Ring-Side-Arm Cooperativity in Cation Inclusion Complexes of 12-Membered Ring Lariat Ethers: Effect of Side-Arm Chain Length and a Clarification of Long-Side-Arm Binding Strengths

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The alkali metal and ammonium cation binding properties of *N*-pivot, 12-crown-4 lariat ethers are recorded here. A reinvestigation of *N*-pivot lariat ethers having $(CH_2CH_2O)_nCH_3$ side arms is presented, and data are reported for fresh samples of these long chain compounds. Details of the X-ray crystal structures obtained for *N*-[(3-oxabutyl)methyl]aza-12-crown-4 are reported. The complex crystallizes in the triclinic space group $P\bar{1}$ with cell constants a = 8.712 (2) Å, b = 8.694 (3) Å, c = 11.740 (3) Å, α = 111.44 (2)°, β = 90.76 (2)°, γ = 103.50 (2)°, and Z = 2 for D_c = 1.591 g^{-3}. Least-squares refinement based on 3723 observed reflections led to a final conventional R value of 0.052. All of the lariat ether donors bind to the alkali metal cation, with the macroring in a crown conformation. The 12-crown-4 system behaves, in many ways, like the 15- and 18-membered ring analogues. The presence of an octakis(ethyleneoxy) side arm does not diminish cation binding strength in this series as reported for the 15- and 18-membered ring compounds. Indeed, the fall off in binding constants previously reported for the longest chain examples of the latter families now appears to be due to sample decomposition rather than solvent encumbrance.

Introduction

Lariat ethers[1] differ from simple monocyclic crown ethers in their ability to utilize both a macroring and side arm to complex cations. When the macroring contains only 12 atoms, no alkali metal cation, with the possible exception of Li^+, can enter the macroring hole. The side arm is thus forced to assume a major role in the complexation if the cation is to be bound by a single macrocycle.[2] Very few homogeneous cation binding constants are available for 12-membered ring crown ethers having either no side arm or no side-arm donor group to augment complexation strength because the equilibrium constants for such compounds in most polar solvents are below the limits of the methods that could be used to determine them.[3] We have been especially interested in the 12-membered ring systems because of their obvious inability to abide by the so-called hole-size concept[4] with any but the smallest cation.

We have now prepared 14, N-substituted aza-12-crown-4 derivatives having as many as eight oxygen atoms in the side arm. We present below a detailed analysis of their binding properties in solution and summarize our current understanding of the side-arm interactions. We also present X-ray crystallographic data for the sodium complex of *N*-(3-oxabutyl)aza-12-crown-4 and compare it with our previously reported[2] potassium complex of *N*-(3,6,9-trioxadecyl)aza-12-crown-4 as well as other sodium and potassium complexes of small-ring lariat ethers.

Results and Discussion

Syntheses. The 12-membered ring, nitrogen pivot lariat ethers described here were obtained by two approaches. The substituted azacrown could be prepared directly from the incipient side arm in the form of a primary amine by cyclization or by N-alkylation of the parent aza-12-crown-4 (**1**). Aza-12-crown-4 was prepared by hydrolysis of *N*-benzylaza-12-crown-4 (**12**). The two approaches are discussed below, and the aza-12-crown-4 derivatives prepared are shown in Table I.

Cyclization. Six of the 12-membered ring nitrogen pivot lariat ethers were synthesized by the method of Calverley and Dale.[5] This procedure involves cyclization of primary amines with 1,11-diiodo-3,6,9-trioxaundecane in the presence of Na_2CO_3 in MeCN solution at reflux

Table I. Syntheses of N-Substituted, 12-Crown-4 Derivatives

compd no.	R[a]	method of prepn[b]	yield, %	bp (mp), °C
1	H[c]	H	95	60 (subl)/0.05
2	$CH_2CH_2CH_2OH$	C	56	110–112/0.03
3	EOMe	C	60	70–72/0.05
4	EOEOMe	A	66	96–101/0.7
5	EOEOEOMe	A	52	155–160/0.03
6	EOEOEOEOMe	A	54	138–141/0.05
7	EOEOEOEOallyl	A	50	160–165/0.03
8	EOEOEOEOEOMe	A	69	175–180/0.15
9	EOEOEOEOEOEOE-OEOMe	A	68	oil[d]
10	2-MeO-Ph	C	26	130–135/0.03
11	4-MeO-Ph	C	40	142–146/0.03
12	benzyl	C	53	122–125/0.03
13	2-methoxybenzyl	C	47	150–153/0.03
14	2-nitrobenzyl	A	86	(37–38)[d]

[a] N-Substituent on aza-12-crown-4, E = CH_2CH_2. [b] Preparation methods: A stands for alkylation. H stands for hydrogenolysis of **12**. C stands for cyclization. [c] This compound forms ligand-to-cation complexes with Na^+ of the type NaL_2. [d] Obtained by chromatography.

Scheme I

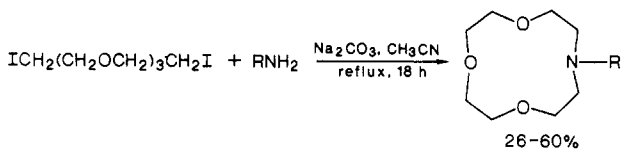

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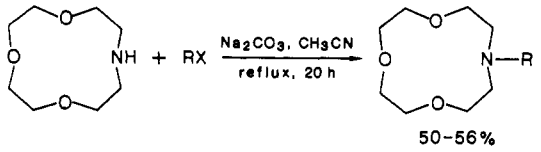
Table II. Comparison of Cation Binding by N-Substituted Lariat Ether Derivatives

compd[a] no.	side arm[b]	log K_S in anhydrous MeOH at 25 °C				
		12C4 Na^+	12C4 K^+	12C4 NH_4^+	15C5 Na^+	18C6 Na^+
1	H				1.70	2.69
2	$CH_2CH_2CH_2OH$	2.35				
3	EOMe	3.25	2.73	3.06	3.88	4.58
4	EOEOMe	3.60			4.54	4.33
5	EOEOEOMe	3.64	3.85	3.29	4.32	4.28
6	EOEOEOEOMe	3.76			4.15	4.27
7	$EOEOEOEOCH_2CH{=}CH_2$	3.97				
8	EOEOEOEOEOMe	3.73	4.34	3.49	4.19	4.22
9	EOEOEOEOEOEOEOEOMe	3.84	4.27	3.45	3.52[c]	3.44[c]
					4.18[d]	4.8[d]
10	2-MeOPh	2.75			3.86	4.59
11	4-MeOPh	1.38			2.12	
12	$PhCH_2$	2.08			2.77	3.41
13	$2\text{-}MeOPhCH_2$	2.49			3.54	
14	$2\text{-}NO_2PhCH_2$	1.77			2.40	

[a] Compound number applies only to 12-membered ring structures. [b] E represents the ethylene unit, CH_2CH_2. [c] See text for discussion of these values. [d] These values are for compounds **15** and **16** (see text and the Experimental Section), and the values reported depend on sample freshness as well as on the cation-to-ligand ration (see text).

Scheme II



temperature for 18 h (Scheme I). The yields for the compounds reported here ranged from 26% to 60%. Both aliphatic and aromatic amines were successful precursors for the cyclization. The following lariat ethers were produced by the cyclization reaction and afforded the indicated macrocycles: 3-aminopropanol (**2**), 2-methoxyethylamine (**3**), 2-methoxyaniline (**10**), 4-methoxyaniline (**11**), benzylamine (**12**), and 2-methoxybenzylamine (**13**).

The reaction mechanism presumably involves two S_N2 substitutions of nitrogen on the diiodide (Menschutkin reaction).[6] Sodium carbonate deprotonates the intermediate iodoammonium salt, and the Na^+ ion may also serve as a template for cyclization. Product yields appear to be lower when nitrogen is sterically hindered. Thus 4-methoxyaniline affords cycle **11** in 40% yield but the ortho isomer (**10**) was isolated in only 26% yield. In addition, it appears that a decrease in amine nucleophilicity diminishes the yield. Thus 2-methoxybenzylamine affords **13** in nearly twice the yield obtained with 2-methoxyaniline (**10**). Of course, the latter may reflect both electronic and steric effects.

Alkylation. When the appropriate precursor amine was unavailable, the product was obtained by alkylation of aza-12-crown-4 (**1**). Unsubstituted parent azacrown (**1**) was obtained from *N*-benzylaza-12-crown-4 (**12**). The latter was prepared by cyclization[5] in 53% yield and then hydrolyzed in a Parr apparatus (H_2, Pd/C, EtOH, 16 h, 95%). Aza-12-crown-4 (**1**) was obtained in about 50% overall yield from benzylamine. Aza-12-crown-4 was alkylated with the appropriate side-arm precursor, usually as the tosylate (Na_2CO_3, MeCN solution), as illustrated in Scheme II. *N*-(2-Nitrobenzyl)aza-12-crown-4 (**14**) was prepared by N-alkylation of **1** with commercially available 2-nitrobenzyl chloride. The $(ethyleneoxy)_n$ derivatives, **3**–**9**, were prepared by using the appropriate tosylates as side-arm precursors.

The azacrowns prepared by alkylation were obtained after chromatography over a column of aluminum oxide and subsequent Kugelrohr distillation. Bulb-to-bulb distillation of the oligomeric side-armed material, **9**, failed, owing to decomposition at the high temperature required (>200 °C at 0.05 Torr). As a result, **9** was characterized and used directly after column chromatography. Heat-sensitive nitrobenzyl derivative **14** was also used directly after chromatography over silica gel (3% $MeOH/CHCl_3$).

Cation Binding Properties. The equilibrium stability (binding) constants (K_S) for the derivatives prepared were measured[7] and are shown in Table II as decadic logarithms (i.e. log K_S). The values are compared to those for their 15- and 18-membered ring analogues.[1c,8]

Two important questions must be addressed concerning cation binding by 12-crown-4 derivatives. The first of these concerns the binding strengths and cation selectivities exhibited by 12-crown-4 compounds and the second is how binding occurs. The latter question revolves around the interplay of macroring and side arm when a cation inclusion complex is formed (see below).

The attractive, but dubious,[4] hole-size concept suggests that small rings bind small cations well and large rings bind large cations well. The binding phenomenon is far more complicated than that. Log K_S values are readily available for 12-crown-4, 15-crown-5, and 18-crown-6 with Na^+, K^+, and Ca^{2+}.[3,4] For all three cations, binding strengths decrease in the order 18-crown-6 > 15-crown-5 > 12-crown-4. It appears that too few donor groups are present in simple 12-crown-4 compounds to complex a metal cation. The large number of dimer structures known for 12-membered ring complexes with Na^+ corroborates this assessment.[9]

Very few homogeneous equilibrium binding constants

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(K_S) for Li^+ are available in the literature. This is because K_S for Li^+ is generally too small to permit accurate measurement. For example, Li^+ binding (log K_S) to 12-crown-4 in anhydrous MeOH is ca. 0 (i.e. $K_S = 1$). Log K_S for K^+ binding to 12-crown-4 is 1.74 in MeOH. The combination of only four macroring donors and the substantial free energy of solvation for Li^+ makes the crown unable to compete for solvation of the cation. The free energies of solvation for Li^+, Na^+, and K^+ in MeOH solution are −121.4, −96.4, and −78.4 kcal/mol, respectively. The free energy of solvation is most positive for K^+ and the crown is able to compete, albeit not well, for solvation of the cation.

Aza-12-crown-4 Lariat Ethers. The presence of a side arm attached at the readily invertable macroring nitrogen affords a compound having more than four donor groups and considerable flexibility. The equilibrium binding constants (log K_S) for Na^+ of the 12-membered ring lariats are lower than for the 15- and 18-membered ring compounds having identical side arms, but binding is considerably higher than for Na^+ to 12-crown-4 (log K_S in MeOH is 1.7).[2,9h] This indicates that the additional donor atom in the side arm is capable of solvating the ring-bound cation, thereby stabilizing the Na^+ complex (see Table II).

Steric accessibility of the side-arm donor group is as important for the small ring systems as for the larger ring compounds. This is apparent from a comparison of binding by *N*-(4-methoxyphenyl)aza-12-crown-4, **11**, with *N*-(2-methoxyphenyl)-substituted **10** or **13**. Note also that **13**, which has an oxygen atom three carbon atoms away from the macroring, is a weaker Na^+ binder than is **10**. When the appended side arm contains three or more oxygen atoms in an aliphatic chain (**5**), log K_S increases to 3.64, a value comparable to some of the 15- and 18-membered ring nitrogen pivot lariats.

Effect of Side-Arm Lengths. In a series of 15- and 18-membered ring nitrogen pivot lariat ethers containing (ethyleneoxy)$_n$monomethyl ether side arms of varying lengths, peak Na^+ binding was observed when the total number of oxygen atoms present was six. The binding constants were 4.54 and 4.58 log units for the 15- and 18-membered ring analogues.[1g] This peak in Na^+ cation binding at six oxygen atoms (seven donors) was observed in a similar series of 12-membered ring lariat ethers.[1g] We have carefully reexamined this binding behavior and found that the 12-membered ring compounds lack such a definite peak. A corrected plot of log K_S for Na^+ versus the total number of donor atoms (n) in the 12-, 15-, and 18-membered-ring ligands (filled triangles, squares, and circles, respectively) is shown in Figure 1. Previously unpublished data points have been obtained for longer chain *N*-pivot lariat ethers.

The binding trend for **3**–**6**, **8**, and **9** now shows a steady increase as side-arm length increases. The apparent exception to this is **7**, a compound having a terminal allyl group rather than a terminal methyl ether. Owing to lack of sample, we have not reexamined the binding constant of **7**, but it is not directly comparable to the other systems anyway. The trend for the polyethyleneoxy methyl ethers is now clearly a steady increase, at least up to a total of 11 oxygen atoms (12 donors including the macroring nitrogen atom). This seems reasonable since space-filling, CPK molecular models suggest that all 12 donors are effectively utilized in a coiled conformation. This contrasts with data previously reported[1e] for the 15- and 18-membered ring compounds having such long side arms which appeared to have excess, nonutilized donors. We have carefully reexamined these cases and now find that the

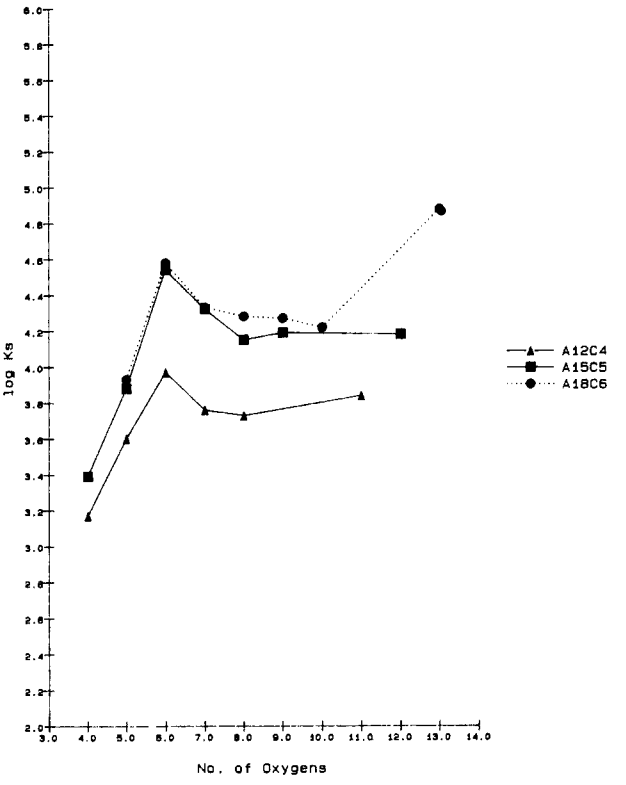

Figure 1. Plot of log K_S for Na^+ in MeOH at 25 °C versus total number of oxygens in the ligand.

octakis(ethyleneoxy) derivatives of the 15- and 18-membered ring, *N*-pivot lariat ethers exhibit a marked and unexpected lack of stability that makes an accurate determination of their binding constants difficult.

We have prepared new samples of the 15- and 18-membered ring derivatives corresponding to **9** (see Table II). If binding constant studies[7] are conducted immediately, the values for log K_S for Na^+ were found to be 4.18 and 4.80–4.95, respectively. After the sample was allowed to stand for 5 months, the binding constant recorded for the 15-membered ring compound was 3.97. We have no comparable data for the 18-membered ring, but we presume[1e] that degradation occurs in that case as well. The reason for this apparent degradation is unclear. The octakis(ethyleneoxy) compounds are oils rather than solids, but other oils in this series are apparently stable.

Another interesting observation concerns the uncertainty in the binding constants depending upon ligand:cation ratios. We usually conduct our binding studies using ratios (ligand:cation) of 2:5–1:5. In this range, the 15- and 18-membered ring compounds exhibited binding constant changes that suggest the binding of two cations by a single species. For example, the 18-membered analogue of **9** exhibited an apparent Na^+ binding constant of 4.80 when the ligand:cation ratio was 1:2.74 and 1:4.95 when the ratio was 1:1.46. We have not previously observed such behavior, but it seems reasonable given the long side arm.

X-ray Crystal Structure of 3·NaI. The atomic positional parameters are given in Table II. Selected torsion angles are presented in Table III. Tables of hydrogen atom coordinates, anisotropic thermal parameters, distances and angles, and structure factors are recorded in the supplementary material. The structure with all atoms is shown in Figure 2, while a skeletal drawing that emphasizes the arrangement of donor atoms about the sodium cation is presented in Figure 3.

The macroring is in the crown conformation [(g^-g^-a)$_4$], in which all heteroatoms are on the same side of the ring.

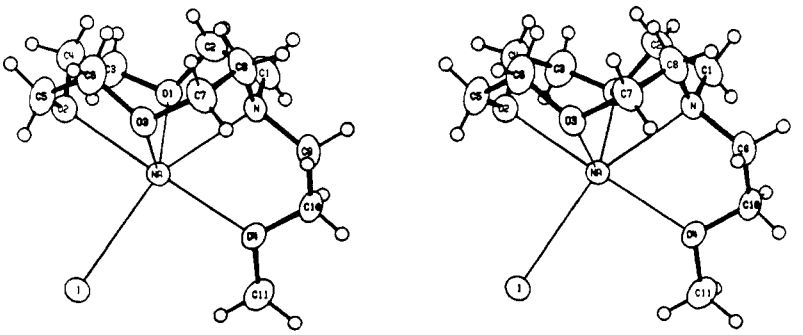

Figure 2. Stereodrawing of the sodium iodide complex of *N*-(3-oxabutyl)aza-12-crown-4 (**3**·NaI).

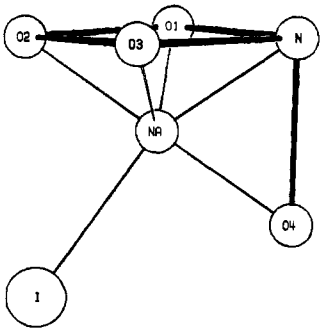

Figure 3. Skeletal drawing of the **3**·NaI complex. Na–donor distances in angstroms. O(1) 2.455 (2), O(2) 2.459 (2), O(3) 2.411 (2), O(4) 2.453 (2), N 2.561 (2), I 3.088 (1).

The four heteroatoms are coplanar to within 0.018 (3) Å, and the sodium cation lies 1.445 Å from the centroid of the four, which is closer than observed in the sandwich complex of bis(aza-12-crown-4) and sodium iodide, 1.528 Å.[9h] The shorter distance is a consequence of having fewer donors in the lariat ether complex than in the sandwich complex as well as the effect of the donor in the side arm holding the cation closer to the macroring.

The sodium cation is coordinated by six donors, five from the lariat ether plus the iodide. The mean cavity radius, *R*, of the lariat ether is 1.04 Å, which is larger than the effective ionic radius[10] for hexacoordinated sodium cation of 1.02 Å. In the bis(aza-12-crown-4) sandwich complex with its eight donors, *R* is 1.12 Å, which is larger than in the lariat ether but smaller than the effective ionic radius for octacoordinated sodium cation (1.18 Å).

Atomic positional parameters for **3**·Na are tabulated in the supplementary material.

Selected sodium complexes are compared in Table III. The trends are clear that the greater the number of donors the bigger the mean cavity radius. There are some notable exceptions such as the sandwich complex with aza-12-crown-4,[9h] and the complex with *N*-(2-hydroxyethyl)aza-18-crown-6.[11] Although there are only two examples to date, lariat ethers and BiBLEs having side arms with pendant hydroxyl oxygens appear to have smaller mean cavity radii than those having pendant ethereal oxygens. We can only speculate that this is because the greater conformational freedom of a hydroxy compared to an ether allows closer contact of all the donors in the host molecule. In summary, the structure reaffirms the power of the lariat ether concept. A single side-arm donor can provide enough stabilization to change the structure of complexation of the macrocycle from a sandwich complex to a 1:1 complex.

Table III. Comparison of Mean Cavity Radius of Sodium Complexes of Mono- and Diazapolyoxamacrocycles with Effective Ionic Radii of Sodium Cation[a]

macrocycle	donors	coordination number	*R*, Å	ref
none	(6)	6	1.02	10
none	(7)	7	1.12	10
none	(8)	8	1.18	10
crowns				
bisN12C4[a]	8	8	1.12	9h
bisN15C5[b]	5	6	1.08	12
lariat ethers				
3-1[c]	5	6	1.05	this work
4-1E[d]	6	7	1.11	12
5-1H[e]	7	8	1.09	to be published
cryptands				
222[f]	8	8	1.19	13
221[g]	7	7	1.10	14
BiBLEs				
1-22-1[h]	8	8	1.19	11
1H-22-1H[i]	8	8	1.14	11

[a] Bis(aza-12-crown-4) sodium iodide. [b] *N*-Phenylaza-15-crown-5·sodium perchlorate. [c] *N*-(2-Methoxyethyl)aza-12-crown-4 sodium iodide. [d] *N*-(Ethoxycarbonylmethyl)aza-15-crown-5 sodium bromide. [e] *N*-(2-Hydroxyethyl)aza-18-crown-6 sodium iodide. [f] [2.2.2]-Cryptand sodium iodide. [g] [2.2.1]Cryptand sodium thiocyanate. [h] *N,N'*-Bis(2-Methoxyethyl)-1,10-diaza-18-crown-6 sodium iodide hydrate. [i] *N,N'*-Bis(2-hydroxyethyl)-1,10-diaza-18-crown-6 sodium iodide.

As we progress in our structural studies of macrocyclic complexes, the critical features of the molecular topography for cation recognition will emerge.

Ammonium and Potassium Cation Binding. The binding properties of the aza-12-crown-4 lariat ethers with cations such as K^+ or NH_4^+ have not been studied extensively. It is known that log K_S for ammonium binding to 12-crown-4 is only 1.3.[3] Binding for these cations to N-substituted, 12-membered ring lariat ethers is expected to increase as the number of side-arm donor atoms increases. The ring-bound cation may be solvated by the additional donor atoms, resulting in a more stable cation complex.

Since the highest equilibrium binding constant for Na^+ was obtained for the 15- and 18-membered ring analogues of *N*-1-(3,6,9-trioxadecyl)aza-12-crown-4 (**5**), and K^+ and NH_4^+ binding constants were determined for this ligand. The values obtained were 3.85 for K^+ and 3.29 for NH_4^+. In a study conducted several years ago, we found that NH_4^+ binding in series of 15- and 18-membered lariat ether compounds suggested that each hydrogen bond was worth about 1.2 log units in binding constant (in MeOH at 25 °C).[12] A study of CPK molecular models suggests that

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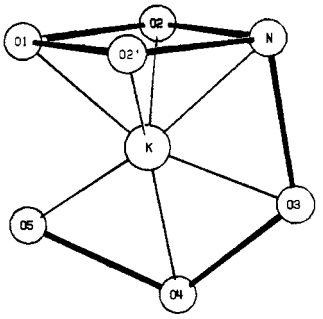

Figure 4. Skeletal drawing of the potassium complex of *N*-(3,6,9-trioxadecyl)aza-12-crown-4.

no more than three hydrogen bonds are possible in the 12-membered ring cases, and the maximum binding is 3.29. Our empirical formula would suggest maximum binding of 3.6 rather than 3.3, but these numbers are close enough to offer confirmation of the three hydrogen bond notion. Similar NH_4^+ binding constants were also found with compounds **8** and **9**, indicating that only three hydrogen bonds form.

The K^+ binding constant is 0.2 log K_S units higher than the Na^+ binding constant for compound **5**. This indicates that the side arm as well as the macroring donors can effectively solvate the cation. The "hole-size" effect[4] is thus not applicable since K_S is higher for K^+ than for Na^+.

Structure and Selectivity in Ion Binding. A comparison of the structures of **3**·NaI (Figure 3) and **5**·KI (Figure 4[2]) reveals that the effective ionic radius of a cation dictates the length of the side arm needed for strong binding. Figure 3 shows that a 3-oxabutyl side arm provides a large enough cavity to encapsulate a hemisphere of the sodium cation. The O2–Na–O4 angle is nearly linear (174.7°) and the O2–N–O4 angle is slightly acute (87.4°). Figure 4 shows that the first side-arm oxygen (O3) does not encapsulate a potassium cation as much as a sodium cation. The O1–K–O3 angle is not linear (160.3°) and the N1–N–O3 angle is obtuse (97.5°). The structural results parallel the chain length effects on binding (see Table II and Figure 1). The 3,6,9-trioxadecyl side arm binds potassium cation 13-fold better than the 3-oxabutyl side arm, but for sodium cation the enhancement is only 2.5-fold.

Conclusion

The complexation phenomenon is too complicated to be explained by the simple hole-size relationship for any size macrocycle. This is especially so for the 12-membered ring, which cannot accommodate either Na^+ or K^+ in the intraring cavity. As demonstrated by our results, other factors such as flexibility and ligand conformation, total number of donors, placement of donors, and solvation energies for the cation, macrocycle, and complex all influence binding.[11]

Experimental Section

^1H NMR spectra were recorded on a Varian EM 360A or on a Hitachi Perkin-Elmer R-600 high-resolution NMR spectrometer in $CDCl_3$ and are reported in ppm (δ) downfield from internal Me_4Si. ^{13}C NMR spectra were recorded on a Varian FT-80 A NMR spectrometer as noted above. IR spectra, recorded on a Perkin-Elmer Model 298 or a 599 infrared spectrophotometer, were calibrated against the 1601-cm^{-1} band of polystyrene. Gas–liquid chromatography was performed on a Varian 1420 instrument (t.c. detector using 6 ft × 0.25 in. 10% SE-30 on NAW Chromosorb P). Melting points were determined on a Thomas-Hoover apparatus in open capillaries and are uncorrected. TLC analyses were performed on aluminum xoide 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). All reactions were conducted under dry N_2 unless otherwise noted. All reagents were the best grade commercially available and were dried, distilled, and/or recrystallized as appropriate, prior to use. 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 percentages.

Equilibrium cation stability (binding) constants (reported here as log K_S) were measured in absolute MeOH at 25 ± 0.1 °C with a Corning 476210 electrode for Na^+ or a Corning 476220 for K^+ and NH_4^+ and an Orion Model 701A Ionalyzer meter according to the method previously described.[7]

$CH_3(OCH_2CH_2)_nOTs$. A slurry of *p*-TsCl (4.0 g, 0.02 mol) and pyridine (5 mL) was stirred while the temperature was maintained at ca. 0 °C (ice–water bath). The desired oligoethylene glycol monomethyl ether (0.02 mol) was obtained by careful vacuum fractionation. Purity was assessed by gas chromatographic methods. The alcohol dissolved in an equal weight of pyridine was added dropwise. After addition, the mixture was stirred for 15–20 min, poured into ice–water (25 mL), and washed with CH_2Cl_2 (2 × 25 mL). The organic layer was washed with ice-cold 6 N HCl (2 × 50 mL) and evaporated to minimum volume. Tosylates thus prepared were ≥90% pure by ^1H NMR spectroscopy and were used as obtained.

Aza-12-crown-4, 1, was obtained as previously described[2,9h] by hydrogenolysis (H_2, 10% Pd–C, absolute EtOH) of *N*-benzylaza-12-crown-4, **12**. Sublimation (60 °C/0.05 Torr) gave **1** (5.0g, 95%) as a white hygroscopic solid with physical and spectroscopic properties identical with those reported.[5]

Alkylation of Aza-12-crown-4. Aza-12-crown-4 (1.0 g, 0.006 mol) was dissolved in MeCN (25 mL) containing anhydrous Na_2CO_3 (0.7 g, 0.007 mol) and heated to reflux. A solution of the incipient side arm as its tosylate (0.006 mol) in MeCN (10 mL) was added dropwise. Reflux was continued for 20–24 h, the mixture was cooled and filtered, and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 or $CHCl_3$ (30 mL) and washed with H_2O (30 mL), brine (30 mL), and again with H_2O (30 mL). The organic layer was dried (Na_2SO_4 or $MgSO_4$) and concentrated in vacuo to yield the crude N-substituted azacrown. The pure crown was obtained after column chromatography (Al_2O_3) and subsequent Kugelrohr distillation.

General Cyclization Procedure. The N-substituted aza-12-crown-4 lariat ethers were prepared essentially as described by Dale.[5] A stirred solution of 1,11-diiodo-3,6,9-trioxaundecane (4.3 g, 0.01 mol) and the primary amine (0.011 mol) in MeCN (150 mL) containing Na_2CO_3 (5.3 g, 0.05 mol) was heated to reflux under N_2 for 18 h. The mixture was cooled, filtered, and concentrated. The residue was stirred in CH_2Cl_2 (150 mL) and filtered to remove residual salts, and the solvent was evaporated. The pure product was obtained after chromatography (Al_2O_3) and molecular distillation in a Kugelrohr apparatus.

***N*-(3-Hydroxyprop-1-yl)aza-12-crown-4, 2,** was prepared in 56% yield as previously described,[1g] bp 112–115 °C (0.1 Torr).

***N*-(3-Oxabut-1-yl)aza-12-crown-4, 3,** was prepared according to the method of Dale[6] as previously described.[1g] The lariat ether was isolated as a solid (60%) NaI complex, which was prepared by adding 1.05 equiv of NaI to a CH_2Cl_2 solution of the ligand. After being stirred at room temperature for approximately 1 h, the solution was filtered and concentrated in vacuo. Recrystallization from anhydrous tetrahydrofuran (THF) provided the pure **3**·NaI as a white crystalline solid (mp 204–205 °C). Anal. Calcd for $C_{11}H_{23}NO_4NaI$: C, 34.47; H, 6.06; N, 3.66. Found: C, 34.60; H, 6.20; N, 3.57.

***N*-(3,6-Dioxahept-1-yl)aza-12-crown-4, 4,** was prepared in 66% yield by alkylation of **1** as previously reported,[1g] bp 96–101 °C (0.7 Torr).

***N*-(3,6,9-Trioxadec-1-yl)aza-12-crown-4, 5,** was prepared in 52% yield by alkylation of **1** as previously reported,[1g] bp 155–160 °C (0.03 Torr).

***N*-(3,6,9,12-Tetraoxatridec-1-yl)aza-12-crown-4, 6,** was prepared in 54% yield by alkylation of **1** as previously described,[1g] bp 138–141 °C (0.05 Torr).

***N*-[11-(Allyloxy)-3,6,9-trioxaundec-1-yl]aza-12-crown-4, 7,** was prepared in 51% yield as described previously,[1g] bp 160–165 °C (0.03 Torr).

Table IV. Crystal Data and Data Collection Parameters

formula	$C_{11}H_{23}NO_4NaI$
fw	383.2
cryst system	triclinic
space group	$P\bar{1}$
a, Å	8.712 (2)
b, Å	8.694 (3)
c, Å	11.740 (3)
α, deg	111.44 (2)
β, deg	90.76 (2)
γ, deg	103.50 (2)
V, Å^3	800.0 (9)
Z	2
D_c, g cm^{-3}	1.591
T, deg	23
μ, cm^{-1}	20.10
$F(000)$	384
cryst size, mm	0.24 × 0.40 × 0.60
θ limits, deg	1–30
scan rates, deg min^{-1}	0.56–4.0
min rel absorption coeff	88.02
precision, $I/\sigma(I)$	25
max. scan time, s	120
unique data	4653
observed data	3723
variables	164
B for H atoms, Å^2	7.0
R	0.035
R (all data)	0.052
R_w	0.044
GOF	2.046
max. residual, e Å^{-3}	0.68

***N*-(3,6,9,12,15-Pentaoxahexadec-1-yl)aza-12-crown-4, 8,** was prepared by alkylation as described above from 3,6,9,12,15-pentaoxahexadecyl tosylate (2.4 g, 0.006 mol). Chromatography of the crude product (Al_2O_3, 50% EtOAc/hexane) and molecular distillation yielded **8** (69%, 1.70 g), bp 175–180 °C (0.15 Torr). ^{1}H NMR: δ 2.67 (t, 6 H), 3.17 (s, 3 H), 3.50 (m, 30 H). ^{13}C NMR: δ 56.31, 56.69, 70.59, 71.10, 71.23, 71.96, 72.64. IR: 2860, 1440, 1360, 1300, 1250, 1120, 1030, 930, 840 cm^{-1}. Anal. Calcd for $C_{19}H_{39}NO_8$: C, 55.71; H, 9.62; N, 3.42. Found: C, 55.80; H, 9.70; N, 3.24.

***N*-[[Methoxyoctakis(ethyleneoxy)]ethyl]aza-12-crown-4, 9,** was prepared by alkylation of **1** as described above from the octaethylene glycol monomethyl ether (obtained by fractionation of material having av MW = 350) tosylate (3.2 g, 0.006 mol). Chromatography of the crude product (Al_2O_3, 50% EtOAc/hexane) yielded **9** as a pale yellow oil (2.2 g, 69%). ^{1}H NMR: δ 2.68 (t, 6 H), 3.30 (s, 3 H), 3.60 (m, 42 H). ^{13}C NMR: δ 56.26, 56.62, 70.50, 71.04, 71.20, 71.91, 72.59. IR: 2850, 1470, 1450, 1350, 1300, 1250, 1110 (broad), 930, 840, cm^{-1}. Anal. Calcd for $C_{25}H_{51}NO_{11}$: C, 55.42; H, 9.51; N, 2.59. Found: C, 55.82; H, 9.70; N, 2.75.

***N*-(2-Methoxyphenyl)aza-12-crown-4, 10,** was prepared by cyclization in 26% yield as previously described,[1g] bp 130–135 °C (0.05 Torr).

***N*-(4-Methoxyphenyl)aza-12-crown-4, 11,** was prepared in 40% yield by cyclization as described above from 4-methoxyaniline as previously reported,[1g] bp 142–143 °C (0.03 Torr).

***N*-Benzylaza-12-crown-4, 12,** was prepared by the method of Dale[6] as previously reported[1g] except that the crown compound was isolated by chromatography over a column of Al_2O_3 (10% EtOAc/hexane). Pure **12** was obtained in 54% yield (1.43 g) after Kugelrohr distillation, bp 122–125 °C (0.05 Torr) [lit.[5] bp 140–143 °C (0.05 Torr)].

***N*-(2-Methoxybenzyl)aza-12-crown-4, 13,** was isolated in 47% yield from the cyclization reaction described above with 2-methoxybenzylamine as previously reported,[1g] bp 150–153 °C (0.03 Torr).

***N*-(2-Nitrobenzyl)aza-12-crown-4, 14,** was prepared in 86% yield by alkylation of **1** with 2-nitrobenzyl chloride as previously reported,[1g] as shiny needles, mp 37–38 °C.

***N*-[[Methoxyoctakis(ethyleneoxy)]ethyl]aza-15-crown-5, 15,** was prepared as previously described[1g] except that the material was used for measurements as soon as possible and the sample was protected against heat and light.

***N*-[[Methoxyoctakis(ethyleneoxy)]ethyl]aza-18-crown-6, 16,** was prepared as previously described,[1g] but the material was used for binding constant measurements as soon as possible and the sample was carefully protected against heat and light.

X-ray Crystal Structure Data. Intensity data were collected by using a crystal sealed in a capillary on an Enraf-Nonius CAD4 diffractometer equipped with Mo Kα radiation (λ = 0.71073 Å) and a graphite monochromator, by θ – 2 scans designed to yield equal relative precision, $I = 25\sigma(I)$, for all observed data, subject to a maximum scan time. Cell dimensions were obtained from a least-squares fit to the setting angles of 25 reflections having $12.0° < \theta < 13.0°$. One hemisphere of data was collected; angular limits and other experimental parameters are listed in Table I. Data reduction included corrections for background, Lorentz, and polarization effects. Absorption corrections were based on ψ scans. Data having $I > 3\sigma(I)$ were considered observed and used in the refinement.

The structure was solved by heavy-atom methods and refined by full-matrix least squares based on F with weights $w = \sigma^{-2}(F_o)$, using the Enraf-Nonius SDP.[15] Scattering factors were those of Cromer and Waber[16] with anomalous coefficients of Cromer.[17] Non-hydrogen atoms were treated anisotropically. Hydrogen atoms were located by difference maps and included as fixed contributions with $B = 7.0$ Å^2. Final R factors and residual electron density are given in Table IV.

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Registry No. **1**, 41775-76-2; **2**, 96530-19-7; **3**, 80649-19-0; **3**·NaI, 116634-75-4; **4**, 98269-19-3; **5**, 96530-20-0; **5**·1H, 116634-76-5; **6**, 98269-20-6; **7**, 96530-21-1; **8**, 116597-15-0; **9**, 116597-16-1; **10**, 90774-27-9; **11**, 96530-17-5; **12**, 84227-47-4; **13**, 90774-28-0; **14**, 96530-18-6; **15**, 116634-73-2; **16**, 116634-74-3; $CH_3(OCH_2CH_2)_5OH$, 23778-52-1; $CH_3(OCH_2)_5OTs$, 80755-67-5; $CH_3(OCH_2CH_2)_8OH$, 25990-96-9; $CH_3(OCH_2CH_2)_8OTs$, 82217-01-4.

Supplementary Material Available: Tables of hydrogen atom coordinates, anisotropic thermal parameters, and bond distances and angles (6 pages); tables of structure factors (20 pages). Ordering information is given on any current masthead page.

(15) Frenz, B. A.; Okaya, Y. *Enraf-Nonius Structure Determination Package*; Delft: Holland, 1980.
(16) Cromer, D. T.; Waber, J. T. *International Tables for X-ray Crystallography*. Kynoch: Birmingham, England, 1974; Vol. IV, Table 2.2B (Distr.: D. Reidel, Dortrecht, Holland).
(17) Cromer, D. T. *International Tables for X-ray Crystallography*; Kynoch: Birmingham, England, 1974; Vol. iV, Table 2.3.1 (Distr.: D. Reidel, Dortrecht, Holland).