Enhancement of Cation Binding in Lariat Ethers Bearing a Methyl Group at the Quaternary, Pivot Carbon Atom†

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A number of carbon-pivot lariat ethers have been prepared and compared, with their counterparts having a methyl group bonded to the side-arm-bearing or pivot carbon. All of the compounds examined are 15-crown-5 derivatives, and in this series, the methyl lariats invariably show a higher affinity for sodium than do the nonmethylated species. The results are less consistent in the case of potassium cation which is larger than the 15-crown-5 compound's cation binding hole. The enhanced stability constant observed for sodium with the methyl lariats is attributed to reduced side-arm mobility or conformational changes in either the side arm or macroring.

The class of molecules to which we have given the cognomen "lariat ethers"[1] is characterized by a macrocylic "crown" polyether ring and a donor group attached to the ring by a suitable, flexible side chain. The two principal groups of molecules thus far explored are the "carbon-pivot" lariats which derive from a glycerol unit[1,2] and the "nitrogen-pivot" molecules which derive from a diethanolamine unit.[3-6] Of these two groups, the nitrogen-pivot molecules have proved to be quite flexible and strong cation binders while the carbon-pivot molecules have proved to be less flexible and to exhibit weaker cation binding strength.[7] We now report that placement of a methyl group on the "pivot carbon atom" significantly influences cation-binding strength in carbon-pivot lariat ethers.[8]

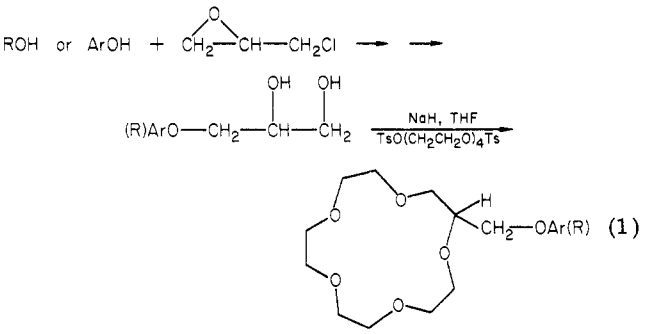
Results and Discussion

Synthesis. The lariat ethers described in this paper all fall into the same category of "carbon-pivot" molecules, i.e., the donor-group-bearing side chain is attached to the macrocycle at carbon.[1] Compounds of this type derive nominally from the glycerol unit but are prepared from the glycerol equivalent epichlorohydrin.[9]

Treatment of epichlorohydrin with a fourfold excess of an alcohol in the presence of catalytic boron trifluoride affords the corresponding chlorohydrin ether in good yield. The excess alcohol can be removed readily if it is volatile, as all in the present case are. Treatment of the halohydrin ether with strong base (50% aqueous NaOH) recloses the epoxide ring to afford the glycidyl ether. Although the chlorohydrin ether could be hydrolyzed directly to the diol, conversion of the epoxide to the diol is more efficacious. This step is accomplished by using aqueous perchloric acid solution.[9]

Cyclization of the diol is accomplished in the standard fashion[10] by using NaH as the base in concert with tetraethylene glycol ditosylate or dimesylate. Although yields are comparable with the two sulfonates, NaOMs which forms as a byproduct from the latter during reaction is more troublesome to remove during the workup. The overall sequence is shown in eq 1.

2-[(Benzyloxy)methyl]-15-crown-5 is prepared in this way from benzyl alcohol. Hydrogenolysis (Pd/C) affords 2-(hydroxymethyl)-15-crown-5 (93%) which is a versatile intermediate in our program. It may be used as a nucleophile and alkylated to form alkoxymethyl crown ethers



(1)

or it may be tosylated to afford an electrophilic precursor to other crown ethers. 2-[(Tosyloxy)methyl]-15-crown-5 is treated with dimethylcopper–lithium to afford 2-ethyl-15-crown-5 (2) in nearly 50% yield.

Synthesis of the methyl lariats is accomplished in three steps. First, treatment of methallyl chloride with a fivefold excess of tetraethylene glycol affords the monoether in nearly 90% yield. The lipophilic monoether tetraethylene glycol mono-2-methylallyl ether (TGME) is readily separated from residual tetraethylene glycol by partitioning it between diethyl ether and water. Virtually no methallyl chloride remains, but any residue can be removed easily by distillation.

In the second step of this reaction sequence, TGME is treated with *N*-bromosuccinimide in 1,2-dichloroethane solution. In this instance, NBS acts as a brominating agent toward the double bond rather than toward the allylic position. Bromination occurs, as expected, from the less

† Crown Cation Complex Effects. 22.

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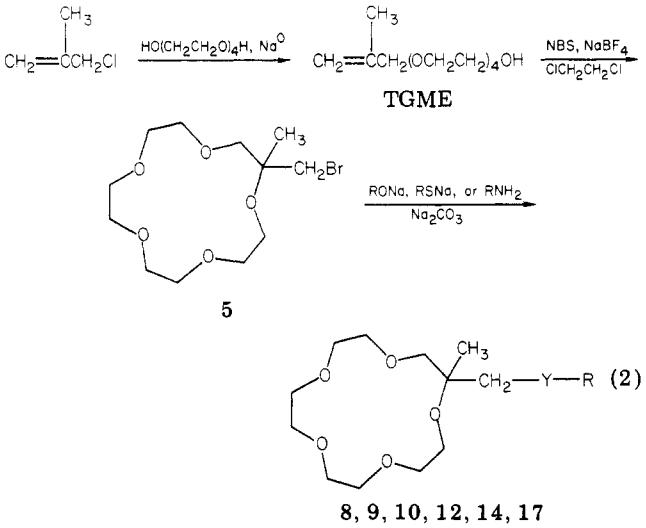
substituted side of the alkene with formation of the more stable carbocation. The tertiary carbocation is intercepted intramolecularly by the hydroxyl group.[11] This reaction is probably favored by the templating effect of sodium cation which is also present in this solution as the tetrafluoroborate salt.[1,6]

Although the intramolecular interception of this cation may seem unusual, in fact, the intermolecular equivalent, styrene being converted into 2-bromo-1-hydroxy-1-phenylethane, has been known for nearly 3 decades.[12] The cyclization affords the crown in 30% yield after distillation. It is interesting to note that if the reaction mixture is allowed to stand, crystals of the $NaBF_4$ complex deposit, and the macrocycle may be isolated from these in 20% yield, as well.

Once 2-methyl-2-(bromomethyl)-15-crown-5 (**5**) has been obtained, it may be converted into various methyl lariats by nucleophilic displacement of the primary bromide. This displacement approach is straightforward despite the fact that the halide is in essentially a neopentyl arrangement. It is not quite a neopentyl situation, however, since one methyl group is replaced by a substantially smaller oxygen atom. Further, it seems likely that crown activation of the nucleophile assists the reaction. The entire sequence is illustrated in eq 2.



Binding Studies. The primary goal of the effort discussed here was to determine the effect of placing a quaternary methyl group bonded to the pivot carbon bearing the side chain. Within this context, the effects of several variables were considered. First, we knew from previously reported work that a simple CH_2OR side chain would not enhance binding.[1,2] This was apprehended from two lines of evidence. First, an examination of Corey–Pauling–Koltun molecular models suggested that the (β) heteroatom could not be extended over the ring-bound cation and afford anything approaching axial solvation. Second, actual measurements of binding between Na^+ and 15-crown-5 (**1**) and (methoxymethyl)-15-crown-5 (**4**) showed a smaller stability constant for the latter complex compared to the former. The information developed from the stability constants was confirmed for less polar solvents by measuring the extraction constants as well.[1] It is interesting to note, however, that as chain length increased, binding strength followed suit. In fact, sodium cation binding was enhanced by a simple increase in lipophilicity as witnessed for **7** and **4** although the opposite effect was observed for potassium cation binding. The binding data are summarized in Table I.

Table I. Stability Constants for Complexes between Lariat Ethers and Sodium or Potassium Chlorides[a]

compd	substituents in the 2-positions of 15-crown-5	log K_s[b] Na^+	log K_s[b] K^+
1	H, H	3.27,[c] 3.31,[d] 3.48[e]	3.60,[c] 3.34,[d] 3.77[e]
2	H, CH_2CH_3	[f]	3.29
3	H, n-C_6H_{13}	3.20	3.13
4	H, CH_2OCH_3	3.03	3.27
5	CH_3, CH_2Br	2.86	2.70
6	H, CH_2O-n-C_7H_7	3.05	[f]
7	H, CH_2O-n-C_8H_{17}	3.18	3.09,[g] 2.41[h]
8	CH_3, CH_2O-n-C_6H_{13}	3.57	3.35
9	CH_3, CH_2S-n-C_6H_{13}	3.08	2.98
10	CH_3, CH_2NH-n-C_6H_{13}	3.08	2.94
11	H, $CH_2OCH_2CH_2OCH_3$	3.05	3.32
12	CH_3, $CH_2OCH_2CH_2OCH_3$	3.87	3.42
13	H, $CH_2O(CH_2CH_2O)_2CH_3$	3.13	3.50[i]
14	CH_3, $CH_2O(CH_2CH_2O)_2CH_3$	3.89	3.98
15	H, $CH_2O(CH_2CH_2O)_3H$	3.04	3.45
16	H, $CH_2O(CH_2CH_2O)_3CH_3$	3.09	3.50
17	CH_3, $CH_2O(CH_2CH_2O)_3CH_3$	3.87	4.00

[a] In anhydrous MeOH at 25.0 ± 1.0 °C; see the Experimental Section for additional details. [b] K_s is the equilibrium constant for the reaction crown + cation = complex. [c] Values determined at the University of Maryland. [d] Values determined at Osaka University. [e] See: Lamb, J. D. Doctoral Thesis, cited in Melson, G.A., Ed. "Coordination Chemistry of Macrocyclic Compounds"; Plenum Press: New York, 1978; p 185. [f] Not determined. [g] Log K_1. [h] Log K_2. [i] This value was previously reported in error as 3.72 in ref 8.

The methyl group plays a key role in altering the binding of the lariat ether systems. It is obvious from a perusal of the table that the methyl group's presence significantly alters the cation binding of crowns which have donor atoms suitably placed to afford secondary axial solvation, but there also seems to be a significant increase in the binding of those compounds which are incapable of strong binding in the absence of the methyl group.

An interesting comparison is seen for compounds **7** and **8**. The former has a fairly lipophilic side chain and is expected to recover some of the binding loss which occurs on addition of any side chain to **1**. In fact, log K_s (Na^+) values for **1** and **7**, respectively, are 3.3 and 3.2. The n-hexyl side chain of **8** is similar to the n-octyl side chain of **7**, and the binding constants should therefore be quite similar in the absence of some substantial methyl group effect. In fact, log K_s values for **7** and **8**, respectively, are 3.18 and 3.57 (K_s = 1513 vs. 3715). It may be that the methyl group is creating enough steric pressure on the ring to force the side-chain heteroatom into a binding configuration (see below).

That oxygen is probably becoming involved in the complexation process is demonstrated conclusively by the identity of Na^+ binding for **9** and **10** which present the macroring-bound cation with a sulfur or nitrogen, respectively. Neither of these is expected to interact well with the relatively hard sodium cation, and no binding enhancement is observed.

A similar large and remarkable difference is observed with compounds **11** and **12** each of which has two oxygens in the side arm and differ only by the presence of the quaternary methyl group at the pivot carbon. Binding of both sodium and potassium cations is substantially greater

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in 12 than in 11. The same relationship holds for the pairs 13, 14 and 16, 17. There are at least two possible explanations for this phenomenon, and these are offered below.

The relatively poor binding of the simple carbon-pivot lariat ether molecules may be attributed to the problem of "sideness". Since the side chain is permanently locked on one side of the macroring, it may become a hindrance rather than an asset to binding. When the quaternary methyl group is present, this is still the case, but now a conformational gearing between the methyl hydrogens and the side-chain methylenes (see eq 2) might prevent the side chain from swinging away from the binding site. Obviously, when a lariat ether–cation encounter occurred, very little reorganization would be required for secondary solvation to supervene.

An alternative explanation is that when the quaternary methyl group is present, the side chain becomes conformationally locked as a result, and the most flexible part of the molecule is actually the macroring. Perhaps the bound cation invariably uses the side-arm heteroatom and augments this with several of the crown oxygens for primary binding. Adjustment for optimal binding might now occur in the macroring to achieve maximal binding. Such molecular motion might account for binding enhancement in 8 compared to 7. Furthermore, the better binding of 12 compared to 11 might be accounted for similarly; i.e.; in the former case seven oxygen atoms are accessible for binding whereas only six are available in the latter complex.

It is an inherent weakness of each argument that the methyl group exhibits a strong interaction with the adjacent side-chain methylene. Although there is clearly the possibility of some interaction between the two as judged by models, it is difficult to convince oneself that this is a high-energy interaction or that it is the sole determinant of this behavior. It seems likely that the quaternary methyl group also influences the macroring conformation. If this interaction helps favor a binding conformation in the macroring, this would certainly help account for the methyl group's effect on binding strength. It seems equally plausible that the presence of the methyl group lowers the degrees of freedom present in the side arm. Since net binding must have both entropic and enthalpic components, a reduction in the side arm's mobilitiy might well be manifested in a stronger cation association constant.

Lariat Ethers in Polymer Systems. There has been considerable interest in polymer-bound macrocycles during the past few years.[14] Efforts have been made at binding the macrocycles to insoluble polymer resins[15] so that they might be used in phase-transfer or other catalytic processes.[16] The ease of synthesis of the methyl lariats and the enhanced binding provided by the side chain recommend them for this application. The special advantage, of course, is that the ether not only serves as a mechanical link between macrocycle and polymer but also participates in the binding.

Summary

A direct comparison of carbon-pivot lariat ethers with the corresponding methyl lariats demonstrates that the quaternary methyl group significantly enhances cation binding between these species and cations like Na^+ and K^+. It seems likely that the methyl group effect is due to a change in the molecules' conformational requirements. Whether it is the side arm, the macroring, or both which are principally affected by the methyl group remains unclear, but there is no question of greater side-arm participation in the cation binding process.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded on either a Perkin-Elmer 281 or a Hitachi 260-10 spectrometer by using neat samples unless otherwise specified and are calibrated against the 1601-cm^{-1} band of polystyrene. Proton NMR spectra were recorded on either a Varian EM 360 or a JEOL JNM-PS 100 spectrometer as ca. 15 wt % solutions in $CDCl_3$ unless otherwise specified. All NMR spectra are for proton nuclei, and chemical shifts are reported in parts per million (δ) downfield from internal Me_4Si. IR and mass spectral data are recorded in the supplementary material. Mass spectra were measured on a Hitachi RMU-6E instrument at an ionizing voltage of 70 eV. Gas chromatographic analyses were conducted on either a Varian 920 equipped with a thermal-conductivity detector and a 1.5 m × 5 mm 1.5% OV-101 on 100–120-mesh Chromosorb G column or on a Shimadzu GC-3BF with a 2 m × 3 mm 10% SE-30 on 60–80-mesh Celite 545 column. All new compounds had acceptable C and H analyses, and the data may be found in the supplementary material.

All reagents were the best grade commercially available and were used without additional purification, unless otherwise specified. THF was distilled from $LiAlH_4$ under an atmosphere of dry N_2 immediately prior to use. DMF was dried by distillation from CaH_2 prior to use. 15-Crown-5 was obtained from the Aldrich Chemical Co. and was distilled before use.

General Procedure for the Preparation of Nonmethyl Lariat Ethers. (A) Synthesis of the Halohydrin Ethers. The appropriate alcohol (4 equiv) and 5% $BF_3{\cdot}Et_2O$ (0.01 equiv) were mixed in a three-necked, round-bottomed flask equipped with a reflux condenser, dropping funnel, and mechanical stirrer. The mixture has heated at ca. 80 °C (oil bath temperature). Epichlorohydrin (1 equiv) was added during 1–2 h and the mixture stirred for an additional 15–20 h. The mixture was then cooled to ambient temperature, diluted with H_2O, and extracted exhaustively with CH_2Cl_2. The combined extracts were washed with brine, dried (Na_2SO_4), and reduced in vacuo to minimum volume. The crude halohydrin ether was vacuum distilled through a 10-cm Vigreux column.

(B) Conversion of the Halohydrin Ethers into the Corresponding Glycidyl Ethers. The halohydrin ether (1 equiv) obtained as described above was cooled to ca. 5 °C (ice bath temperature and NaOH (50% aqueous solution, 1.25 equiv) was added dropwise during 1 h. When the reaction was complete (as judged by TLC), water was added and the phases separated. The aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O until neutral and then with brine, dried (Na_2SO_4), and reduced to minimum volume in vacuo. If necessary, the glycidyl ether was purified by vacuum distillation.

(C) Hydrolysis of the Glycidyl Ethers. The glycidyl ether (1 equiv), H_2O (ca. 50 equiv), and 72% $HClO_4$ (0.01) equiv) were stirred at ca. 80 °C overnight. The mixture was cooled and neutralized (5% Na_2CO_3), and the water was evaporated in vacuo. Each crude 3-substituted-1,2-propanediol was purified either by recrystallization or by vacuum distillation using a 10-cm Vigreux column.

(D) Cyclization To Form Substituted 15-Crown-5 Ethers. A three-necked, round-bottomed flask, equipped with a mechanical stirrer, N_2 inlet, reflux condenser, and additional funnel, was charged with NaH (50% in oil, 10.56 g, 0.22 mol) which was washed with hexanes (3 × 100 mL) and then suspended in the THF (400 mL) with vigorous stirring. The 3-substituted 1,2-propanediol (0.10 mol) and tetraethylene glycol ditosylate (TEGTs; 50.2 g, 0.10 mol) or tetraethylene glycol dimesylate (TEGMs; 35.0 g, 0.10 mol) were dissolved in THF (100 mL) and added dropwise to the vigorously stirred, refluxing base solution. Reflux was continued for 24 h, and the reaction mixture was

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allowed to cool. If the tosylate was used, NaOTs was removed by filtration and the THF evaporated. If the mesylate was used, the solvent was evaporated directly since the NaOMs was too fine to filter. The residue from the mesylate reaction was mixed with H_2O (300 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 × 150 mL) and the solvent evaporated. The crude product from either workup was chromatographed over alumina with 0–10% (v/v) 2-propanol/hexane as the eluent. The purified products were obtained as colorless to pale yellow oils. Further purification was achieved in some cases by Kugelrohr distillation.

2-[(Tosyloxy)methyl]-15-crown-5. A 10-mL flask was charged with *p*-TsCl (0.76 g, 4.0 mmol) and pyridine (1.0 mL) and cooled in ice. (Hydroxymethyl)-15-crown-5 (see below; 1.00 g, 4.0 mmol) in pyridine (1 mL) was added over 5 min and the mixture stirred for 1 h. The mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL), and the extracts were washed with cold 6 N HCl (3 × 10 mL) and brine (10 mL) and dried (Na_2SO_4). 2-[(Tosyloxy)methyl]-15-crown-5 was obtained (87%) as a pale yellow oil which was used directly in the next step: NMR 2.45 (s, 3 H), 3.64 (m, 19 H) 4.15 (m, 2 H), 7.7 (q, 4 H).

2-Ethyl-15-crown-5 (2). Compound **2** was prepared from the above tosylate (1.4 g, 3.5 mmol) and Me_2CuLi (7.0 mmol) by using the method of Johnson and Dutra.[17] Pure **2** was obtained (49%) as a pale yellow oil after chromatography over alumina (15 g, 0–2% 2-PrOH/hexanes): NMR 0.96 (t, 3 H), 1.5 (m, 2 H), 3.7 (m, 19 H).

2-[(Benzyloxy)methyl]-15-crown-5. The title compound was prepared as described in the general procedure except that equimolar amounts of benzyl alcohol (324 g, 3.0 mol) and epichlorohydrin (278 g, 3.0 mol) were used. The chlorohydrin ether (353 g, 58%) was obtained as a colorless oil, bp 95–120 °C (0.03 torr) [lit.[18] bp 104 °C (0.01 torr)].

The halohydrin ether above (353 g, 1.76 mol) was converted into the glycidyl ether as described in the general procedure. 3-(Benzyloxy)propene 1,2-epoxide was obtained (263 g, 92%) as a colorless oil which was pure by GC analysis and NMR: 2.3–2.75 (m, 2 H), 2.8–3.3 (m, 2 H), 4.47 (s, 2 H), 7.15 (s, 5 H).

The epoxide (262 g, 1.6 mol) was hydrolyzed and then distilled to afford 3-(benzyloxy)-1,2-propanediol: 264 g (90%); bp 127–136 °C (0.04 torr) [lit.[19] bp 142–146 °C (0.6 torr)]; NMR 2.8–4.0 (m, 7 H), 4.50 (s, 2 H), 7.25 (s, 5 H).

2-(Benzyloxy)-15-crown-5 was prepared as described in the general procedure from the diol (see above; 18.2 g, 0.10 mol) and TEGTs (50.2 g, 0.10 mol). It was obtained (18.0 g) as a yellow liquid which was distilled (Kugelrohr) to give the pure crown; 12.4 g (36%); bp 164–166 °C (0.02 torr); NMR 3.6 (m 21 H), 4.5 (s, 2 H), 7.26 (s, 5 H).

2-*n*-Hexyl-15-crown-5 (3). This compound was prepared as previously reported.[20]

2-[(Methoxy)methyl]-15-crown-5 (4). Compound **4** was prepared according to the general procedures from 1-chloro-3-methoxypropan-2-ol derived in turn from MeOH (128 g, 4 mol). The crude halohydrin was purified by vacuum distillation (10-cm Vigreux column): yield 77 g (62%); bp 81–85 °C (25 torr) [lit.[21] bp 79–79.3 °C (23 torr)]; NMR 2.93 (d, 1 H), 3.37 (s, 3 H), 3.4–4.1 (m, 5 H). 3-Methoxypropene 1,2-epoxide was prepared from the above halohydrin (50 g, 0.40 mol) and purified by distillation (10-cm Vigreux column) to yield the pure oxirane: 31 g (88%); colorless liquid; bp 105–107 °C (760 torr) [lit.[10] bp 110.5 °C (760 torr)]; NMR 2.63 (m, 2 H), 3.13 (m, 1 H), 3.30 (s, 3 H), 3.60 (m, 2 H). Hydrolysis of the epoxide (29.3 g, 0.33 mol) gave (after vacuum distillation) 3-methoxy-1,2-propanediol as a colorless oil: 29.2 g (83%); bp 115–119 °C (25 torr) [lit.[22] bp 73–75 °C (0.3 torr)]; NMR 3.38 (s, 3 H); 3.4–4.1 (m, 7 H). Compound **4** was prepared from 3-methoxy-1,2-propanediol (10.5 g, 0.10 mol) and TEGTs. The crude product was chromatographed (alumina, 0–4% 2-PrOH/ligroin) to give pure **4**: 6.04 g (23%); NMR 3.46 (s, 3 H), 3.76 (br s, 21 H).

Tetraethylene Glycol Mono-2-methylallyl Ether (15-Hydroxy-2-methyl-4,7,10,13-tetraoxa-1-pentadecane, TGME). 2-Methylallyl chloride (29.9 g, 0.33 mol) was added dropwise to a solution prepared by dissolving sodium metal (6.9 g, 0.3 mol) in tetraethylene glycol (291.3 g, 1.5 mol) over a 2-h period at 80 °C. The resulting mixture was stirred for an additional 2 h at 80 °C and was then cooled to room temperature. TGME was readily separated from excess tetraethylene glycol by extraction with ether. The product was further purified by distillation in vacuo to give a colorless liquid: bp 100 °C (0.05 torr; (Kugelrohr apparatus); yield 89%; NMR (CCl_4) 1.70 (s, 3 H), 3.05 (s, 1 H), 3.44–3.64 (m, 16 H), 3.84 (s, 2 H), 4.88 (m, 1 H).

2-(Bromomethyl)-2-methyl-15-crown-5 (5). Tetraethylene glycol mono-2-methylallyl ether (TGME; 12.42 g, 0.05 mol) in 1,2-dichloroethane (150 mL) was added dropwise to a stirred suspension of *N*-bromosuccinimide (NBS; 8.9 g, 0.05 mol) and $NaBF_4$ (21.96 g, 0.2 mol) in 1,2-dichloroethane (250 mL) over a 2-h period at 45 °C; the mixture was stirred for 5 h at 50 °C. The reaction progress was followed by GLC and continued until no halide remained. The reaction mixture was filtered and the solvent evaporated. Ether was added to this residue, and the insoluble matter (mainly succinimide) was removed by filtration. The filtrate was evaporated under reduced pressure to give 16.7 g of a brown viscous liquid. The crude product was purified by chromatography over silica gel (hexane/acetone, 95:5) and then distilled [Kugelrohr, bp 100 °C (0.05 torr)] to give **5** (4.91 g, 30%) as a slightly yellow liquid.

When the filtrate (without succinimide) was allowed to stand for a few days at room temperature, a white precipitate (crown ether–$NaBF_4$ complex) separated out. The crystals were collected by filtration and were subjected to distillation under reduced pressure [Kugelrohr, bp 140 °C (0.05 torr)] to give **5** (20%) as a slightly yellow liquid. With this purification method the yield is relatively low, but the operation is very easy compared to the column purification method.

Pure **5** had the following: n_D^{20} 1.4913; NMR (CCl_4) 1.20 (s, 3 H), 3.44–3.68 (m, 20 H).

2-[(Allyloxy)methyl]-15-crown-5. The title compound was prepared according to the general procedure from commercial (Aldrich) allyl glycidyl ether (500 g, 4.38 mol) which was hydrolyzed to 3-(allyloxy)-1,2-propanediol. Pure diol (498 g, 86%) was obtained after distillation: bp 76–83 °C (0.04 torr) [lit.[11] bp 111–114 °C (3.0 torr)]; NMR[23] and IR[24] spectra were identical with those reported. The title compound was prepared from 3-(allyloxy)-1,2-propanediol (54.1 g, 0.41 mol) and TEGTs (206 g, 0.41 mol). The crude material (96 g) was extracted exhaustively (hexanes) to afford a pale yellow oil (66 g) which was vacuum distilled to give pure crown: 40 g (34%); bp 134–140 °C (0.05 torr); NMR (CCl_4) 3.53 (br s, 21 H), 3.8–4.0 (d, 2 H), 4.9–5.3 (m, 2 H), 5.5–6.1 (m, 1 H).

2-(*n*-Propoxymethyl)-15-crown-5 (6). Hydrogenation of 2-[(allyloxy)methyl]-15-crown-5 (1.45 g, 5.0 mmol) in absolute EtOH (50 mL) and 10% Pd/C (0.5 g) for 6 h at 25 °C afforded **6** (1.2 g, 82%) as a colorless oil: NMR (CCl_4) 0.7–1.1 (t, 3 H), 1.1–1.7 (m, 2 H), 3.55 (br s, 23 H).

2-(Hydroxymethyl)-15-crown-5. A 500-mL Parr bottle was charged with 2-[(benzyloxy)methyl]-15-crown-5 (see above; 12.4 g, 0.036 mol), EtOH (absolute, 100 mL), and 10% Pd/C catalyst (200 mg). The reaction mixture was shaken for 24 h at 25 °C under H_2 (60 psi) and then filtered through a bed of Celite in a Büchner funnel, and the solvent was evaporated, affording 8.8 g of crude crown. The residue was distilled (Kugelrohr) to yield 8.4 g (93%) of analytically pure crown: NMR 2.6 (br t, 1 H), 3.63 (br s, 21 H).

Preparation of [(Octyloxy)methyl]-15-crown-5 (7). A 100-mL, three-necked flask was charged with NaH (0.42 g, 8 mmol) which was washed with hexanes (3 × 15 mL). The NaH was suspended in THF (30 mL) and the mixture heated to reflux. (Hydroxymethyl)-15-crown-5 (2.00 g, 9 mmol) in THF (8 mL) was

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added dropwise over 0.5 h, and stirring was continued for 0.5 h. *n*-Bromooctane (1.54 g, 8 mmol) in THF (8 mL) was added in a stream. The mixture was stirred for 10 h at reflux and then cooled, filtered, and concentrated in vacuo. The residue was taken up in CH_2Cl_2 (50 mL), washed with H_2O (25 mL) and brine (25 mL), dried (Na_2SO_4), and then reduced to minimum volume in vacuo. The crude product was Kugelrohr distilled. Compound **7** (1.86 g, 64%) was isolated as a colorless oil: bp 162–164 °C (0.20 torr); NMR 0.88 (t, 3 H), 1.27 (br s, 12 H), 3.3–3.9 (m, 23 H).

General Procedure for the Synthesis of 2-Substituted-2-Methyl-15-crown-5. A suspension of **5** (1.80 g, 5.5 mol), the alcohol, thiol, or amine (206 mmol), and Na_2CO_3 (0.80 g, 7.5 mmol) was stirred at 120 °C for 24 h. After cooling to room temperature, the mixture was filtered to remove undissolved solids and then reduced to minimum volume in vacuo. The residue was flash distilled [120–180 °C (0.02 torr)]. The volatiles were then redistilled by using a Kugelrohr apparatus.

2-Methyl-2-[(hexyloxy)methyl]-15-crown-5 (8). The title compound was prepared as described in the general procedure and was obtained (68%) as a colorless oil: n_D^{20} 1.4619; NMR (CCl_4) 0.87 (t, 3 H), 1.16 (s, 3 H), 1.20–1.34 (m, 8 H), 3.40 (t, 2 H), 3.50 (s, 2 H), 3.60–3.68 (m, 18 H).

2-Methyl-2-[(*n*-hexylthio)methyl]-15-crown-5 (9). Compound **9** was prepared as described in the general procedure except that the reaction was conducted at 80 °C for only 9 h. The product was obtained (82%) as a colorless oil (n_D^{20} 1.5010); NMR (CCl_4) 0.88 (t, 3 H), 1.20–1.34 (s + m, 11 H), 2.50 (t, 2 H), 2.70 (m, 2 H), 3.54 (s, 2 H), 3.62–3.70 (m, 16 H).

2-Methyl-2-[(*n*-hexylamino)methyl]-15-crown-5 (10). Compound **10** was prepared as described in the general procedure and was obtained (94%) as a colorless oil: n_D^{20} 1.4704; bp 125 °C (0.02 torr); NMR (CCl_4) 0.88 (t, 3 H), 1.20–1.38 (s + m 11 H), 2.52–2.68 (s + t, 5 H), 3.56 (s, 2 H), 3.62–3.72 (m, 16 H).

2-[(2-Methoxyethoxy)methyl]-15-crown-5 (11). Compound **11** was prepared as described in the general procedure. 1-Chloro-3-(2-methoxyethoxy)propan-2-ol was prepared from 2-methoxyethanol (243 g, 3.2 mol). The crude chlorohydrin (122 g, 73%) was sufficiently pure (GC, NMR) for further use: NMR 3.40 (s, 3 H), 3.45–4.20 (m, 10 H). 3-(2-Methoxyethoxy)propene 1,2-epoxide was prepared from the halohydrin (120 g, 0.71 mol). The epoxide was purified by distillation (10-cm Vigreux column): 58 g (62%); bp 97–98 °C (25 torr) [lit.[25] bp 80–81 °C (13 torr)]; NMR 2.6–2.9 (m, 2 H), 3.20 (m, 1 H), 3.40 (s, 3 H), 3.45–4.0 (m, 6 H). Hydrolysis of this epoxide (52 g, 0.39 mol) afforded after distillation 3-(2-methoxyethoxy)-1,2-propanediol: 22.8 g (39%); bp 155–157 °C (25 torr); NMR 3.40 (s, 3 H), 3.45–4.1 (m, 11 H); IR 3400 cm^{-1} (OH). Compound **11** was prepared from the preceding diol (15.0 g, 0.10 mol) and TEGTs. Crude **11** (32 g) was chromatographed (Al_2O_3, 300 g, 0–4% 2-PrOH/hexanes) to afford a pale yellow oil. A 2-g sample was further purified (Kugelrohr): 18.7 g (61%); bp 150–155 °C (0.15 torr); NMR 3.33 (s, 3 H), 3.56 (br s, 25 H).

2-Methyl-2-[(2-Methoxyethoxy)methyl]-15-crown-5 (12). Sodim metal (0.50 g, 26 mmol) was dissolved in 2-methoxyethanol (15.0 g, 197 mmol), and **5** (1.90 g, 5.8 mmol) was added to the solution at 120 °C. The reaction's progress was followed by gas chromatography (10% SE-30) and terminated when no **5** remained. After cooling to room temperature, the mixture was filtered, and excess alcohol was removed by evaporation in vacuo. The residue was pyrolized [120–180 °C (0.02 torr)] and then distilled 120 °C (0.02 torr) by using a Kugelrohr apparatus to give **12**: 1.53 g (82%); colorless oil; n_D^{20} 1.4632; NMR (CCl_4) 1.17 (s, 3 H), 3.35 (s, 3 H), 3.42–3.68 (m, 24 H).

2-[[2-(2-Methoxyethoxy)ethoxy]methyl]-15-crown-5 (13). Compound **13** was prepared as described in the general procedure. 1-Chloro-3-[[2-(2-methoxyethoxy)ethoxy]methyl]propan-2-ol was prepared from diethylene glycol monomethyl ether (480 g, 4.0 mol). The halohydrin was obtained as a colorless oil: 119 g (56%); bp 96–100 °C (0.7 torr); NMR 3.37 (s, 3 H), 3.45–4.1 (m, 14 H). 3-[2-(Methoxyethoxy)ethoxy]propane 1,2-epoxide was prepared from the above halohydrin (106 g, 0.50 mol): yield 85 g (97%); NMR 2.67 (m, 2 H), 3.2 (m, 1 H), 3.4 (s, 3 H), 3.5–3.8 (m, 10 H). Hydrolysis of this epoxide gave 3-[2-(2-methoxyethoxy)ethoxy]-1,2-propanediol: 64 g (73%); 110–115 °C (0.05 torr); NMR 3.2 (t, 1 H), 3.37 (s, 3 H), 3.4–4.0 (m, 14 H). Compound **13** (34 g) was prepared from the preceding diol (19.4 g, 0.10 mol) and TEGTs and was isolated after chromatography (Al_2O_3) as a pale yellow oil: 16.9 g (48%); NMR 3.33 (s, 3 H), 3.7 (br s, 29 H).

2-Methyl-2-[[2-(Methoxyethoxy)ethoxy]methyl]-15-crown-5 (14). The title compound was prepared as described in the general procedure and was obtained (88%) as a colorless oil: n_D^{20} 1.4640; NMR (CCl_4) 1.14 (s, 3 H), 3.34 (s, 3 H), 3.40–3.68 (m, 28 H).

2-[[2-[2-(2-Hydroxyethoxy)ethoxy]ethoxy]methyl]-15-crown-5 (15). A 50-mL, three-necked flask was charged with NaH (50% in oil, 0.24 g, 5.0 mol) and THF (10 mL) to which **3** (1.25 g, 5.0 mol) in THF (5 mL) was added dropwise. After 20 min 2-[2-[2-(benzyloxy)ethoxy]ethoxy]ethyl *p*-toluenesulfonate (1.97 g) in THF (5 mL) was added to the flask in a stream, and the mixture was stirred for 2 h at ambient temperature, filtered, and reduced in volume. The crude amber oil (2.1 g) was column chromatographed (Al_2O_3, 20 g) to give pure benzyl-protected **15** as a colorless oil, 1.6 g (68%). Benzyl-protected **15** (4.0 g, 8.5 mol) was hydrogenolyzed (Parr bottle; EtOH, 75 mL; 10% Pd/C, 0.1 g). After 23 h under H_2 (60 psi) at ambient temperature the mixture was filtered and stripped of solvent to give **15** as a nearly colorless oil: 3.04 g (94%); NMR 2.83 (t, 1 H), 3.69 (m, 33 H).

2-[[2-[2-(2-Methoxyethoxy)ethoxy]ethoxy]methyl]-15-crown-5 (16). A 50-mL, three-necked flask was charged with NaH (50% in oil, 0.13 g, 2.7 mmol) and washed with hexanes (3 × 15 mL) followed by THF (15 mL), and then **15** (1.00 g, 2.6 mmol) in THF (5 mL) was added to the reaction flask over a 5-min period. The mixture was stirred for 20 min. Dimethyl sulfate (0.33 g, 2.6 mmol) was added in one portion. The mixture was stirred for 1 h, filtered, and stripped of solvent. Chromatography (Al_2O_3, 20 g) of the crude amber oil (1.00 g) afforded **16** as a colorless oil: 0.72 g (70%); NMR 3.37 (s, 3 H), 3.68 (m, 33 H).

2-Methyl-2-[[2-[2-(2-Methoxyethoxy)ethoxy]ethoxy]-methyl]-15-crown-5 (17). The title compound was prepared as described in the general procedure and was obtained (80%) as a colorless oil: n_D^{20} 1.4656; NMR (CCl_4) 1.17 (s, 3 H), 3.34 (s, 3 H), 3.40–3.68 (m, 32 H).

Measurement of Stability Constants. All of the binding or stability constants herein reported were determined for NaCl or KCl in anhydrous MeOH at 25 ±1.0 °C. Binding constants for the methyl lariats were determined by using Toko Na^+ 1100 and Toko K^+ 1200 electrodes for Na^+ and K^+, respectively. The emf was measured with a Beckmann 4500 digital pH meter. Binding of the nonmethylated lariat ethers was determined by using a Corning 476210 electrode for sodium and a Corning 476220 monovalent cation electrode for potassium. The temperature was maintained at 25 ± 0.1 °C in a water-free, nitrogen-purged drybox with di-*n*-butyl phthalate as the heat-transfer medium. Emf changes were determined by using Orion Model 501 or 701 Ionalyzer meters. The procedures used were those described by Frensdorff.[26] The experimental error is ± 0.02 log units in log K_s.

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Registry No. 1, 33100-27-5; **2**, 75507-15-2; **3**, 65743-07-9; **4**, 76719-73-8; **5**, 78827-95-9; **5**·$NaBF_4$, 84836-39-5; **6**, 84130-85-8; **7**, 83585-72-2; **8**, 82517-44-0; **9**, 82517-45-1; **10**, 82517-46-2; **11**, 76719-78-3; **12**, 82517-47-3; **13**, 76726-87-9; **14**, 82517-49-5; **15**, 84130-90-5; **15** (benzyl derivative), 84131-05-5; **16**, 84130-91-6; **17**, 82517-48-4; Na^+, 17341-25-2; K^+, 24203-36-9; TMGE, 78827-93-7; $TsO(CH_2CH_2O)_4Ts$, 37860-51-8; $MsO(CH_2CH_2O)_4Ms$, 55400-73-2; $HO(CH_2CH_2O)_4H$, 112-60-7; $NaBF_4$, 13755-29-8; 3-(benzyloxy)-1,2-propanediol, 4799-67-1; 1-chloro-3-methoxypropan-2-ol, 4151-97-7; 3-methoxypropene 1,2-epoxide, 930-37-0; 3-methoxy-1,2-propanediol, 623-39-2; allyl glycidyl ether, 106-92-3; 3-(allyloxy)-1,2-propanediol, 123-34-2; epichlorohydrin, 106-89-8; glycerol, 56-81-5; benzyl alcohol, 100-51-6; 2-[(benzyloxy)methyl]-15-crown-5, 75507-17-4; 2-(hydroxymethyl)-15-crown-5, 75507-25-4; 2-[(tosyloxy)methyl]-15-crown-5, 84131-00-0; methallyl

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Supplementary Material Available: Spectral and analytical data for compounds in this paper (4 pages). Ordering information is given on any current masthead page.

Crown Cation Complex Effects. 21. Spectral Evidence Bearing on the Interaction between Arenediazonium Cations and 21-Crown-7 in Nonpolar Solutions

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15-Crown-5 does not complex arenediazonium tetrafluoroborates, but 21-crown-7 is known to complex them more strongly than does 18-crown-6. Despite this, the infrared and ultraviolet band shifts for complexed vs. noncomplexed forms are far smaller for the former than for the latter. It is suggested that instead of the crown completely and tightly surrounding the diazonio function, the crown collars (nearly encircling) the diazonio group and then uses the remaining donor atom(s) either to solvate the terminal nitrogen atom or interact as a base with the π-acidic aromatic ring, providing additional stability. Since the mode by which 18-crown-6 and 21-crown-7 solvate the diazonium ion in each case differs, the spectral manifestations of this interaction differ.

Since the original observation of arenediazonium cation complexation by crown ethers,[1] there has been considerable interest in the nature of the interaction,[2-4] its effect on both the crown and cation,[5] and utilization of crown-complexed arenediazonium cations as synthetic intermediates in a variety of reactions.[6-9] Much of this work has recently been reviewed.[10]

It was established in the first report of the arenediazonium cation–crown interaction that crown rings containing fewer than about 18 members do not complex the salt, but a variety of larger ones do.[1] In later work, these observations were quantitated by kinetic studies.[11] It was shown, for example, that the rate of thermal decomposition (by the Schiemann reaction) of 4-*tert*-butylbenzenediazonium tetrafluoroborate was slowed more by 21-crown-7 than by any of the other macrocycles surveyed. A tenfold difference in decomposition rate was observed for the above reaction when 21-crown-7 was compared to the next lower homologue, 18-crown-6. This difference in reaction rate was correlated by Zollinger and co-workers[4] to an approximately tenfold difference in stability constant for the respective complexes. Although the 21-crown-7 complex of a typical arenediazonium cation is certainly stronger

Table I. Comparison of Infrared Spectral Data of Crown Complexed Arenediazonium Salts

substituent[b]	$\nu_{N\equiv N}$,[f] cm^{-1}	crown (equiv)[g]	solvent	notes
4-Me	2286	none	mull	
4-Me	2283	21-C-7 (1)	mull	*a*
4-Me	2286	21-C-7 (1)	$CHCl_3$	*c*
4-Me	2287	21-C-7 (5)	$CHCl_3$	*c*
4-Me	2275	24-C-8 (5)	$CHCl_3$	
4-MeO	2247	none	mull	
4-MeO	2261	21-C-7 (1)	mull	*a*
4-MeO	2262	21-C-7 (1)	$CHCl_3$	*c*
4-MeO	2254	24-C-8 (5)	$CHCl_3$	
4-*t*-Bu	2277	none	mull	
4-*t*-Bu	2306	18-C-6 (1)	mull	
4-*t*-Bu	2271, 2306	18-C-6 (1)	$CHCl_3$	*c, d*
4-*t*-Bu	2282	21-C-7 (1)	mull	*a*
4-*t*-Bu	2286	21-C-7 (1)	$CHCl_3$	*c*
4-*t*-Bu	2287	21-C-7 (5)	$CHCl_3$	*c*
4-*t*-Bu	2278	24-C-8 (5)	$CHCl_3$	*c*
4-*n*-BuO	2245	none	$CHCl_3$	*c*
4-*n*-BuO	2245, 2294	18-C-6 (1)	$CHCl_3$	*c, e*
4-*n*-BuO	2262	21-C-7 (1)	mull	*a*
4-*n*-BuO	2262	21-C-7 (1)	$CHCl_3$	*c*
4-*n*-BuO	2260	21-C-7 (1)	CH_2Cl_2	*c*

[a] The solid complexes had the following melting points (°C): **3**, 113-115; **4**, 118-119; **5**, 104-104.5; **6**, 78-80. [b] Benzenediazonium tetrafluoroborate salts with the indicated substituents. [c] The indicated components (0.2 mmol/equiv) were stirred with solvent (0.5 mL) until solution occurred. [d] The peak intensities were approximately 2271 (1):2308 (1.36). [e] The peak intensities were approximately 2245 (1):2294 (1). [f] Calibrated against the 1601.8-cm^{-1} line of polystyrene. [g] "C" in the abbreviations means "crown".

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