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Synthesis and Alkali Metal Picrate Extraction Capabilities of Novel, Cage-Functionalized Diazacrown Ethers. Effects of Host Preorganization on Avidity and Selectivity Toward Alkali Metal Picrates in Solution

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Abstract. The synthesis of a series of cage-functionalized bis(monoazacrown) ethers and bis(diaza-crown) ethers is described. Alkali metal picrate extraction profiles have been determined for several members of this novel series of ionophores. The increased level of preorganization achieved when a cage-functionalized bis(diaza-crown) ether is incorporated into a "molecular box" results in higher levels of avidity and selectivity of the resulting host system toward alkali metal picrates in solution.

Introduction. Pursuant to our ongoing interests in the synthesis and chemistry of novel polycarbocyclic "cage compounds",[1] we have recently prepared several examples of cage functionalized molecular clefts[2,3] and crown ethers.[4,5] Compounds of this type are of interest as members of a new class of "host" systems for the study of host-guest interactions (i.e., molecular recognition and inclusion phenomena). As an extension of these past studies, our attention has turned to the synthesis of new, cage-functionalized diaza(12-crown-4) ethers. The requisite syntheses and subsequent determination of the alkali metal picrate extraction profiles of representative members of this new class of crown ethers/ionophores are described herein.

The present study employs appropriately 3,5-difunctionalized 4-oxahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]-dodecanes as templates for the development of a series of novel host systems. These compounds are of interest as a new class of complexing agents for metal ion separation and transport. Thus, e.g., several diaza(12-crown-4) moieties (Scheme 1) have been prepared and subsequently have been affixed as pendant "arms" to the polycyclic template by employing the synthetic strategy shown in Scheme 2.

Results and Discussion. 1-Aza(12-crown-4) (i.e., 1,4,7-trioxa-10-azacyclododecane, **1**) and several substituted 1,4-diaza(12-crown-4) derivatives (i.e., **2-7**, Scheme 1) were employed in this study. The procedure used to synthesize *N*-protected 1,4-diaza(12-crown-4) ethers is shown in Scheme 1. Lithium aluminum hydride proved to be useful for deprotection of *N*-tosyl groups. The preparation of diaza(12-crown-4) ethers containing *N*-ethyl groups could be performed either via (i) $LiAlH_4$ promoted reduction of the corresponding *N*-acetyl derivatives or (ii) direct alkylation of R_2NH by using diethyl sulfate in the presence of base.

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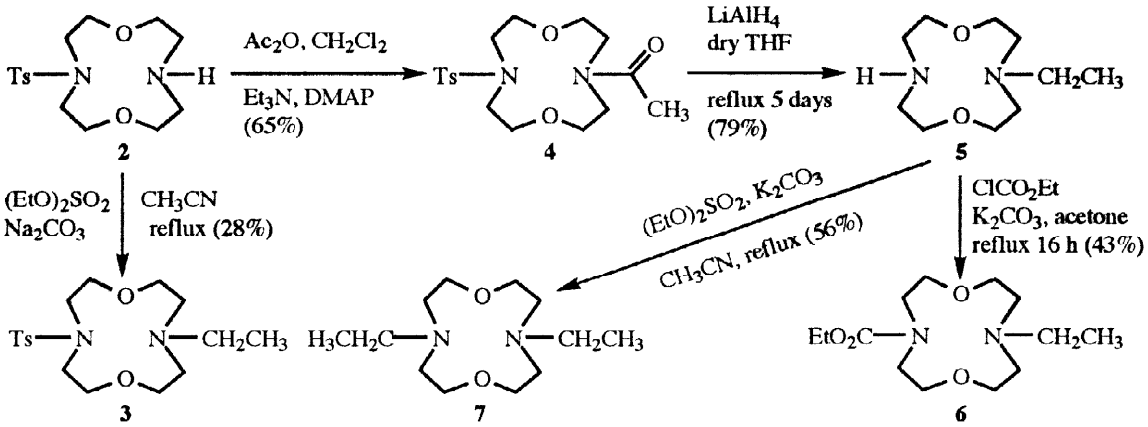
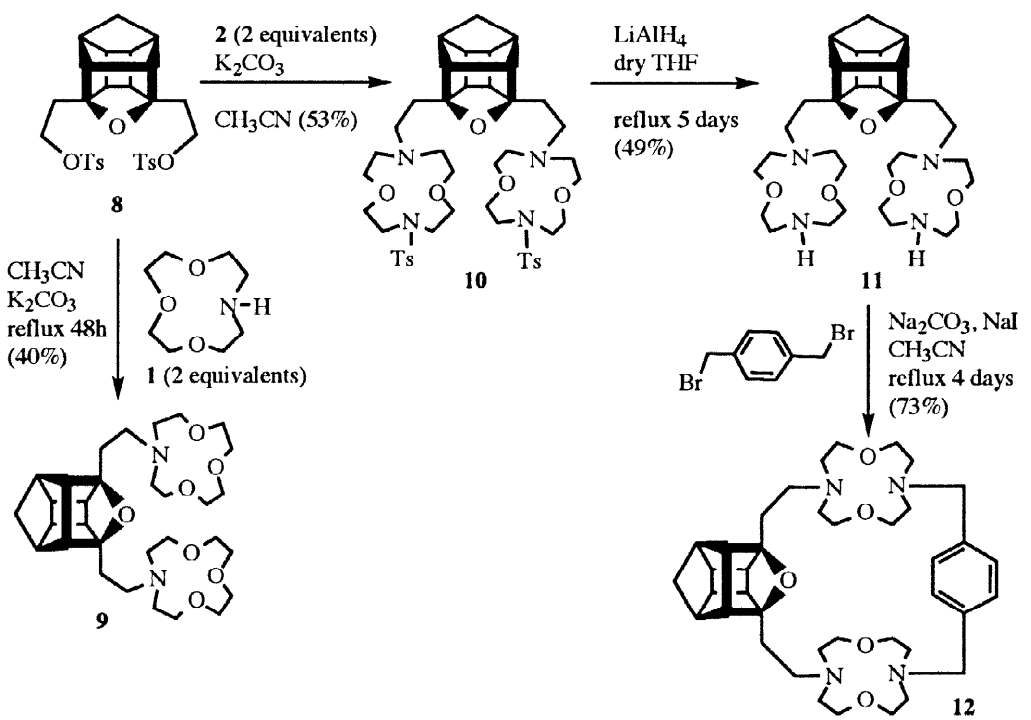
An oxahexacyclic ditosylate, **8**,[4] was used as the starting material for the preparation of crown ethers **9-12** (Scheme 2). Thus, base promoted reaction of **2**[6] (2 equivalents) with **8** produced **10** (53%), which subsequently was reduced with $LiAlH_4$ to afford **11** (49%). Bis[1,4-diaza(12-crown-4)] ether **11** then was converted into a "molecular box" (i.e., **12**) in 73% yield via base promoted reaction with α,α'-dibromo-*p*-xylene.

Scheme 1



Scheme 2



Results of Alkali Metal Picrate Extraction Experiments. Alkali metal picrate extraction data obtained for model compounds **1**, **3**, **5** and **7** and for the corresponding cage-functionalized bis(monoazacrown) ethers and bis(diazacrown) ethers (i.e., **9-12**, respectively) are shown in Table 1. In each case, it was necessary to perform the extraction experiments by using 2 equivalents of the model system to permit direct comparison with the corresponding cage-functionalized host, each of which contains two 1-aza- or 1,4-diaza(12-crown-4) moieties.

Table 1. Alkali metal picrate extraction data.

Host Molecule	Percent of Picrate Extracted				
	Li^+	Na^+	K^+	Rb^+	Cs^+
1[a]	8.2 ± 0.6	8.0 ± 0.4	8.3 ± 0.3	6.2 ± 0.9	9.2 ± 0.4
9[b]	10.6 ± 0.6	8.6 ± 0.3	8.8 ± 0.5	7.4 ± 0.9	8.9 ± 0.7
3[a]	8.5 ± 0.7	1.4 ± 0.5	2.8 ± 0.5	1.1 ± 0.9	1.6 ± 0.3
10[b]	7.9 ± 0.5	1.9 ± 0.5	6.1 ± 0.1	6.0 ± 0.7	6.5 ± 0.5
5[a]	40.3 ± 0.5	34.1 ± 0.7	24.3 ± 0.6	19.2 ± 0.7	15.3 ± 0.7
11[b]	41.7 ± 0.6	55.6 ± 0.8	44.3 ± 0.5	34.8 ± 0.1	31.6 ± 0.5
7[a]	46.9 ± 0.4	12.4 ± 1.4	11.8 ± 0.7	10.4 ± 0.9	6.8 ± 0.3
12[b]	66.8 ± 0.2	86.0 ± 0.3	58.0 ± 0.6	62.4 ± 0.4	65.3 ± 0.1

[a]Extraction conditions employed: 10.0 mM host in $CHCl_3$ solvent (0.5 mL). Aqueous phase (0.5 mL) was 5.0 mM in alkali metal picrate. [b] 5.0 mM host in $CHCl_3$ solvent (0.5 mL). Aqueous phase (0.5 mL) was 5.0 mM in alkali metal picrate. Values given in the table are an average of at least four independent extraction experiments. Extraction samples were shaken for 1 h at 20 °C and were allowed to equilibrate during 1 h prior to undertaking UV spectrophotometric analysis of the aqueous phase at 374 nm.

Inspection of the data in Table 1 reveals that bis(crown) ethers **9** and **10** display low avidity toward extraction of alkali metal picrates from aqueous solution. Furthermore, there is no evidence for cooperativity[3] between the 1-aza- or 1,4-diaza(12-crown-4) moieties situated therein.

A small difference between the alkali metal picrate extraction capabilities (or selectivities) of host molecules **9** and **10** was noted. However, we observed very little difference between the extraction capability of either of these host systems and that of the corresponding model compound (i.e., two equivalents of **1** or **3**, respectively). Finally, there appears to be no substantial difference between the alkali metal picrate extraction ability (or selectivity) between two host molecules **9** and **10** or between either of these host systems and the corresponding model compound (i.e., two equivalents of **1** or **3**, respectively).

The picture brightens somewhat with bis(diazacrown) ether **11**, which shows improved avidity toward extraction of alkali metal picrates *vis-à-vis* (i) systems **9** and **10** as well as (ii) the corresponding model crown ether (i.e., two equivalents of **5**). Further improvement is noted when opposing crown ether moieties are placed in close mutual proximity, as is the situation in bis(crown) ether **12**. Here, "forced cooperativity" between the 1,4-diaza-(12-crown-4) moieties occurs when these species are constrained into a "molecular box"[5] via covalent attachment to a *p*-xylyl moiety. In this situation, a dramatic improvement in avidity toward extraction of alkali metal picrates is observed. Furthermore, host molecule **12** displays both high avidity and good selectivity for Na^+ picrate in solution.

The results of the extraction experiments along the series of bibrachial crown ethers studied herein (Table 1) clearly demonstrates the advantages conferred by the high degree of preorganization that exists in host system **12** and that is absent in all of the other systems studied. Future studies will be directed toward the synthesis of increasingly highly preorganized host molecules related to **12** in the hope of achieving increased metal ion avidity and extraction selectivity in solution.

Experimental Section

Melting points are uncorrected. Elemental microanalyses were performed by personnel at M-H-W Laboratories, Phoenix, AZ. High-resolution mass spectral data were obtained at the Mass Spectrometry Facility at the Department of Chemistry and Biochemistry, University of Texas, Austin, TX by using a ZAB-E double sector high-resolution mass spectrometer (Micromass, Manchester, England) operated in the chemical ionization mode.

***N*-Acetyl-*N*'-toluenesulfonyldiaza(12-crown-4) (4).** To a solution of 4-(*p*-toluenesulfonyl)-1,7-dioxa-4,10-diazacyclododecane (**2**)[6] (240 mg, 0.73 mmol) in CH_2Cl_2 (15 mL) at ambient temperature was added sequentially 4-(dimethylamino)pyridine (DMAP, 20 mg, 0.15 mmol) and Et_3N (221 mg, 2.19 mmol). The reaction vessel was capped with a rubber septum, and Ac_2O (81 mg, 0.8 mmol) was added dropwise with stirring to the reaction mixture. After all of the *N*-acylating agent had been added, the reaction vessel was fitted with a heating mantle, and the reaction mixture was refluxed overnight. The reaction then was allowed to cool to ambient temperature, and water (2 mL) was added dropwise with stirring to quench the reaction. After all of the water had been added, the reaction mixture was stirred at ambient temperature for 15 minutes. The resulting aqueous suspension was placed in a separatory funnel, and the layers were separated. The organic layer was washed with water (2 × 5 mL). The organic layer was then dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The oily residue was purified on neutral alumina by eluting with CH_2Cl_2. Pure **4** (176 mg, 65%) was thereby obtained as a colorless oil; IR (film) 3001 (w), 2937 (m), 2870 (m), 1635 (s), 1437 (m), 1344 (m), 1130 (s), 727 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 2.07 (s, 3 H), 2.35 (s, 3H), 3.17 (m, 4 H), 3.39 (t, J = 4.8 Hz, 4 H), 3.55 (t, J = 4.4 Hz, 2 H), 3.66 (t, J = 4.4 Hz, 2 H), 3.74 (m, 4 H), 7.25 (*AB*, J_{AB} = 8.2 Hz, 2 H), 7.60 (A*B*, J_{AB} = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.9 (q), 22.8 (q), 49.6 (t), 51.0 (t), 51.8 (t), 52.4 (t), 69.0 (t), 69.4 (t), 70.2 (t), 71.1 (t), 127.8 (d), 130.2 (d), 135.9 (s), 144.0 (s), 172.1 (s). Anal. Calcd for $C_{17}H_{26}N_2O_5S$: C, 55.11; H, 7.08. Found: C, 54.97; H, 6.82.

4-Ethyl-1,7-dioxa-4,10-diazacyclododecane [*N*-Ethyldiaza(12-crown-4), 5]. To a suspension of $LiAlH_4$ (170 mg, 4.5 mmol) in dry THF (10 mL) under argon was added **4** (140 mg, 0.38 mmol), and the resulting mixture was refluxed for 5 days. The reaction was quenched via careful, dropwise addition of EtOAc (3 mL) with stirring to the reaction mixture. The resulting mixture was filtered, and the residue was concentrated *in vacuo*. The oily residue, crude **5**, was purified via column chromatography on neutral alumina by eluting with 1:1 (v/v) EtOAc-CH_2Cl_2. Pure **5** (60 mg, 79%) was thereby obtained as a yellow oil; IR (film) 3262 (br, w), 2937 (s), 2861 (s), 1455 (m), 1117 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (t, J = 7.2 Hz, 3 H), 2.61 (m, 6 H) , 2.77 (t, J = 4.8, 4 H), 3.53 (t, J = 4.7 Hz, 4 H), 3.64 (t, J = 4.8, 4 H); ^{13}C NMR ($CDCl_3$) δ 11.3 (q), 48.1 (t), 48.5 (t), 54.8 (t), 68.6 (t), 68.9 (t).

Compound **5** was further characterized via subsequent conversion to the corresponding ethoxycarbonylurethane derivative, **6**. Thus, a mixture of **5** (486 mg, 2.3 mmol), $ClCO_2Et$ (1.00 g, 9.2 mmol), K_2CO_3 (1.90 g, 13.8 mmol) and acetone (7 mL) was refluxed for 16 h, at which time the reaction mixture was allowed to cool gradually to ambient temperature and then was filtered. The filtrate was concentrated *in vacuo*, and the residue was purified via column chromatography on neutral alumina by using 20% CH_2Cl_2-hexane. Pure 4-ethyl-10-ethoxycarbonyl-1,7-dioxa-4,10-diazacyclododecane (**6**) was thereby obtained as a yellow oil (269 mg, 43%); IR (film) 2934 (s), 1707 (s), 1469 (m), 1426 (m), 1138 (m), 766 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.03 (t,J = 7.1 Hz, 3 H), 1.24 (t, J = 7.1 Hz, 3 H), 2.60 (q, J = 7.1 Hz, 2 H), 2.62-2.68 (m, 4 H), 3.43-3.57 (m, 8 H), 3.74 (t, J = 4.7 Hz, 2 H), 3.82 (t, J = 5.2 Hz, 2 H), 4.08 (q, J = 7.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 12.6 (q), 15.4 (q), 49.6 (t), 50.3 (t),

51.1 (t), 55.2 (t), 55.6 (d), 61.6 (t), 69.2 (t), 70.1 (t), 70.2 (t), 70.8 (t), 157.2 (s). HRMS Calcd for $C_{13}H_{26}N_2O_4$: $[M_r + H]^+$ 275.1971. Found: $[M_r + H]^+$ 275.1972.

4-(*p*-Toluenesulfonyl)-10-ethyl-1,7,-dioxa-4,10-diazacyclododecane (3). To a solution of **2** (450 mg, 1.37 mmol) in dry CH_3CN (10 mL) at ambient temperature was added anhydrous Na_2CO_3 (290 mg, 2.74 mmol). The reaction vessel was capped with a rubber septum, and the contents were purged with argon. Diethyl sulfate (211 mg, 1.37 mmol) was added dropwise with stirring to the reaction mixture. After all of the alkylating agent had been added, the reaction vessel was fitted with a heating mantle, and the reaction mixture was refluxed overnight. The reaction mixture then was allowed to cool gradually to ambient temperature. The reaction mixture was filtered, the residue was washed with CH_2Cl_2 (15 mL), and the combined filtrates were concentrated *in vacuo*. The residue, a yellow oil, was purified via column chromatography on neutral alumina by eluting with 1 : 1 CH_2Cl_2-hexane. Pure **3** (140 mg, 29%) was thereby obtained as a pale yellow oil; IR (film) 3049 (w), 2928 (s), 2868 (s), 1686 (m), 1603 (m), 1450 (m), 1327 (s), 1111 (s), 800 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.01 (t, J = 7.1 Hz, 3 H), 2.48 (s, 3 H), 2.54 (m, 6 H), 3.26 (t, J = 5.3 Hz, 4 H), 3.53 (t, J = 4.6 Hz, 4 H), 3.82 (t, J = 5.2 Hz, 4 H), 7.29 (*AB*, J_{AB} = 8.3 Hz, 2 H), 7.67 (A*B*, J_{AB} = 8.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 12.7 (q), 22.0 (q), 50.9 (t), 51.1 (t), 55.4 (t), 69.8 (t), 70.8 (t), 127.8 (d), 130.1 (d), 136.5 (s), 143.7 (s). Anal. Calcd for $C_{17}H_{28}N_2O_4S$: C, 57.28; H, 7.92. Found: C, 57.32; H, 7.90.

4,10-Diethyl-1,7-dioxa-4,10-diazacyclododecane (7). To a solution of **5** (165 mg, 1.19 mmol) in dry CH_3CN (10 mL) at ambient temperature was added Na_2CO_3 (250 mg, 2.78 mmol). Diethyl sulfate (183 mg, 1.19 mmol) was added slowly with rapid stirring to the reaction mixture via microliter syringe in three portions during 20 minutes. The resulting mixture was stirred at ambient temperature for 6 h and then was refluxed gently with stirring for an additional 12 h. The resulting slurry was filtered, the filter cake (residue) was washed with CH_2Cl_2 (3 × 15 mL), and the combined filtrates were concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with CH_2Cl_2. Pure **7** (151 mg, 56%) was thereby obtained as a clear, colorless oil; IR (film) 2964 (s), 2857 (s), 1464 (m), 1360 (m), 1290 (m), 1122 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 0.99 (t, J = 6.8 Hz, 6 H), 2.56 (q, J = 6.8 Hz, 4 H), 2.62 (t, J = 4.6 Hz, 8 H), 3.56 (t, J = 4.6 Hz, 8 H); ^{13}C NMR ($CDCl_3$) δ 11.9 (q), 50.7 (t), 54.5 (t), 69.8 (t). Anal. Calcd for $C_{12}H_{26}N_2O_2$: C, 62.55; H, 11.38. Found: C, 62.45; H, 11.32.

Synthesis of Cage Annulated Bis(azacrown) Ether 9. A mixture of **8**[4] (514 mg, 90 mmol), K_2CO_3 (1.24 g, 9.0 mmol), and **1** (314 mg, 1.80 mmol) in CH_2Cl_2 (50 mL) was refluxed under argon for 48 h. The resulting slurry was filtered, and the filter cake (residue) was washed with CH_2Cl_2 (3 × 25 mL). The combined filtrates were washed with water (3 × 25 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. The residue thereby obtained was purified via column chromatography on neutral alumina by eluting with 1 : 1 EtOAc-CH_2Cl_2. Pure **9** (203 mg, 40%) was thereby obtained as a yellow oil; IR (film) 2953 (s), 2856 (s), 1460 (m), 1361 (m), 1302 (m), 1134 (s), 920 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.46 (d, J = 10.3 Hz, 1 H), 1.81 (d, J = 10.3 Hz, 1 H), 1.95 (t, J = 7.2 Hz, 4 H), 2.4-2.7 (m, 20 H), 3.60 (m, 24 H); ^{13}C NMR ($CDCl_3$) δ 29.9 (t), 41.7 (d), 43.4 (t), 44.3 (d), 47.9 (d), 53.0 (t), 54.9 (t), 58.8 (d), 70.4 (t), 71.2 (t), 94.7 (s). Anal. Calcd for $C_{31}H_{50}N_2O_6$: C, 68.10; H, 9.22. Found: C, 68.71; H, 9.26.

Synthesis of Cage Annulated Bis(diazacrown) Ether 10. To a solution of **8**[4] (700 mg, 1.25 mmol) and **2** (831 mg, 2.52 mmol) in dry CH_3CN (20 mL) under argon at ambient temperature was added K_2CO_3 (1.74 g, 12.6 mmol), and the resulting slurry was refluxed for 6 days. At that time, thin layer chromatographic (tlc) analysis of the reaction mixture revealed the absence of **1**. The reaction mixture was poured into water (20 mL), and the resulting aqueous suspension was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The oily residue was purified via col-umn chromatography on neutral alumina by eluting with 25% EtOAc-CH_2Cl_2. Pure **10** (575 mg, 53%) was there-by obtained as a yellow oil; IR (film) 3057 (w), 2947 (s), 2859 (s), 1732 (m), 1672 (w), 1606 (w), 1452 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.51 (d, J = 10.7 Hz, 1 H), 1.95, (m, 5 H), 2.30-2.70 (m, 26 H), 3.26 (t, J = 5.0 Hz, 8 H), 3.53 (t, J = 4.1 Hz, 8 H), 3.83 (t, J = 5.0 Hz, 8 H), 7.30 (*AB*, J_{AB} = 8.5 Hz, 4 H), 7.69 (AB,

J_{AB} = 8.5 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 21.3 (q), 29.8 (s), 41.5 (d), 43.2 (t), 44.2 (d), 47.7 (d), 50.3 (t), 52.7 (t), 55.2 (t), 58.6 (d), 69.0 (t), 70.1 (t), 94.6 (t), 127.0 (d), 129.4 (d), 135.8 (s), 143.4 (s). **Anal Calcd for** $C_{45}H_{64}N_4O_9S_2$: C, 62.19; H, 7.42. Found: C, 61.96; H, 7.33.

Synthesis of Cage Annulated Bis (diazacrown) Ether 11. To a suspension of $LiAlH_4$ (150 mg, 3.89 mmol) in dry THF (15 mL) under argon at ambient temperature was added a solution of **10** (340 mg, 0.39 mmol) in dry THF (5 mL), and the resulting mixture was refluxed for 5 days. The reaction was quenched via careful, dropwise addition of 50% aqueous THF (4 mL) to the stirred reaction mixture. The resulting mixture was filtered, and the filtrate was concentrated *in vacuo*. The oily residue was purified via column chromatography on neutral alumina by eluting with 90% EtOAc-MeOH. Pure **11** was thereby obtained as a yellow oil; IR (film) 2945 (s), 2862 (s), 1674 (m), 1460 (m), 1354 (m), 1300 (m), 1120 (m), 914 (m), 737 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.49 (d, J =10.6 Hz, 1 H), 1.9 (m, 5 H), 2.3-2.9 (m, 28 H), 3.2 (br s, 2 H), 3.5 (t, J = 4.5 Hz, 8 H), 3.62 (t, J = 4.5 Hz, 8 H); ^{13}C NMR ($CDCl_3$) δ 28.9 (s), 42.2 (d), 43.9 (t), 44.9 (d), 48.3 (t), 48.5 (d), 50.7 (t), 55.0 (t), 59.2 (d), 68.3 (t), 68.8 (t), 95.2 (t). HRMS Calcd for $C_{31}H_{52}N_4O_5$: $[M_r + H]^+$ 561.4016. Found: $[M_r + H]^+$ 561.4007.

Synthesis of Cage Annulated Bis(diazacrown) Ether 12. To a solution of **11** (155 mg, 0.27 mmol) and α,α' dibromoxylene (73 mg, 0.27 mmol) in CH_3CN (20 mL) at ambient temperature was added sequentially Na_2CO_3 (293 mg, 2.76 mmol) and NaI (82 mg, 0.55 mmol), and the resulting mixture was refluxed vigorously for 4 days. The reaction mixture was allowed to cool gradually to ambient temperature and then was concentrated *in vacuo* to *ca.* 2/3 of its original volume. Dichloromethane (10 mL) was added, and the resulting slurry was filtered. The filtrate was concentrated *in vacuo*, and the oily residue was purified via column chromatography on neutral alumina by eluting with EtOAc. Pure **12** (130 mg, 73%) was thereby obtained as a clear, colorless oil; IR (film) 2987 (s), 2860 (s), 1660 (m), 1449 (m), 1354 m), 1287 (w), 1120 (s), 912 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.45 (d, J =10.1 Hz, 1 H), 1.95 (m, 5 H), 2.40-2.70 (m, 30 H), 3.35-3.70 (m, 20 H), 7.35 (br s, 4 H); ^{13}C NMR ($CDCl_3$) δ 30.3 (s), 41.5 (d), 43.2 (t), 44.1 (d), 47.5 (d), 52.6 (t), 54.0 (t), 56.1 (t), 59.0 (d), 61.6 (t), 69.3 (t), 69.5(t), 94.7 (t), 128.4 (d), 138.8 (s). HRMS Calcd for $C_{39}H_{60}N_4O_5$: $[M_r + H]^+$ 663.4485. Found: $[M_r + H]^+$ 663.4479.

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