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Synthesis and Alkali Metal Picrate Extraction Capabilities of Novel, Cage-Functionalized Diaza(17-crown-5) Ethers

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Abstract. The syntheses of novel cage-annulated diaza (17-crown-5) lariat crown ethers, i.e., **10**-**16** are reported. A series of alkali metal picrate extraction experiments have been performed by using this new class of synthetic ionophores in order to evaluate the effects of cage-annulation and the influence of *N*-pivot side-arms upon complexation properties. The results thereby obtained indicate that complexation of these lariat crown ethers with alkali metal cations is influenced by both of these structural features. In particular, the cage-annulated diaza crown ether **11** displays much greater avidity toward all alkali metal cations studied than does the corresponding model system (**1**). It was observed that ligands **11** and **13** display bimodal behavior toward extraction of alkali metal picrates, whereas ligands **15** and **16** behave as relatively non-selective alkali metal picrate extractants. A cage-annulated cryptand, **19**, was prepared, and its alkali metal picrate extraction profile was obtained. Highly preorganized cryptand **19** displays particularly high avidity toward complexation of K^+ and Rb^+ picrates in solution.

Keywords. Cage compounds, Host compounds, Crown ethers, Cryptands.

Introduction. Lariat crown ethers[1] have been widely explored as mimics of naturally occuring ionophores; valinomycin,[2] which is known to be a ideal carrier for K^+, serves as an example in this regard. Lariat crown ethers are designed to achieve strong and selective three-dimensional binding of metal cations via their cooperative binding with both crown ether and electron donor-containing side-arm moieties. A variety of thermodynamic studies on the complexation of lariat crown ethers have been performed in an effort to elucidate the factors that influence cation-ligand complexation.[3] In particular, the influence of *N*-pivot and *C*-pivot side-arms have been investigated extensively via study of a variety of appropriately functionalized lariat crown ethers.[1b] Several molecules of this type have been found to display significantly enhanced avidity and selectivity toward complexation of metal cations *vis-à-vis* the corresponding parent crown ethers, in each case.[4-9]

We have previously reported the synthesis and the results of alkali metal picrate extraction studies of cage-functionalized crown ethers and cryptands.[10-13] The presence of a cage moiety confers both rigidity and lipophilicity upon the resulting crown ethers and cryptands; both factors have been shown to affect the selectivity and avidity of the resulting host systems.[10-13]

In the present study, we report the synthesis of new, cage-functionalized diaza(17-crown-5) lariat crown ethers and cryptand. We have also assessed the alkali metal picrate extraction capabilities of these compounds, which represent a new class of synthetic ionophores. The extraction efficiency of each of the new cage-annulated

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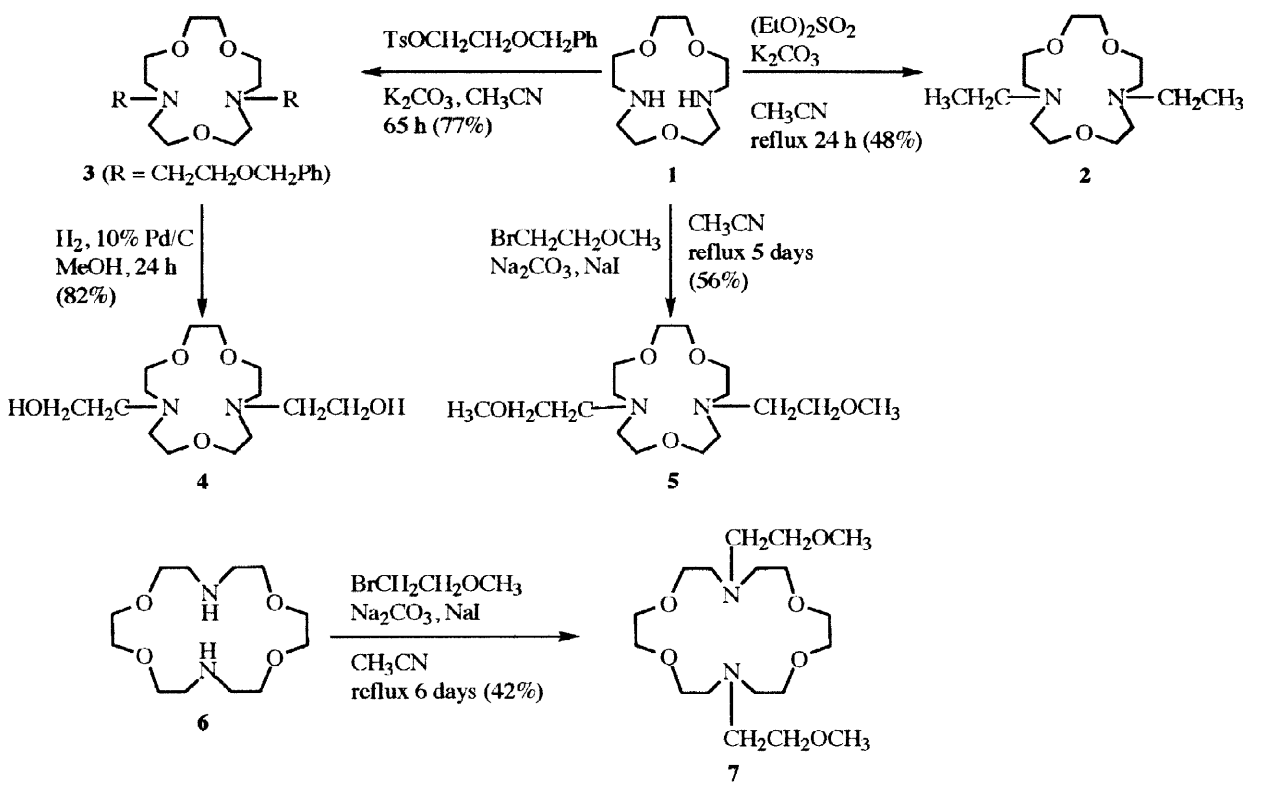
crown ethers (**11**, **13**, **15**, and **16**) was compared to that of the corresponding (non-cage annulated) model compounds (i.e., **1**, **4**, **5**, and **2**, respectively). The results obtained for alkali metal picrate extraction experiments performed by using the various lariat crown ethers (i.e., **13**, **15**, and **16**) also were compared with the extraction results obtained for the corresponding parent crown ether (**11**). Based upon the results thereby obtained, the influence of the various *N*-pivot side-arms upon the complexation properties of diazacrown ethers with alkali metal cations can be assessed. Finally, cage-functionalized cryptand **19** was synthesized, and the results of the extraction experiments were compared with those obtained for the corresponding of a non-cage-annulated model compound (**7**).

Results and Discussion. In order to evaluate the effects of cage-annulation on the complexation properties of our new cage-functionalized crown ethers and cryptands, it was neccessary to compare them with a series of structually related model compounds that lack the cage moiety. The model systems chosen for study and the procedures used to prepare these compounds are shown in Scheme 1. Thus, model compound **2** was prepared in 48% yield via base promoted reaction of **1**[14] with $(EtO)_2SO_2$. Compound **4** was prepared from **1** by using a modification of an existing literature procedure[15] (see Scheme 1). Thus, base promoted reaction of **1** with 1-benzyloxy-2-tosyloxyethane afforded the corresponding *N*-benzylated crown ether (**3**) in 77% yield. Subsequent *bis*(de-*O*-benzylation) of **3** produced **4**.[15] Model crown ethers **5**[14] and **7**[16] were prepared via a modification of a literature procedure that employs the base promoted reaction of 1-bromo-2-methoxyethane with **1** and **6**[14], respectively.

Scheme 1

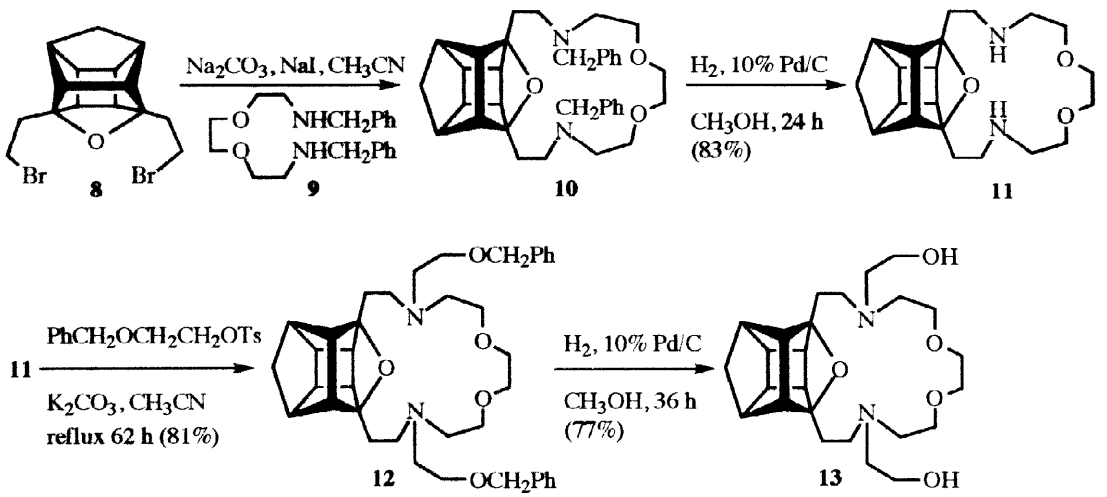


Our approach to the synthesis of cage-functionalized diaza(17-crown-5) systems is shown in Scheme 2. Thus, base promoted reaction of **8**[17] with **9**[14] afforded the corresponding *N*,*N*'-dibenzylated diaza(17-crown-5)

ether (i.e., **10**, Scheme 2). Catalytic hydrogenolysis of **10** produced **11**. Subsequent base promoted reaction of **11** with 1-benzyloxy-2-tosyloxyethane produced benzyl-protected crown ether, i.e., **12**, in 81% yield. *Bis*(de-*O*-benzylation) of **12** produced lariat crown ether **13** in 77% yield (Scheme 2).

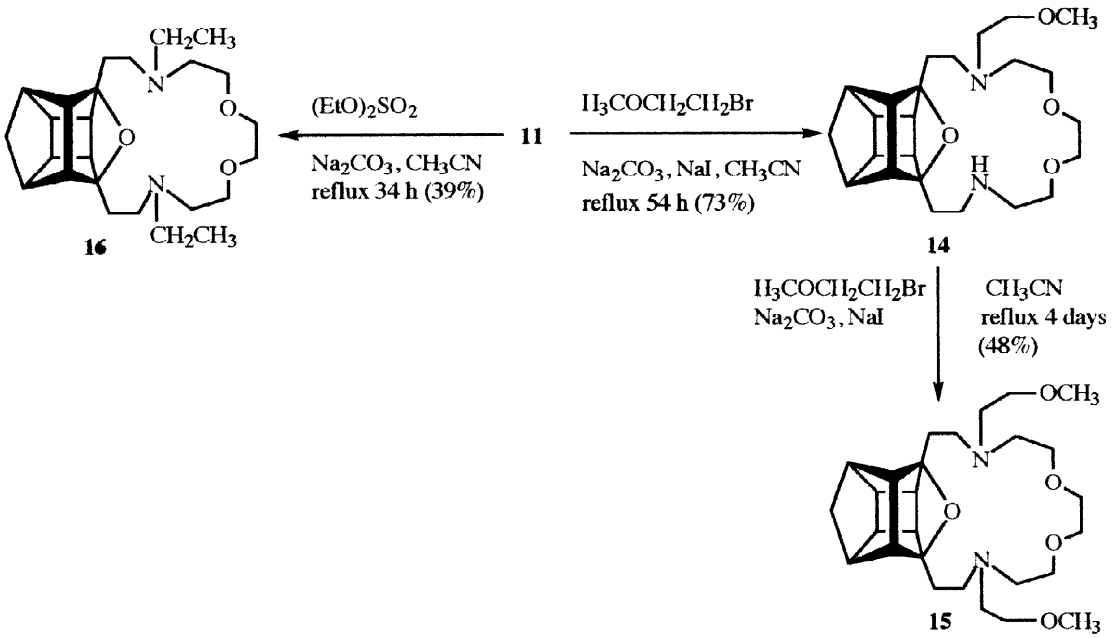
The method employed to prepare lariat crown ethers, i.e., **14**, **15**, and **16** is shown in Scheme 3. Thus, base promoted reaction of **11** with 1-bromo-2-methoxyethane produced *mono*brachial lariat crown ether, i.e., **14**,

Scheme 2



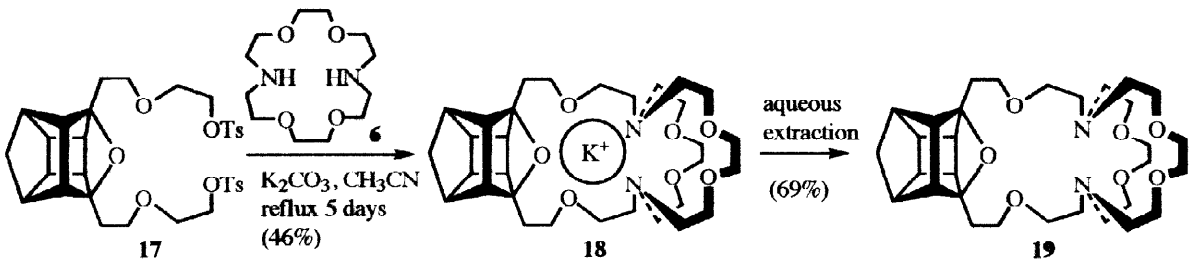
in 73% yield. Subsequent reaction of **14** with 1-bromo-2-methoxyethane afforded the corresponding *bi*brachial lariat ether, **15**, in 48% yield. Finally, crown ether **16** was obtained in 39% yield via base promoted reaction of **11** with $(EtO)_2SO_2$ (Scheme 3).

Scheme 3



The synthesis of a cage-annulated cryptand, i.e., **19**, is described in Scheme 4. Thus, K^+ templated reaction of diaza(18-crown-6) (**6**) with cage ditosylate **17**[18] produced the corresponding K^+ cryptate, **18**, in 46% yield. Subsequent continuous aqueous extraction of **18** during 24 h afforded the corresponding noncomplexed cryptand (**19**) in 69% yield. The structures of the K^+ cryptate (**18**) and the corresponding free ligand (**19**) were confirmed via analysis of their respective ^1H NMR and ^{13}C NMR spectra and via HRMS analysis (see the Experimental Section).

Scheme 4



Results of Alkali Metal Picrate Extraction Experiments. In an effort to evaluate the effect of cage-annulation and *N*-pivot side-arms, a series of alkali metal picrate extraction experiments have been performed by using the new host molecules reported herein. The results thereby obtained are shown in Table 1.

We note that cage-annulated crown ether **11** appears generally to be a more efficient alkali metal picrate extractant than its corresponding model compound, **1**. The cage moiety confers both lipophilicity and rigidity upon the crown ether moiety in **11** and also may serve to orient the donor atoms therein in a manner that is particularly favorable to promote enhanced binding between the resulting, cage-annulated host system and the various metal cations studied. Interestingly, **11** displays bimodal behavior, i.e., increased extraction avidity toward Li^+, K^+, and Cs^+ picrates *vis-à-vis* its corresponding performance as a Na^+ and Rb^+ picrate extractant. Similar discrimination among alkali metal picrates is *not* apparent in the extraction behavior of the corresponding model system, **1**.

With the exception of the extraction behavior of **16** toward Rb^+ picrate, there appears to be relatively little difference between the alkali metal picrate extracting abilities of this ligand and that of its corresponding model crown ether, **2**. It is interesing to note that **16**, which bears only alkyl side-arms (i.e., ethyl groups), displays slightly higher extracting ability toward Na^+ and Rb^+ picrates than does **11**. We suggest that the presence of the *N*-ethyl groups may induce more favorable conformational arrangement of the donor atoms in the crown moiety in **16**, thereby resulting in enhanced avidity of **16** *vis-à-vis* **11** toward Na^+ and Rb^+ picrates. We note also the reduced extracting ability of **16** toward Li^+, K^+ and Cs^+ picrates *vis-à-vis* that of **11**.

Ligand **13** appears to display bimodal behavior in a manner that is somewhat akin to that of **11**. Thus, **13** displays increased extraction avidity toward K^+ and Cs^+ picrates relative to its corresponding performance as a Li^+, Na^+, and Rb^+ picrate extractant. In contrast, its corresponding model crown ether, **4**, appears to be a virtually non-selective alkali metal picrate extractant.

Ligand **15**, which contains $CH_2CH_2OCH_3$ lariat side-arms, displays distinctly inferior ability to extract all of the alkali metal picrates studied herein when compared with the behavior of its corresponding model crown ether, **5**. In addition, **15** also is a significantly less effective alkali metal picrate extractant than **13**. Indeed, the data in Table 1 indicate that **15** displays both low avidity and low selectivity toward extraction of alkali metal picrates.

It thus becomes apparent that the binding abilities of crown ethers toward alkali metal cations indeed are influenced by (i) the presence of *N*-pivot side-arms and (ii) the nature of the electron-donating groups situated therein.

The presence of the lariat side-arms in **13**, **15** and **16** appears to have a generally deleterious effect upon the ability of these crown ethers to serve as Li^+ and K^+ picrate extractants. Thus, we note that **13**, which contains CH_2CH_2OH lariat side-arms, displays slightly greater extraction avidity toward Na^+, Rb^+, and Cs^+ picrates *vis-à-vis* **11**.

Table 1. Results of alkali metal picrate extraction experiments

	Percent of Picrate Extracted				
Host Molecule	**Li^+**	**Na^+**	**K^+**	**Rb^+**	**Cs^+**
1	13.2 ± 0.6	14.1 ± 0.6	12.6 ± 0.4	12.1 ± 0.4	8.5 ± 0.5
11	30.3 ± 0.9	17.4 ± 0.7	39.7 ± 1.1	19.4 ± 0.8	31.5 ± 1.1
2	18.8 ± 2.4	25.1 ± 1.0	22.5 ± 1.0	8.3 ± 0.6	14.4 ± 0.8
16	21.0 ± 0.8	19.7 ± 1.4	23.6 ± 0.8	24.3 ± 0.7	16.2 ± 0.7
4	29.8 ± 0.6	37.4 ± 0.5	33.4 ± 0.7	31.9 ± 0.5	33.0 ± 0.5
13	16.5 ± 1.3	22.7 ± 0.7	34.9 ± 1.6	19.9 ± 0.9	36.1 ± 1.4
5	28.6 ± 1.2	46.8 ± 0.8	37.2 ± 0.5	28.5 ± 0.7	26.9 ± 0.7
15	16.6 ± 0.6	19.1 ± 1.2	22.6 ± 0.6	16.0 ± 0.4	15.4 ± 0.8
7	17.5 ± 0.5	36.0 ± 0.7	46.3 ± 0.8	34.6 ± 0.9	21.3 ± 0.5
19	36.3 ± 0.6	50.0 ± 0.7	74.4 ± 0.8	68.4 ± 1.0	60.9 ± 0.8

[a] Averages and standard deviations calculated for data obtained from three independent extraction experiments.

The data in Table 1 indicate that incorporation of lariat side-arms into model crown ether **1** produces a dramatic effect upon its properties as an alkali metal picrate extractant. In general, we observe the following order of avidity toward extraction of alkali metal picrates: **1** ≈ **2** < **4** ≈ **5**. Whereas **4** and **5** generally are superior to **1** and **2** as alkali metal picrate extracting agents, model crown ether **5** is clearly superior to all the other model crown ethers studied as a Na^+ picrate extractant

Finally, we note that highly preorganized, cage-functionalized cryptand **19** is the most efficient alkali metal picrate extracting agent among those studied herein. As might be anticipated on the basis of the size-match principle, **19** displays particularly high avidity toward K^+ and Rb^+ picrates (74% and 68%, respectively). However, it should be noted that **19** generally displays enhanced avidity *vis-à-vis* its corresponding model crown ether, **7**, toward *all* alkali metal picrates studied.

Summary and Conclusions. A series of novel, cage-annulated 17-crown-5 ethers, i.e., **10-16** was prepared, and the ability of these host molecules to function as alkali metal picrate extraction agents has been assessed. In particular, the effects of cage-annulation and the potential influence of *N*-pivot side-arms upon the complexation properties of these host molecules have been assessed via comparison of their alkali metal extraction characteristics *vis-à-vis* the corresponding model compounds, in each case. Thus, cage-annulated diaza crown ether **11** displays much greater avidity than its corresponding model system (**1**) toward extraction of all alkali metal picrates studied, thereby attesting to the value of cage-annulation in the former system. However, there appears to be relatively little difference between the alkali metal picrate extracting capabilities of **16**, **13**, and **15** and that of their corresponding model crown ethers, i.e., **2**, **4**, and **5**, respectively. We conclude that incorporation of a cage moiety does not necessarily lead to a marked improvement the selectivity and/or avidity of crown ethers as alkali metal picrate extractants.

Lariat crown ethers that contain different side-arms display different extraction characteristics toward alkali metal cations. Thus, cage-annulated lariat crown ethers **13** and **16** (which contain CH_2CH_3 and CH_2CH_2OH side-arms, respectively) display slightly enhanced avidity toward extraction of Na^+ and Rb^+ when compared with the corresponding behavior of **11**. However, **15** (which contains $CH_2CH_2OCH_3$ side-arms) generally displays *decreased* avidity compared with the corresponding behavior of **11** toward extraction of alkali metal picrates. In order for lariat side-arms to function effectively as complexation adjuncts, it appears that electon-donor groups must be appropriately situated therein in a manner that is likely to lead to cooperative binding among the metal cation, the crown ether moiety, and the lariat side-arm. In general, we find that there appears to be no clear advantage to be gained by incorporating lariat side-arms into the cage-annulated crown ethers studied herein in terms of their ability to perform effectively as alkali metal picrate extractants.

Finally, a cage-annulated bicyclic cryptand **19** was synthesized. This highly preorganized host molecule proved to be the most efficient alkali metal picrate extractant among the various host systems included in this study. Indeed, **19** displays particularly high avidity toward K^+ and Rb^+ picrates.

Experimental Section

Melting points are uncorrected. Absorption intensities of alkali metal picrate solutions were measured at $\lambda = 374$ nm by using a Hewlett-Packard Model 84524 Diode Array UV-visible spectrophotometer. High-resolution mass spectral data reported herein were obtained by Professor Jennifer S. Brodbelt at the Mass Spectrometry Facility at the Department of Chemistry and Biochemistry, University of Texas at Austin by using a ZAB-E double sector high-resolution mass spectrometer (Micromass, Manchester, England) that was operated in the chemical ionization mode. Elemental microanalyses were performed by personnel at M-H-W Laboratories, Phoenix, AZ.

***N,N'*-Diethyl-4,10-diaza(15-crown-5) (2).** To a mixture of **1** (300 mg, 1.37 mmol) and Na_2CO_3 (580 mg, 5.49 mmol) in CH_3CN (10 ml) was added $(EtO)_2SO_2$ (420 mg, 2.75 mmol), and the resulting mixture was refluxed with stirring during 24 h. The reaction mixture was allowed to cool gradually to ambient temperature

and then was filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in boiling CH_2Cl_2 (10 mL). The resulting mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 1% MeOH-EtOAc. Pure **2** (180 mg, 48%) was thereby obtained as a colorless oil; IR (neat) 2943 (s), 1430 (m), 1312 (w), 1112 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.16 (t, J = 7.5 Hz, 6 H), 2.48 (q, 4 H), 2.55-2.70 (m, 8 H), 3.42-3.58 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 11.8 (q), 50.3 (t), 53.7 (t), 53.9 (t), 69.7 (t), 70.5 (t), 70.6 (t). Exact mass (CI HRMS) Calcd for $C_{14}H_{30}N_2O_3$: $[M_r + H]^+$ m/z 275.23347. Found: $[M_r + H]^+$ m/z 275.23318.

***N,N'*-*Bis*[(2'-benzyloxy)ethyl]-4,10-diaza(15-crown-5) (3).** To a solution of **1** (170 mg, 0.78 mmol) and 1-benzyloxy-2-tosyloxyethane (520 mg, 1.71 mmol) in CH_3CN (15 mL) under argon was added K_2CO_3 (1.10 g, 7.78 mmol), and the resulting mixture was refluxed with stirring during 65 h. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 20% EtOAc-hexane. Pure **3** (295 mg, 77%) was thereby obtained as a colorless oil. IR (neat) 3052 (w), 3031 (w), 2943 (s), 1634 (w), 1457 (m), 1120 (m), 723 (m), 698 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 2.70-2.92 (m, 12 H), 2.56-3.65 (m, 16 H), 4.55 (s, 4 H), 7.32-7.45 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 54.3 (t), 54.6 (t), 55.3 (t), 68.7 (t), 69.3 (t), 70.0 (t), 70.1 (t), 73.1 (t), 127.1 (d), 127.2 (d), 127.9 (d), 138.0 (s). Exact mass (CI HRMS) Calcd for $C_{28}H_{42}N_2O_5$: $[M_r + H]^+$ m/z 487.31720. Found: $[M_r + H]^+$ m/z 487.31690.

***N,N'*-*Bis*[(2'-hydroxy)ethyl]-4,10-diaza(15-crown-5) (4).**[15] To a solution of **3** (200 mg, 0.41 mmol) in MeOH (50 mL) was added 10% palladized charcoal (150 mg, catalytic amount). The resulting mixture was subjected to hydrogenolysis by agitation with excess H_2 (g) at 55 psig in a Parr hydrogenation apparatus at ambient temperature during 24 h. The reaction mixture was filtered through Celite®, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 10% MeOH-EtOAc. Pure **4** (100 mg, 82%) was thereby obtained as a colorless oil. The IR, ^1H NMR, ^{13}C NMR spectra of this material is essentially identical with the corresponding spectral data that has been reported previously for authentic **4**.[15]

***N,N'*-*Bis*(2-methoxyethyl)-4,10-diaza-15-crown-5 (5).** To a solution of **1** (160 mg, 0.73 mmol) and 1-bromo-2-methoxyethane (570 mg, 4.10 mmol) in CH_3CN (25 mL) under argon were added sequentially Na_2CO_3 (813 mg, 3.65 mmol) and NaI (54 mg, 1.5 mmol), and the resulting mixture was refluxed with stirring during 5 days. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (20 mL), and the resulting solution was extracted with 6 N aqueous HCl (2 × 10 mL). The combined aqueous layers were adjusted to pH 8-10 by careful, portionwise addition of solid Na_2CO_3, and the resulting mixture was extracted with $CHCl_3$ (2 × 20 mL) The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with EtOAc. Pure **5** (115 mg, 56%) was thereby obtained as a colorless oil. The IR, ^1H NMR, ^{13}C NMR spectra of this material are essentially identical with the corresponding spectral data that has been reported previously for authentic **5**.[14]

***N,N'*-*Bis*(2-methoxyethyl)-5,12-diaza-18-crown-6 (7).** To a solution of **6** (250 mg, 1.90 mmol) and 1-bromo-2-methoxyethane (396 mg, 5.70 mmol) in CH_3CN (50 mL) under argon were added sequentially Na_2CO_3 (2.10 g, 9.50 mmol) and NaI (145 mg, 2.1 mmol), and the resulting mixture was refluxed with stirring for 6 days. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (30 mL), and the resulting solution was extracted with 6 N aqueous HCl (2 × 15 mL). The combined aqueous phases were adjusted to pH 8-10 by careful, portionwise addition of solid Na_2CO_3, and the resulting mixture was extracted with $CHCl_3$ (2 × 30 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 25% EtOAc-hexane followed by continued elution of the chromatography column with 3% MeOH-EtOAc. Pure **7** (159 mg, 42%) was thereby obtained as a colorless oil. The IR, ^1H NMR, ^{13}C NMR spectra of this material are essentially identical with the corresponding spectral data that has been reported previously for authentic **7**.[16]

Synthesis of *N,N'*-Dibenzyl Crown Ether (10). To a solution of **8** (740 mg, 1.98 mmol) and **9**[14] (542 mg, 1.65 mmol) in CH_3CN (44 mL) were added sequentially Na_2CO_3 (1.84 g, 16.5 mmol) and NaI (130 mg, 0.875 mmol), and the resulting mixture was refluxed with stirring during 24 h. The reaction mixture was

allowed to cool to ambient temperature and then was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (30 mL), and the resulting solution was washed with water (3 × 30 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 20% EtOAc-hexane. Pure **10** (610 mg, 63%) was thereby obtained as a colorless oil: IR (neat) 2968 (s), 1630 (m), 1450 (m), 1148 (m), 1358 (w), 730 and 700 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.50 (d, J = 10.0 Hz, 1 H), 1.78-2.04 (m, 5 H), 2.35 (s, 2 H), 2.50-2.70 (m, 10 H), 3.33 (s, 6 H), 3.45 (t, J = 6.6 Hz, 4 H), 3.55-3.62 (m, 8 H), 7.18-7.32 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 30.3 (t), 41.9 (d), 44.2 (t), 44.4 (d), 48.6 (d), 51.0 (t), 53.6 (t), 59.2 (d), 59.4 (t), 95.4 (s), 127.3 (d), 128.7 (d), 129.4 (d), 140.4 (s). Anal. Calcd for $C_{35}H_{44}N_2O_3$: C, 77.74; H, 8.20. Found: C, 77.53; H, 7.96.

Hydrogenolysis of the *N*-Benzyl Groups in 10. To a solution of **10** (900 mg, 1.6 mmol) in MeOH (70 mL) was added 10% palladized charcoal (200 mg, catalytic amount). The resulting mixture was subjected to hydrogenolysis by agitation with excess H_2 (g) at 55 psig at ambient temperature during 24 h on a Parr shaker hydrogenation apparatus. The reaction mixture was filtered through Celite®, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 15% MeOH-EtOAc. Pure **11** (480 mg, 83%) was thereby obtained as a colorless oil; IR (neat) 3347 (br, s), 2982 (s), 1468 (m), 1350 (w), 1135 cm^{-1} (m) ; ^1H NMR ($CDCl_3$) δ 1.52 (*AB*, J_{AB} = 9.9 Hz, 1 H), 1.75-2.02 (m, 5 H), 2.32 (s, 2 H), 2.41-2.60 (m, 8 H), 2.70-2.83 (m, 8 H), 3.50-3.62 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 31.8 (t), 41.2 (d), 43.4 (t), 43.7 (d), 46.2 (t), 47.6 (d), 49.2 (t), 58.2 (d), 70.0 (t), 71.0 (t), 96.2 (s). Anal. Calcd for $C_{21}H_{32}N_2O_3$: C, 69.97; H, 8.95. Found: C, 69.79; H, 8.97.

Synthesis of Crown Ether 12. To a solution of **11** (380 mg, 1.05 mmol), 1-benzyloxy-2-tosyloxyethane (700 mg, 2.1 mmol) in CH_3CN (45 mL) was added K_2CO_3 (1.45 g, 10.5 mmol), and the resulting mixture was refluxed with stirring during 62 h. The reaction mixturewas allowed to cool gradually to ambient temperature and then was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 10% MeOH-EtOAc, thereby affording pure **12** (430 mg, 81%) as a colorless oil; IR (neat) 3073 (w), 3041 (w), 2962 (s), 1620 (w), 1468 (m), 1116 (m), 730 (m), 700 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.42 (*AB*, J_{AB} = 8.3 Hz, 1 H), 1.85-1.92 (m, 5 H), 2.34 (s, 2 H), 2.45-2.53 (m, 6 H), 2.65-2.85 (m, 12 H), 3.42-3.65 (m, 12 H), 4.45-4.52 (m, 4 H), 7.18-7.30 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 29.3 (t), 41.3 (d), 43.5 (t), 43.7 (d), 47.9 (d), 50.4 (t), 53.8 (t), 54.0 (t), 58.6 (d), 68.9 (t), 70.5 (t), 71.1 (t), 73.1 (t), 94.7 (s), 127.4 (d), 127.4 (d), 128.2 (d), 138.4 (s). Anal. Calcd for $C_{39}H_{52}N_2O_5$: C, 74.49; H, 8.33. Found: C, 74.28; H 8.40.

Hydrogenolysis of the *O*-Benzyl Groups in 12. To a solution of **12** (350 mg, 0.78 mmol) in MeOH (50 mL) was added 10% palladized charcoal (150 mg, catalytic amount). The resulting mixture was subjected to hydrogenolysis by agitation with excess H_2 (g) at 55 psig at ambient temperature during 36 h on a Parr shaker hydrogenation apparatus. The reaction mixture was filtered through Celite®, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 10% MeOH-EtOAc. Pure **13** (200 mg, 77%) was thereby obtained as a colorless oil; IR (neat) 3334 (br, s), 2982 (s), 1475 (m), 1347 (m), 1113 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.53 (*AB*, J_{AB} = 10.2 Hz, 1 H), 1.98-2.02 (m, 5 H), 2.36 (s, 2 H), 2.45-2.79 (m, 16 H), 3.45 (t, J = 5.3 Hz, 4 H), 3.56-3.64 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 29.8 (t), 41.4 (d), 43.3 (t), 44.1 (d), 47.9 (d), 52.5 (t), 53.6 (t), 55.7 (t), 56.5 (t), 58.3 (d), 64.7 (t), 70.4 (t), 96.4 (s). Anal. Calcd for $C_{25}H_{40}N_2O_5$: C, 66.94; H, 8.99. Found: C, 66.74; H, 8.70.

Synthesis of Crown Ether 14. To a solution of **11** (270 mg, 1.98 mmol) in CH_3CN (15 mL) under argon were added sequentially Na_2CO_3 (740 mg, 3.33 mmol) and NaI (110 mg, 2.18 mmol), and the resulting mixture was refluxed with stirring during 54 h. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (20 mL), and the resulting solution was washed with water (3 × 20 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 20% EtOAc-hexane followed by continued elution of the chromatography column with 3% MeOH-EtOAc. Compound **14** (190 mg, 73%) was thereby obtained as a colorless oil; IR (neat) 2969 (s), 1461 (m), 1351 (w), 1116 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.46 (*AB*, J_{AB} = 9.9 Hz, 1 H), 1.74-2.02 (m, 5 H), 2.28 (s, 2 H), 2.38-3.79 (m, 17 H), 3.26 (s, 3 H), 3.36 (t, J = 5.6 Hz, 2 H), 3.45-3.60 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 29.6 (t), 31.1 (t), 41.3 (d, 2 C), 43.5 (t, 2 C), 43.78 (d), 43.84 (d), 47.0 (t), 47.5 (d), 47.8 (d), 49.8 (t),

50.2 (t), 53.4 (t, 2 C), 58.1 (d), 58.6 (d), 58.8 (q), 70.1 (t), 70.3 (t), 71.2 (t), 71.3 (t), 95.4 (s), 96.6 (s), Anal. Calcd for $C_{24}H_{38}N_2O_4$: C, 68.87; H, 9.15. Found: C, 68.96; H, 9.09. This material was used as obtained in the next synthetic step.

To a solution of **14** (190 mg, 0.48 mmol) and 1-bromo-2-methoxyethane (200 mg, 1.44 mmol) in CH_3CN (15 mL) under argon were added sequentially Na_2CO_3 (640 mg, 2.88 mmol) and NaI (430 mg, 2.88 mmol), and the resulting mixture was refluxed with stirring during 4 days. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (15 mL), and the resulting solution was washed with water (3 × 10 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 25% EtOAc-hexane followed by continued elution of the chromatography column with 3% MeOH-EtOAc. Pure **15** (97 mg, 48%) was thereby obtained as a colorless oil; IR (neat) 2962 (s), 1481 (m), 1341 (w), 1122 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.55 (*AB*, J_{AB} = 9.9 Hz, 1 H), 1.78-1.97 (m, 5 H), 2.35 (s, 2 H), 2.46-3.66 (m, 18 H), 3.33 (s, 6 H), 3.45 (t, J = 5.0 Hz, 4 H), 3.55-3.65 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 29.2 (t), 41.3 (d), 43.5 (t), 43.8 (d), 47.9 (d), 50.4 (t), 53.6 (t), 53.8 (t), 58.5 (d), 58.7 (q), 70.4 (t), 71.0 (t), 71.2 (t), 94.6 (s). Anal. Calcd for $C_{27}H_{44}N_2O_5$: C, 68.04; H, 9.30. Found: C, 67.87; H, 9.10.

Synthesis of Crown Ether 16. To a mixture of **11** (270 mg, 1.98 mmol) and Na_2CO_3 (250 mg, 2.33 mmol) in CH_3CN (10 mL) was added $(EtO)_2SO_2$ (180 mg, 1.17 mmol), and the resulting mixture was refluxed with stirring during 34 h. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered, and the filtrate was concentrated *in vacuo*. Dichloromethane (10 mL) was added to the residue; the resulting mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 10% MeOH-EtOAc. Compound **16** (85 mg, 39%) was thereby obtained as a colorless oil; IR (neat) 2969 (s), 1461 (m), 1370 (w), 1122 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.03 (t, J = 6.7 Hz, 6 H), 1.51 (*AB*, J_{AB} = 10.5 Hz, 1 H), 1.75-2.05 (m, 5 H), 2.35 (s, 2 H), 2.38-2.62 (m, 10 H), 2.66 (t, J = 5.4 Hz, 4 H), 2.76 (t, J = 6.2 Hz, 4 H), 3.55 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 12.3 (q), 29.0 (t), 41.4 (d), 43.5 (t), 43.8 (d), 47.9 (t), 48.0 (d), 49.3 (t), 52.5 (t), 58.6 (d), 70.5 (t), 71.1 (t), 94.8 (s). Exact mass (CI HRMS) Calcd for $C_{25}H_{40}N_2O_3$: $[M_r + H]^+$ *m/z* 416.30389. Found: $[M_r + H]^+$ *m/z* 416.30304.

K^+ Cryptate 18. To a mixture of **17** (220 mg, 0.34 mmol) and K_2CO_3 (186 mg, 1.34 mmol) in CH_3CN (15 mL) was added **6** (84 mg, 0.32 mmol), and the resulting mixture was refluxed with stirring during 4 days. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 10% MeOH-CH_2Cl_2. Pure K^+ cryptate **18** (121 mg, 46%) was thereby obtained as a colorless, waxy solid; IR ($CHCl_3$) 3430 (br, s), 2960 (s), 2850 (s), 1724 (w), 1585 (m), 1460 (m), 1323 (s), 1354 (w), 1108 (m), 751 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.53 (*AB*, J_{AB} = 11.1 Hz, 1 H), 1.70-2.03 (m, 5 H), 2.21-2.70 (m, 17 H), 3.35-3.78 (m, 30 H), 7.10 (*AB*, J_{AB} = 7.0 Hz, 2 H), 7.85 (*AB*, J_{AB} = 7.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.2 (q), 32.5 (t), 41.4 (d), 43.4 (t), 43.8 (d), 47.9 (d), 54.3 (t, 2 C), 58.4 (d), 68.3 (t), 68.4 (t), 69.5 (t), 69.6 (t), 94.8(s), 126.4 (d), 128.3 (d), 133.8 (s), 139.5 (s). Exact mass (CI HRMS) Calcd for $C_{38}H_{57}KN_2O_{10}S$: $[M_r + H]^+$ *m/z* 773.33905. Found: $[M_r + H]^+$ *m/z* 773.34160.

Cryptand 19. A solution of **18** (163 mg, 0.21 mmol) in $CHCl_3$ (20 mL) was placed in a separatory funnel, placed on a mechanical shaker apparatus, and extracted with H_2O (15 mL). The layers were separated at 12 h intervals, the water layer was replaced at that time with fresh water (15 mL), and the extraction procedure was continued during 24 h. The presence (or absence) of KOTs was confirmed by withdrawing aliquots at 12 h intervals. Each aliquot was concentrated *in vacuo*, and the residue was analyzed via careful inspection of its ^1H NMR and ^{13}C NMR spectra. After the water-extraction procedure had been completed, the layers were separated; the organic layer was filtered, and the filtrate was concentrated *in vacuo*. Pure **19** (82 mg, 69%) was thereby obtained as a colorless oil; IR (neat) 3376 (br, s), 2945 (s), 2871 (s), 1462 (m), 1363 (s), 1117 (m), 769 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.54 (*AB*, J_{AB} = 10.8 Hz, 1 H), 1.76-1.90 (m, 5 H), 2.20-2.90 (m, 24 H), 3.40-3.70 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 32.4 (t), 41.6 (d), 43.5 (d), 44.0 (t), 48.2 (d), 55.2 (t), 55.3 (t), 59.1 (d), 68.2 (t), 69.7(t), 70.1 (t), 70.8 (t), 94.5(s). Exact mass (CI HRMS) Calcd for $C_{31}H_{50}N_2O_7$: $[M_r + H]^+$ *m/z* 563.36963. Found: $[M_r + H]^+$ *m/z* 563.37043.

Alkali Metal Picrate Extraction Experiments. The extraction experiments were performed by using 5mM solutions of each compounds in $CHCl_3$. The procedure that was used for this purpose has been described elsewhere.[11]

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