **45**, CH_2Ph;[19] **46**, *o*-methoxybenzyl;[19] **47**, *o*-nitrobenzyl;[19] **48**, *p*-nitrobenzyl;[19] **49**, COO-cholesteryl;[50] **50**, CH_2COO-cholesteryl;[50] **51**, CH_2COO-cholestanyl;[50] **52**, CH_2CH_2OPh (see below); and **53**, $CH_2CH_2OCH_2Ph$ (see below).

***N*-Carboxymethylaza-15-crown-5, 19**, was obtained by hydrolysis of **27** (see below) in refluxing distilled water. Crystallization proved difficult and appeared to depend on the sample. In one case, **19** was crystallized from cold acetone, the solvent was evaporated *in vacuo*, and the product crystallized by slow addition of diethyl ether. The ether was then removed by pipette and the residue recrystallized from EtOAc (5 mL/g). The product, a white solid (mp 80–81 °C), was obtained in 85% yield. ^{1}H-NMR: 3.08 (m, 4H), 3.25–3.82 (m, 18H), 9.99 (s, 1H). ^{13}C-NMR: 55.3, 58.2, 70.1, 70.3, 70.5, 171.1. Anal. calcd for $C_{12}H_{23}NO_6$: C, 51.97; H, 8.36; N, 5.05%. Found: C, 52.08; H, 8.65; N, 4.93%.

***N*-Ethoxycarbonylmethylaza-15-crown-5, 27**. A 250-mL, round-bottomed flask was charged with aza-15-crown-5 (2.0 g, 0.009 mol), Na_2CO_3 (4.0 g, 0.038 mol), and MeCN (100 mL). Ethyl bromoacetate (1.5 g, 0.009 mol) was dissolved in MeCN (50 mL), and added at once. The reaction mixture was stirred at reflux temperature and followed by tlc. After *ca.* 3 h, the mixture was cooled, filtered, and the solvent evaporated. The resulting oil was dissolved in water (50 mL), extracted with CH_2Cl_2 (2×30 mL) and evaporated. Chromatography over alumina (10 g/g crude product; eluent: 9 column volumes of hexanes, then 1% 2-propanol/hexanes) afforded **27** (1.5 g, 53%) as a pale yellow oil. ^{13}C-NMR ($CDCl_3$): 14.3, 54.9, 57.3, 60.0, 70.0, 70.6, 71.1, 171.4. Anal. calcd for $C_{14}H_{27}NO_6$: C, 55.07; H, 8.91; N, 4.59%. Found: C, 54.85; H, 9.20; N, 4.59%.

Sodium Bromide Complex of **27**. A 500-mL, round-bottomed flask was charged with aza-15-crown-5 (10.0 g, 0.046 moles), Na_2CO_3 (5.0 g, 0.047 moles), and MeCN (260 mL). Ethyl bromacetate (7.8 g, 0.047 moles) was dissolved in 100 mL of MeCN, and added to the flask. The reaction mixture was refluxed for 3 hours, cooled, filtered, and the solvent was evaporated. After standing at room temperature for several hours, white crystals separated from a yellow oil. THF was added to the mixture (250 mL), and the crystals were collected over a sintered glass filter, washed with more THF, and dried. The crystals were then dissolved in $CHCl_3$ and filtered. The solvent was evaporated, and the residue dried for several hours *in vacuo* to afford a white powder (15.2 g, 80%). The melting point was determined in a sealed tube: 114–115 °C. ^{1}H-NMR: 1.3 (t, 3 H), 2.88 (t, 4 H), 3.5–3.9 (m, 18 H), 4.2 (m, 2 H). IR (thin film from $CHCl_3$): 2880, 1730, 1450, 1350, 1210, 1110. ^{13}C-NMR: 14.3, 55.0, 56.4, 61.2, 67.4, 68.7, 69.1, 69.3, 172.4. Anal. calcd for $C_{14}H_{27}NO_6BrNa$: C, 41.19; H, 6.66; N, 3.43; Br, 19.57%. Found: C, 41.02; H, 6.84; N, 3.22; Br, 20.10%. A portion of the complex (1.1 g) was vaccum distilled (Kugelrohr, 115–120 °C, 0.01 torr) to afford **27** (0.8 g, 95%) as a clear oil.

***N*-(*n*-Hexyloxycarbonylmethyl)aza-15-crown-5, 32**. *n*-Hexyl chloroacetate was prepared by esterification of 2-chloroacetic acid with 1-hexanol in C_6H_6 using a Dean-Stark apparatus. The product was distilled under reduced pressure (bp 113–116 °C) prior to use. A 500-mL round-bottomed flask was charged with aza-15-crown-5 (3.0 g, 0.014 moles), Na_2CO_3 (2.5 g, 0.024 moles), and MeCN (250 mL). Hexyl chloroacetate (2.5 g, 0.014 moles) was dissolved in 50 mL of MeCN and added to the flask. The reaction mixture was heated at reflux for 24 h, cooled, filtered, and the solvent was evaporated. The residue was dissolved in water (100 mL), extracted with CH_2Cl_2 (2×100 mL), evaporated *in vacuo* of the solvent afforded a yellow oil which was chromatographed on alumina (25 g of adsorbent per gram of crude; 10 bed volumes of hexanes, then 1% 2-propanol in the hexanes until complete elution) to provide the product (2.8 g, 56%) as a pale yellow oil. ^{1}H-NMR: 0.9 (m, 3 H), 1.3 (m, 9 H), 2.9 (m, 4 H), 3.2–3.8 (m, 18 H), 4.1 (m, 2H). IR (neat): 2850, 1740, 1460, 1350, 1130. Anal. calcd for $C_{18}H_{35}NO_6$: C, 59.81; H, 9.76; N, 3.87%. Found: C, 59.96; H, 9.78; N, 3.80%.

***N*-(*n*-Dodecyloxycarbonylmethyl)aza-15-crown-5, 36**. Compound **36**: dodecyl chloroacetyate was prepared form 1-dodecanol and 2-chloroacetic acid as described before; the compound was used without further purification. Aza-15-crown-5 (2.0 g, 0.009 moles), Na_2CO_3 (2.0 g, 0.019 moles), and MeCN (200 mL) were added to a 500 mL flask equipped with magnetic stirrer and N_2 purge. Dodecyl chloroacetate (2.4 g, 0.009 moles) was

dissolved in 50 mL MeCN and added to the flask. The reaction mixture was refluxed for 24 hours, cooled, filtered, and the solvent was evaporated. The crude product was dissolved in 2,2,1-dichlorodifluoroethane (20 mL) and washed with water (3×15 mL). Evaporation of the organic layer afforded **36** (3.6 g, 89%) as a pale yellow oil. ^{1}H-NMR: 1.3 (m, 23H), 2.9 (t, 4H), 3.4–3.8 (m, 18H), 4.1 (m, 2H). IR (neat): 2950, 2880, 1750, 1480, 1370, 1140 cm^{-1}. ^{13}C NMR: 14.0, 22.7, 26.0, 28.8, 29.3, 29.6, 31.9, 54.9, 57.3, 64.2, 70.3, 70.6, 71.1, 171.4. Anal. calcd for $C_{24}H_{47}NO_6$: C, 64.69; H, 10.63; N, 3.14%. Found: C, 64.95; H, 10.90; N, 3.30%.

***N*-(*n*-Hexadecyloxycarbonylmethyl)aza-15-crown-5, 37.** Hexadecyl chloroacetate was prepared from 1-hexadecanol and 2-chloroacetic acid as described before; the compound was used without further purification. Monoaza-15-crown-5 (2.0 g, 0.009 moles), Na_2CO_3 (2.0 g, 0.019 moles), and MeCN (200 mL) were added to a 500 mL flask equipped with magnetic stirrer and nitrogen purge. Hexadecyl chloroacetate (2.9 g, 0.009 moles) was dissolved in 50 mL of MeCN, and added to the flask. The reaction mixture was refluxed for 24 hours, cooled, filtered, and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with water (2×100 mL). After evaporation of the organic layer, the resulting yellow oil was chromatographed on silica (22 g of adsorbent per g of crude; eluent: 8 bed volumes of $CHCl_3$:EtOAc 95.5 (v/v), the gradually to $CHCl_3$MeOH 9:1 v/v until complete elution of the product) to afford the product (3.2 g, 69%) as a yellow pale oil. ^{1}H-NMR: 1.3 (m, 31 H), 2.9 (t, 4 H), 3.4–3.8 (m, 18 H) 4.1 (m, 2H). IR (neat): 2940, 2880, 1750, 1480, 1370, 1140 cm^{-1}. ^{13}C-NMR: 14.0, 22.7, 26.0, 28.8, 29.3, 29.7, 31.9, 54.9, 57.3, 64.2, 70.3, 70.6, 71.1, 171.4. Anal. calcd for $C_{28}H_{55}NO_6$: C, 67.03; H, 11.05; N, 2.79%. Found: C, 66.84; H, 11.20; N, 2.70%.

***N*-(2-Phenoxyethyl)aza-15-crown-5, 52.** *Preparation of 2-phenoxyethyl tosylate.* To a solution of tosyl chloride (21.5 g, 0.113 mol) in pyridine (20 mL) was added dropwise a solution of 2-phenoxyethanol (13.0 g, 0.094 mol) in pyridine (10 mL) at 0 °C. The reaction mixture was stirred for 30 min, poured into ice-water (100 mL), and extracted with $CHCl_3$ (200 mL then 100 mL). The combined organic phases were washed with 6N HCl (3×100 mL), and concentrated *in vacuo*. Recrystallization from EtOH gave the tosylate (25.5 g, 93%) as a white solid, mp 76.0–77.0 °C; ^{1}H-NMR: 2.44 (s, 3H), 4.01–4.45 (m, 4H), 6.67–7.86 (m, 9H); Anal. calcd for $C_{15}H_{16}O_4S$; C, 61.62; H, 5.53%. Found: C, 61.64; H, 5.55%.

Alkylation to form N-(2-phenoxyethyl)aza-15-crown-5, **52.** A solution of aza-15-crown-5 (2.00 g, 9.12 mmol), 2-phenoxyethyl tosylate, (3.05 g, 10.40 mmol), Na_2CO_3 (1.00 g, 9.43 mmol), NaI (1.61 g, 10.73 mmol) was stirred at ambient temperature for 7 days. The reaction mixture was filtered and concentrated *in vacuo*. CH_2Cl_2 was added and washed with water. Chromatography (alumina, 10% 2-propanol-hexane) followed by distillation (Kugelrohr, apparatus, 165–173 °C at 0.15–0.20 torr) gave **52** (1.60 g, 52%) as a colorless oil: ^{1}H-NMR 2.77–3.16 (m, 6H), 3.53–3.74 (m, 16H), 3.94–4.15 (t, 2H), 6.78–7.38 (m, 5H). IR (neat): 2880, 1610, 1600, 1500, 1485, 1360, 1300, 1260, 1130, 760, 695 cm^{-1}; Anal. calcd for $C_{18}H_{29}NO_5$; C, 63.68; H, 8.63; N, 4.12%. Found: C, 63.17; H, 8.67; N, 4.06%.

Preparation of *N*-(2-benzyloxethylaza-15-crown-5, 53. A 50-mL flask was charged with aza-15-crown-5 (1.44 g, 6.56 mmol), 2-benzyloxyethyl tosylate (2.31 g, 7.54 mmol), Na_2CO_3 (1.0 g, 9.43 mmol) and CH_3CN (10 mL). The reaction mixture was heated at reflux for 3 d, cooled, and then $CHCl_3$ was added. This suspension was filtered and concentrated *in vacuo*. Chromatography (alumina, 2% MeOH-CH_2Cl_2) followed by Kugelrohr distillation (140–150 °C at 0.01 torr) gave 53 as a colorless oil (1.91 g, 82%); ^{1}H-NMR 2.71–2.91 (t, 6H), 3.49–3.73 (m, 18H), 4.50 (s, 2H), 7.30 (s, 5H). IR (neat): 2890, 1455, 1360, 1300, 1250, 1130, 750, 700 cm^{-1}; Anal. calcd for $C_{19}H_{31}NO_5$; C, 64.55; H, 8.86; N, 3.96%. Found: C, 64.29; H. 8.92; N, 3.88%.

Derivatives of aza-18-crown-6 lariat ethers. 54, H;[19] **55**, CH_3;[19] **56**, *n*-propyl (see below); **57**, allyl (see below); **58**, $CH_2CH_2OCH_3$;[19] **59**, CH_2COOEt (see below); **60**, $(CH_2CH_2O)_2CH_3$;[19] **61** $CH_2CONHCH_2COOCH_3$;[46c] **56**, $CH_2CONHCH(i\text{-Pr})COOCH_3$;[46c] **57**, $CH_2CONHCH(s\text{-Bu})COOCH_3$;[46c] **58**, $(CH_2CH_2O)_3CH_3$;[19] **59**, $(CH_2CH_2O)_4CH_3$;[19] **60**, $(CH_2CH_2O)_5CH_3$;[19] **61**, $(CH_2CH_2O)_8CH_3$;[19] **62**, 2-MeO-Ph;[19] **63** benzyl.[19]

***N*-*n*-Propylaza-18-crown-6, 56.** *N*-*n*-Propyldiethanolamine (14.7 g, 0.1 mol), tetraethylene glycol ditosylate (50.2 g, 0.1 mol), and NaH (10.1 g, 0.5 mol) in 500 mL of anhydrous THF were heated at reflux overnight. Column chromatography on alumina (4% 2-propanol in hexanes), followed by distillation (Kugelrohr, 140–145 °C, 0.6 torr) afforded **56** (5.7 g, 18.6%). ^{1}H-NMR: 0.80 (t, 3H), 1.41 (m, 2H), 2.45 (t, 2H), 2.72 (t, 4H), 3.45–3.70 (m, 20H). Anal. calcd for $C_{15}H_{31}NO_5$: C, 58.98: H, 10.23; N, 4.58%. Found: C, 59.12: H, 10.40; N, 4.62%.

***N*-Allylaza-18-crown-6, 57.** To a virgorously stirred solution containing NaH (17 g, 0.7 mol) in anhydrous THF (900 mL) were added dropwise *N*-allyldiethanolamine (50 g, 0.34 mol) and tetraethylene glycol ditosylate (104.2 g, 0.21 mol) diluted to 250 mL with THF. After the addition was completed, the reaction mixture was refluxed for 22 hours, cooled, and the excess of NaH was quenched with water. The reaction mixture was then filtered, and concentrated *in vacuo*. The residue was dissolved in 500 mL of water, extracted with CH_2Cl_2 (3×250 mL). The combined organic layers were dried

over Na_2SO_4, filtered, and the solvent was evaporated. Column chromatography over alumina (2% 2-propanol in hexanes) followed by three distillations (Kugelrohr, 130 °C, 0.4 torr) afforded the product (30.2g, 47%) as a colorless oil. ^{1}H-NMR: 2.78 (t, 4H), 3.17 (d, 2H), 3.60–3.70 (m, 20 H) 5.19 (m, 2 H), 5.87 (m, 1 H). ^{13}C-NMR: 53.6, 58.7, 69.7, 70.2, 7.05, 76.7, 116.6, 135.9. Anal. calcd for $C_{15}H_{29}NO_5$: C, 53.39; H, 9.63; N, 4.63%. Found: C, 53.49; H, 10.00; N, 4.79%.

***N*-Allylaza-18-crown-6, 57** (alternate preparation). Aza-18-crown-6 (1.0g, 0.0038 mol), allyl chloride (0.5g, 0.006 mol), and anhydrous Na_2CO_3 (2 g, 0.02 mol) were combined with 15 mL of MeCN in a 100 mL flask heated under gentle reflux while stirring for 20 h, cooled, and the salts were filtered. The solvent was evaporated *in vacuo*, and the resulting yellow oil and solid were dissolved in 25 mL of $CHCl_3$. The solution was washed with water (3×20 mL), and the combined aqueous layers were extracted with $CHCl_3$ (15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solution was concentrated *in vacuo*. The resulting oil was distilled (Kugelrohr, 120–125 °C, 0.25 torr) affording compound **57** (0.8 g, 70%) as a colorless oil which was characterized as described above.

***N*-(Ethoxycarbonylmethyl)aza-18-crown-6, 59**. Aza-18-crown-6 (0.53 g, 2.0 mmol), Na_2CO_3 (0.23 g, 2.2 mmol), MeCN (50 mL), and $ClCH_2COOEt$ (0.26 g, 2.1 mmol) were stirred and heated to reflux for 12 h. The mixture was then cooled, filtered, and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (150 mL) and washed with H_2O (2×150 mL). After drying (Na_2SO_4), the organic phase was reduced *in vacuo*. The residue was chromatographed [alumina, 60 g, 2-PrOH/hexane, 9:1 (v/v)], distilled (Kugelrohr) and obtained as a colorless oil (0.55 g, 79%), bp 140–145 °C/0.1 torr. ^{1}H-NMR: 1.20 (t, 3H); 2.90 (t, 4H); 3.60 (m, 22H); 4.13 (q, 2H). ^{13}C-NMR: 12.18, 51.99, 54.14, 57.90, 68.00, 68.20, 68.62, 169.59 ppm. IR: 2860, 1740, 1450, 1350, 1300, 1250, 1180, 1110, 1020, 980, 940, 830 cm^{-1}. Anal. calcd for $C_{16}H_{31}NO_7$: C, 54.98; H, 8.96%. Found: C, 54.87; H, 8.96%.

Derivatives of 4,10-diaza-15-crown-5 lariat ethers. 78, H;[21] **79**, $CH_2CH_2OCH_3$;[21] **80**, CH_2COOEt;[21] **81**, 2-furanylmethyl;[21] **82**, benzyl;[21] **83**, 2-methoxybenzyl.;[21]

Derivative of 4,10-Diaza-18-crown-6. 84, benzyl.[21]

Derivatives of 4,13-diaza-18-crown-6 lariat ethers. 85, H;[21] **86**, CH_2CH_2OH;[20] **87**, CH_2CONH_2;[20] **88**, n-propyl;[21] **89**, allyl;[21] **90**, propargyl;[21] **91**, cyanomethyl (see below); **92**, $CH_2CH_2OCH_3$;[20] **93**, *n*-butyl;[21] **94**, CH_2COOEt;[20] **95**, $CH_2CON(C_5H_{11})_2$;[37] **96**, $CH_2CONHCH_2COOCH_3$;[46] **97**, $CH_2CONHCH(Me)COOCH_3$;[46] **98**, $CH_2CONHCH(i\text{-}Pr)COOCH_3$;[46] **99**, $CH_2CONHCH(i\text{-}Bu)COOCH_3$;[46] **100**, $CH_2CONHCH(s\text{-}Bu)COOCH_3$;[46] **101**, *n*-hexyl;[21] **102**, *n*-nonyl;[21] **103**, *n*-dodecyl;[21] **104**, 2-furanylmethyl;[21] **105**, benzyl;[20] **106**, 2-methoxybenzyl;[20] **107**, 4-methoxybenzyl;[43] **108**, 2-hydroxybenzyl;[20] **109**, 4-chlorobenzyl;[44] **110**, 4-cyanobenzyl.[44]

***N,N'-bis*(Cyanomethyl)-4,13-diaza-18-crown-6, 91.** To a stirred solution of 4,13-diaza-18-crown-6 (0.52 g, 2 mmol) and chloroacetonitrile (0.38 g, 5 mmol) in dry acetone (30 mL) was added Na_2CO_3 (0.32 g). The mixture was heated at reflux while stirring vigorously for 10 h, cooled, and then filtered. After evaporation, the dark yellow solid was decolorized (activated C in C_6H_6, 50 mL). Recrystallization from THF (20 mL) gave pure **91** (0.54 g, 75%) as a white solid, mp 105–105.5 °C. ^{1}H-NMR: 3.92 (s, 4H); 3.60 (m, 16H); 2.75 (t, 8H). IR (KBr): 2260 cm^{-1}. Anal. calcd for $C_{16}H_{28}N_4O_4$: C, 56.44; H, 8.30; N, 16.46%. Found: C, 56.50; H, 8.31; N, 16.38%.

Determination of cation binding constants. Reagent grade methanol was distilled from magnesium turnings through a 20-cm. Vigreux column. Either ClO_4- or Cl-salts were used. $NaClO_4$, $KClO_4$, NaCl, and KCl were the purest available from Aldrich Chemical Co., recrystallized from water, and dried in a vacuum oven [60 °C (0.05 torr)] for 2 days.

Apparatus and procedure. Potentials to within ±0.1 mV were measured by using an Orion Model 701A voltmeter. Sodium activity was determined with a sodium ion selective electrode (ISE, Corning Model No. 476210). Potassium and ammonium cation activities were determined by a Corning monovalent cation electrode, Model No. 476220. A Corning Ag/AgCl reference electrode (Model 476029) was used with each of the ion selective electrodes. A water bath placed on a magnetic stirrer, was maintained at 25±0.2 °C with a Cole Parmer circulator heater (Model 125200). Calcium cation binding constants were determined in methanol by our previously described competition method[18] or as described above but using a standard calcium-selective electrode in water. Sample cells were constructed as previously described.[17] The procedure and applicable calculations have also been described.[17]

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