

## Synthesis and Alkali Metal Picrate Extraction Capabilities of Novel, Cage-functionalized, Pyridine Containing Crown Ethers and Cryptands

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**Abstract.** The syntheses of novel cage-functionalized crown ethers, **11–13**, that contain one or more pyridyl units are reported. The results of alkali metal picrate extraction experiments performed by using **11** and **12** are compared with those obtained by using the corresponding model (non-cage) crown ethers. Cage-functionalized crown ether **11** displays greater avidity toward  $\text{Li}^+$  picrate *vis-à-vis* the corresponding model system, **2**, whereas **12** displays considerably lower avidity than its corresponding model system, **3**, toward extraction of alkali metal picrates from aqueous solution into  $\text{CHCl}_3$ . In addition, a highly preorganized, cage-annulated cryptand, **16**, was prepared; this unusual host molecule was found to be both highly avid and highly selective toward extraction of  $\text{Li}^+$  and  $\text{Na}^+$  picrates. © 1999 Elsevier Science Ltd. All rights reserved.

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

**Introduction.** Pyridine containing macrocycles have been the focus of considerable attention as an important class of ligands that are capable of forming stable complexes with a variety of transition metals.<sup>1–4</sup> In addition, compounds of this type have been employed as host-ligands in studies of molecular recognition and inclusion phenomena that focus upon the complexation and transport of alkylammonium cations.<sup>5–7</sup> Chiral pyridine containing macrocycles have been synthesized from natural products.<sup>8–11</sup> Recently, pyridine containing macrocycles have been shown to possess significant levels of antibacterial activity.<sup>12</sup>

Incorporation of pyridine rings into crown ethers provides a Lewis base center (pyridine nitrogen) in an aromatic ring that lends rigidity and a measure of lipophilicity to the resulting crown ethers with consequent impact upon the ability of such host systems to form complexes with a variety of neutral and ionic guest species.<sup>13–15</sup> Numerous pyridine containing crown ethers have been synthesized;<sup>16–21</sup> however relatively few studies have been performed that are designed to evaluate the ability of systems of this type to complex effectively with e.g., alkali metal cations.

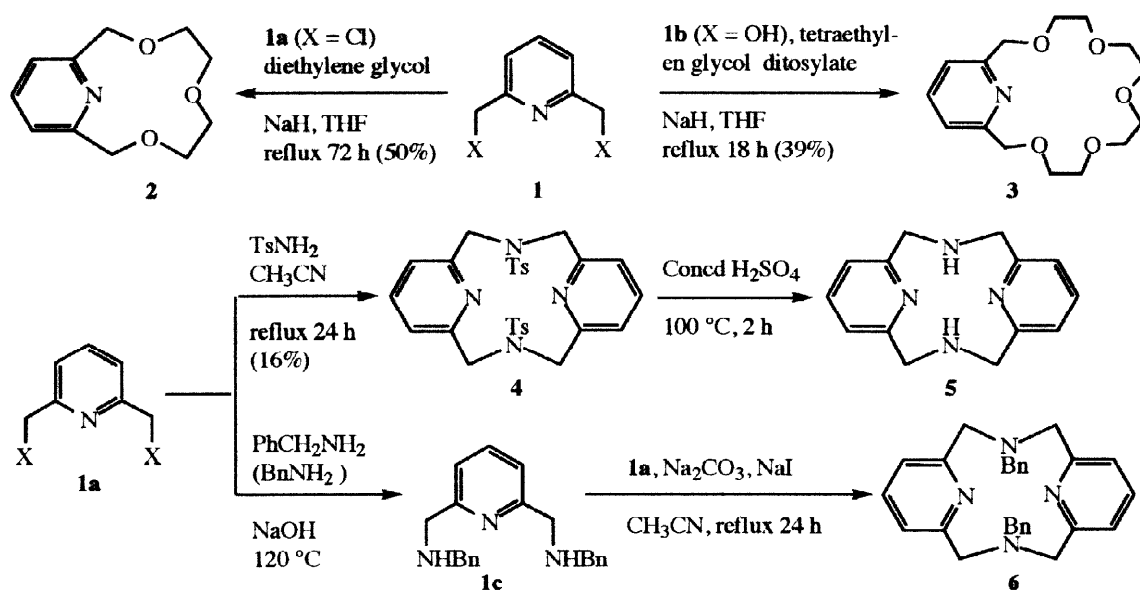
In the present study, we report the synthesis and alkali metal picrate extraction capabilities of several novel, cage-functionalized, pyridine containing crown ethers (**11–13**) and cryptands (**15** and **16**, *vide infra*). The lipophilicity and rigidity of these systems is significantly greater than those of simple monocyclic, nitrogen-containing

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crown ethers that contain neither aromatic rings nor a rigid polycyclic cage moiety. We have previously reported the synthesis of cage-functionalized crown ethers and cryptands and the results of alkali metal picrate extraction studies that involve these species as host systems.<sup>22,23</sup> Not surprisingly, the more highly preorganized cryptands display significantly enhanced avidities and selectivities toward particular alkali metal cations than do their monocyclic (crown ether) analogs.<sup>23</sup>

**Synthesis of Pyridine Containing Crown Ethers, Cryptands, and Model Compounds.** In order to gauge the effects of cage-annulation on the complexation properties of our new pyridine containing crown ethers and cryptands, it was necessary to compare them with a series of structurally related model compounds that do not contain the cage moiety. The model systems chosen for study and the procedures used to prepare these compounds are shown in Scheme 1. Thus, **2** was prepared in 50% yield via base promoted, Na<sup>+</sup> templated reaction of 2,6-bis(chloromethyl)pyridine (**1a**)<sup>25</sup> with ethylene glycol. Model compound **3** was prepared via modification of a literature procedure that employs the reaction of tetraethylene glycol ditosylate with 2,6-pyridinedimethanol (**1b**).<sup>25</sup>

Scheme 1

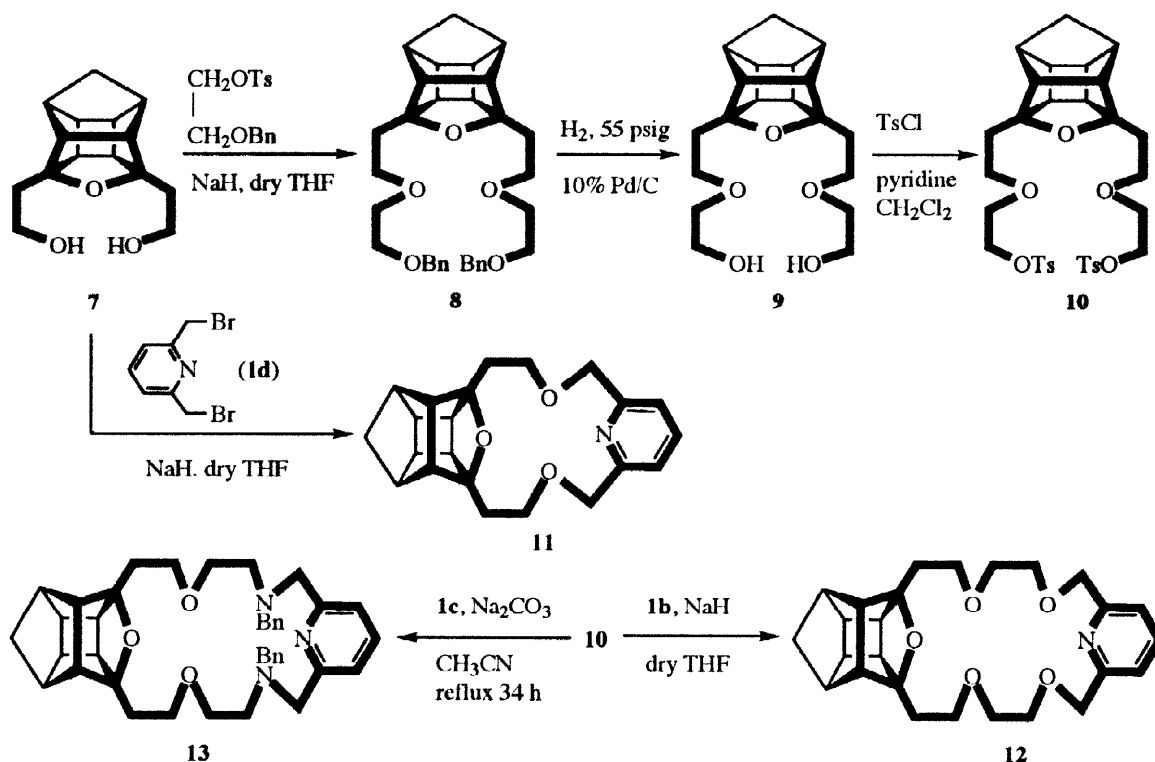


A multistep synthesis of **4** has been reported previously by other investigators.<sup>21,25</sup> In this study, we found that **4** could be prepared in one step, albeit in low yield (16%) via base promoted cyclization of 2,6-bis(chloromethyl)pyridine (**1a**)<sup>25</sup> with tosylamine. Subsequent acid hydrolysis<sup>21</sup> of the resulting bis(*p*-toluenesulfonamide) thereby obtained afforded **5**.

Crown ether **6** was prepared via a modification of a procedure that has been reported previously.<sup>26</sup> First, 2,6-bis(*N*-benzylaminomethyl)pyridine (**1c**)<sup>3</sup> was prepared by reacting 2,6-bis(chloromethyl)pyridine (**1a**)<sup>25</sup> with benzylamine at ambient temperature during 24 h. Subsequent base promoted reaction of **1a** with **1c** afforded **6** in 12% yield. The structure of **6** thereby obtained was established unequivocally via application of X-ray diffraction methods (*vide infra*).

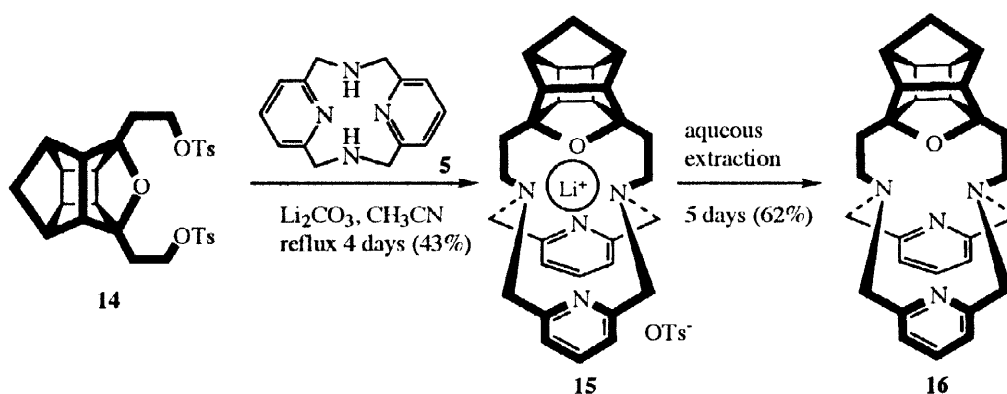
The procedures used to prepare new cage-functionalized crown ethers **11–13** are shown in Scheme 2. Thus, base promoted reaction of diol **7**<sup>22</sup> with 1-benzyloxy-2-tosyloxyethanol produced **8**. Reductive debenzyla-tion of **8** afforded a new "extended" diol, **9**, whose subsequent base promoted reaction with TsCl afforded the corresponding ditosylate (**10**) in 70% overall yield. In addition, base promoted reaction of **7**<sup>22</sup> with 2,6-bis-(bromomethyl)pyridine (**1d**) gave **11**. Finally, crown ethers **12** and **13** were synthesized via base promoted reac-tion of **10** with **1b** and **1c**,<sup>3</sup> respectively (Scheme 2).

Scheme 2



Lithium carbonate promoted reaction of **5** with ditosylate **14**<sup>23</sup> produced the corresponding Li<sup>+</sup> cryptate, **15** (Scheme 3), in 43% yield. The free ligand (i.e., cryptand **16**) was isolated in 62% yield after **15** had been subjected to aqueous extraction for 5 days.

Scheme 3



**Results of Alkali Metal Picrate Extraction Studies.** Alkali metal picrate extraction studies have been performed by using a  $\text{CHCl}_3\text{-H}_2\text{O}$  extraction system for cage-functionalized crown ethers **11**, **12**, and **16**, and also for a series of model compounds (i.e., **2**, **3**, and **5**, respectively). The results thereby obtained are shown in Table 1.

**Table 1.** Results of Alkali Metal Picrate Extraction Experiments.

Host Molecule	Percent of Picrate Extracted (%) <sup>a</sup>				
	Li <sup>+</sup>	Na <sup>+</sup>	K <sup>+</sup>	Rb <sup>+</sup>	Cs <sup>+</sup>
18-crown-6	23 ± 0.9	5.7 ± 0.9	68.3 ± 0.7	52.0 ± 0.6	31.0 ± 1.0
<b>2</b>	3.3 ± 0.6	3.0 ± 1.5	1.3 ± 0.4	1.7 ± 0.5	1.3 ± 0.7
<b>11</b>	19.5 ± 1.0	6.3 ± 1.3	5.1 ± 0.7	4.3 ± 1.4	2.6 ± 0.7
<b>3</b>	2.2 ± 0.4	7.5 ± 1.0	51.5 ± 1.0	33.2 ± 1.4	16.1 ± 1.2
<b>12</b>	1.7 ± 0.6	1.9 ± 1.3	3.4 ± 0.4	1.8 ± 0.9	5.2 ± 0.7
<b>5</b>	31.1 ± 0.6	30.9 ± 1.3	30.3 ± 0.5	33.0 ± 0.9	29.8 ± 1.4
<b>16</b>	81.9 ± 0.7	70.7 ± 0.8	40.3 ± 0.5	46.0 ± 0.6	40.9 ± 0.9

<sup>a</sup>Averages and standard deviations calculated for data obtained from three independent extraction experiments.

Inspection of the results in Table 1 indicate that **12** is a very inefficient extraction agent for alkali metal ions. The results of MM2 calculations<sup>27</sup> suggest that the pyridine ring nitrogen is oriented away from the center of the cavity in **3**, so its ability to interact constructively with a guest metal ion is correspondingly reduced. This situation appears to be further exacerbated in **12** due to additional constraints imposed upon the conformational flexibility of the crown system by the presence of a rigid cage moiety. In this context, it is interesting to note that **11** proved to be a more efficient alkali metal picrate extractant than its corresponding model compound, i.e., **2**, particularly toward Li<sup>+</sup> picrate.

The most promising host system among those studied herein is the highly preorganized, cage-functionalized cryptand, i.e., **16**. Compound **16** appears to be a highly efficient and somewhat selective extracting agent for Li<sup>+</sup> and Na<sup>+</sup>. Indeed, **16** proved to be *considerably* more avid toward all alkali metal cations studied than its corresponding model crown ether, i.e., **5**.

Interestingly, crown ether **5** proved to be both an inefficient and virtually indiscriminate alkali metal cation complexing agent. Three factors may be responsible primarily for this result: (i) The tetraazadodecyl cavity within macrocycle **5** is relatively small and cannot directly accommodate large alkali metal cation guests on a size-fit basis in 1:1 host-guest complexes. (ii) The X-ray structure obtained for **6** suggests that the pyridyl moieties in **5** most

likely do not lie in the approximate plane of the 12-membered ring, with concomitant decrease in the stacking ability of **5** that otherwise could lead to the formation of 2:1 "sandwich-type" complexes with larger alkali metal cation guests. (iii) Importantly, in the solid state, the lone-pairs of electrons on the aliphatic nitrogen atoms in the *N*-benzyl groups are oriented in a manner that precludes them from interacting cooperatively with the pyridyl ring nitrogen atoms as donor ligands to stabilize an alkali metal cation guest.

**Summary and Conclusions.** New crown ethers **11–13** and a highly preorganized cage-functionalized cryptand (**16**), each of which contains a pyridyl moiety in addition to an oxahexacyclic cage unit, have been prepared. The behavior of host molecules **11**, **12**, and **16** toward extraction of alkali metal picrates from water into CHCl<sub>3</sub> has been examined, and the results thereby obtained have been compared with the corresponding extraction behavior displayed by corresponding model crown ethers, i.e., **2**, **3**, and **5**, respectively.

Examination of the extraction results shown in Table 1 reveals that crown ether **12** displays considerably lower avidity toward all alkali metal cations studied than does its corresponding model compound (i.e., **3**) under comparable conditions. By way of contrast, **11**, which possesses a smaller-sized cavity than does **12**, displays higher avidity toward all alkali metal cations studied when compared with the corresponding behavior of model compound **2**. With the lone exception of its behavior toward Cs<sup>+</sup>, crown ether **11** proved overall to be a more efficient alkali metal extracting agent than **12**. The reasons that underlie the notably poor performance of **12** in this regard are not apparent to us at present.

Finally, we note that cryptand **16** appears to be the most effective alkali metal cation complexing agent among the three host molecules whose extraction profiles have been studied herein. This result is not surprising, since **16** is the most highly preorganized of these three host systems. Interestingly, whereas **16** displays relatively high avidity toward all of the alkali metal cations studied, it appears to form complexes selectively with Li<sup>+</sup> and Na<sup>+</sup>.

## 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.

**Model Crown Ether 2.** To a suspension of NaH (obtained as a dispersion of 60% w/w NaH in mineral oil, 520 mg, 2.08 mmol) in dry THF (12 mL) under argon was added with stirring a solution of diethylene glycol (110 mg, 1.04 mmol) in dry THF (35 mL). The resulting mixture was refluxed for 0.5 h, at which time a solution of 2,6-bis(chloromethyl)pyridine (**1a**, 196 mg, 1.04 mmol) in dry THF (60 mL) was added dropwise with stirring during 0.5 h. The reaction mixture was refluxed for 72 h and then was allowed to cool gradually to ambient temperature. The reaction was quenched via addition of water (5 mL), and the resulting aqueous suspension was extracted with CHCl<sub>3</sub> (4 × 45 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 50% EtOAc-hexane. Pure **2** (100 mg, 50%) was thereby obtained as a colorless oil: IR (film) 3449 (s), 2870 (s), 1602 (w), 1452 (w), 1350 (w), 1118 cm<sup>-1</sup> (m); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  3.64–3.71 (m, 8 H), 4.70 (s, 4 H), 7.31

(d,  $J = 7.6$  Hz, 2 H), 7.42 (t,  $J = 6.9$  Hz, 1 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  70.2 (t), 70.6 (t), 73.1 (t), 119.7 (d), 137.9 (d), 157.9 (s). Anal. Calcd for  $\text{C}_{11}\text{H}_{15}\text{NO}_3$ : C, 63.14; H, 7.23. Found: C, 63.20; H, 7.19.

**Model Crown Ether 3.** To a suspension of NaH (obtained as a dispersion of 60% w/w NaH in mineral oil, 77 mg, 2.53 mmol) in dry THF (23 mL) under argon was added with stirring a solution of 2,6-bis(hydroxymethyl)pyridine (**1b**, 140 mg, 1.0 mmol) in dry THF (38 mL). The resulting mixture was refluxed for 0.5 h, at which time a solution of tetraethyleneglycol ditosylate (510 mg, 1.0 mmol) in dry THF (58 mL) was added dropwise with stirring during 20 minutes. The reaction mixture was refluxed for 18 h and then was allowed to cool gradually to ambient temperature. The reaction was quenched via addition of water (20 mL), and the resulting aqueous suspension was extracted with  $\text{CHCl}_3$  ( $4 \times 50$  mL). The combined organic layers were dried ( $\text{MgSO}_4$ ) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 50% EtOAc-hexane. Pure **3** (116 mg, 39%) was thereby obtained as a colorless oil. The IR,  $^1\text{H}$  NMR, and  $^{13}\text{C}$  NMR spectra of the material thereby obtained is essentially identical with the corresponding spectral data that has been reported previously for authentic **3**.<sup>24</sup>

**Crown Ether 4.** A solution of **1a** (207 mg, 1.10 mmol),  $\text{TsNH}_2$  (753 mg, 4.4 mmol), and  $\text{Na}_2\text{CO}_3$  (2.92 g, 27.5 mmol) in  $\text{CH}_3\text{CN}$  (10 mL) 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 purified via column chromatography on neutral alumina by eluting with EtOAc. Pure **4** (96 mg, 16%) was thereby obtained as a colorless oil. The IR,  $^1\text{H}$  NMR, and  $^{13}\text{C}$  NMR spectra of the material thereby obtained is essentially identical with the corresponding spectral data that has been reported previously for authentic **3**.<sup>21</sup>

**2,6-Bis(*N*-benzylaminomethyl)pyridine (1c).** A solution of benzylamine (23.0 g, 72 mmol, large excess) and **1a** (2.30 g, 12 mmol) was heated with stirring in an external oil bath at 120 °C for 28 h. The reaction mixture was allowed to cool gradually to ambient temperature, crushed NaOH pellets (1.00 g, 25 mmol) then was added, and the resulting mixture was heated with stirring in an external oil bath at 120 °C for 1 h. The reaction mixture was allowed to cool gradually to ambient temperature, and the resulting mixture was concentrated *in vacuo* (water aspirator) to remove excess benzylamine. The residue was dissolved in  $\text{CHCl}_3$  (100 mL); the resulting solution was filtered, and the filtrate was washed with water (50 mL). The layers were separated, and the aqueous layer was extracted with  $\text{CHCl}_3$  ( $3 \times 50$  mL). The combined organic layers were dried ( $\text{MgSO}_4$ ) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via bulb-to-bulb distillation (Kügelrohr apparatus), thereby affording **1c** (1.64 g, 43%) as a pale yellow oil. The IR,  $^1\text{H}$  NMR, and  $^{13}\text{C}$  NMR spectra of the material thereby obtained is essentially identical with the corresponding spectral data that has been reported previously for authentic **1c**.<sup>3</sup>

**Crown ether 6.** A solution of **1c** (360 mg, 1.13 mmol),  $\text{Na}_2\text{CO}_3$  (600 mg, 5.65 mmol), NaI (85 mg, 0.65 mmol) in  $\text{CH}_3\text{CN}$  (25 mL) was refluxed with stirring during 0.5 h. To the hot reaction mixture was added portionwise with stirring **1a** (200 mg, 1.13 mmol), and the resulting mixture was refluxed during 24 h. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered. The filtrate was concentrated *in vacuo*, and the residue thereby obtained was purified via column chromatography on neutral alumina by eluting with 20% EtOAc-hexane. Pure **6** (26 mg, 12%) was thereby obtained as a colorless oil. The IR,  $^1\text{H}$  NMR, and  $^{13}\text{C}$  NMR spectra of the material thereby obtained is essentially identical with the corresponding spectral data that has been reported previously for authentic **6**.<sup>26</sup>

**3,5-Bis[2-(2'-benzyloxyethoxy)ethyl]-4-oxahexacyclo[5.4.1.0<sup>2,6</sup>.0<sup>3,10</sup>.0<sup>5,9</sup>.0<sup>8,11</sup>]dodecane (8).** A suspension of NaH (60% suspension in mineral oil, 660 mg, 16.4 mmol) in dry DMF (10 mL) under argon was cooled to 0 °C via application of an external ice-water bath. To this cooled solution was added dropwise with stirring a solution of **7<sup>22</sup>** (1.85 g, 7.45 mmol) in DMF (10 mL). The resulting white suspension was stirred at 0 °C for 10 minutes, at which time the external ice-water bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring during 2 h. The reaction mixture again was

cooled to 0 °C via application of an external ice-water bath, and to the cooled reaction mixture was added dropwise with stirring a solution of 1-(benzyoxy)-2-(*p*-toluenesulfonyloxy)ethane (5.02 g, 16.4 mmol) in DMF (10 mL). The resulting suspension was stirred at 0 °C for 10 minutes, at which time the external cold bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature and was stirred at that temperature for 2 days. The reaction mixture was concentrated *in vacuo*, and ice-water (50 mL) was added to the residue. The resulting aqueous suspension was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 40 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 20% EtOAc-hexane. Pure **8** (1.7 g, 44%) was thereby obtained as a colorless viscous oil. IR (film) 2951 (s), 2870 (s), 1450 (m), 1111 (vs), 736 cm<sup>-1</sup> (s); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.45 (AB, *J*<sub>AB</sub> = 10.3 Hz, 1 H), 1.82 (AB, *J*<sub>AB</sub> = 10.3 Hz, 1 H), 2.10 (t, *J* = 7.14 Hz, 4 H), 2.36 (br s, 2 H), 2.48–2.54 (m, 6 H), 3.51–3.59 (m, 12 H), 4.55 (s, 4 H), 7.27–7.34 (m, 10 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 32.8 (t), 41.8 (d), 43.4 (t), 44.5 (d), 48.4 (d), 58.8 (d), 68.4 (t), 69.5 (t), 70.2 (t), 73.2 (t), 94.4 (s), 127.6 (d), 127.7 (d), 128.3 (d), 138.3 (s). Anal. Calcd for C<sub>33</sub>H<sub>40</sub>O<sub>5</sub>: C, 76.71; H, 7.80; Found: C, 76.48; H, 7.70.

**3,5-Bis[2-(2'-hydroxyethoxy)ethyl]-4-oxahexacyclo[5.4.1.0<sup>2,6</sup>.0<sup>3,10</sup>.0<sup>5,9</sup>.0<sup>8,11</sup>]dodecane (9)**. To a solution of **8** (1.70 g, 3.29 mmol) in EtOH (50 mL) was added 10% Pd-C (180 mg), and the resulting mixture was hydrogenated by using H<sub>2</sub> (g) (58 psi) on a Parr shaker apparatus during 24 h. The reaction mixture was filtered through a bed of Celite to remove spent catalyst. The filtrate was concentrated *in vacuo*, thereby affording **9** (990 mg, 89%), as a colorless viscous oil; IR (film) 3416 (s), 2945 (s), 2864 (s), 1367 (w), 1128 (s), 1066 cm<sup>-1</sup> (s); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.44 (AB, *J*<sub>AB</sub> = 10.4 Hz, 1 H), 1.80 (AB, *J*<sub>AB</sub> = 10.4 Hz, 1 H), 2.01 (t, *J* = 6.6 Hz, 4 H), 2.32 (br s, 2 H), 2.40–2.53 (m, 6 H), 3.04 (s, 2 H, peak disappears when NMR sample is shaken with D<sub>2</sub>O), 3.40–3.61 (m, 12 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 32.2 (t), 41.5 (d), 43.3 (t), 44.2 (d), 48.1 (d), 58.5 (d), 61.4 (t), 67.8 (t), 71.7 (t), 94.7 (s). Anal. Calcd for C<sub>19</sub>H<sub>28</sub>O<sub>5</sub>: C, 67.83; H, 8.39; Found: C, 67.60; H, 8.23.

**3,5-Bis[2-(2'-*p*-toluenesulfonyloxyethoxy)ethyl]-4-oxahexacyclo[5.4.1.0<sup>2,6</sup>.0<sup>3,10</sup>.0<sup>5,9</sup>.0<sup>8,11</sup>]dodecane (10)**. A solution of *p*-TsCl (0.697 g, 3.66 mmol) in dry pyridine (6 mL) was placed in a round-bottom flask that previously had been thoroughly flushed with argon. This solution was cooled to 0 °C via application of an external ice-water bath. To the this cooled solution was added dropwise with stirring a solution of **9** (410 mg, 1.22 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL) during 15 minutes. After the addition of **9** had been completed, the external ice-water bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring overnight. The reaction mixture was poured into ice-water (150 mL), and the resulting aqueous suspension was extracted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL). The organic layer was washed with ice-cold 5 M HCl (2 × 50 mL), dried (MgSO<sub>4</sub>), and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 50% EtOAc-hexane. Compound **10** (550 mg, 70%) was thereby obtained as a colorless viscous oil; IR (film) 2958 (s), 2872 (m), 1356 (s), 1178 (vs), 1024 (m), 927 (s), 665 cm<sup>-1</sup> (m); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.45 (AB, *J*<sub>AB</sub> = 10.4 Hz, 1 H), 1.81 (AB, *J*<sub>AB</sub> = 10.4 Hz, 1 H), 1.97 (t, *J* = 7.0 Hz, 4 H), 2.30 (br s, 2 H), 2.42 (s, 10 H), 2.49–2.58 (m, 2 H), 3.45 (t, *J* = 7.0 Hz, 4 H), 3.57 (t, *J* = 4.8 Hz, 8 H), 4.11 (t, *J* = 4.8 Hz, 4 H), 7.31 (AB, *J*<sub>AB</sub> = 8.2 Hz, 2 H), 7.77 (AB, *J*<sub>AB</sub> = 8.2 Hz, 2 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 21.6 (q), 32.6 (t), 41.7 (d), 43.4 (t), 44.4 (d), 48.3 (d), 58.7 (d), 68.1 (t), 68.4 (t), 69.2 (t), 94.2 (s), 127.9 (d), 129.8 (d), 133.0 (s), 144.7 (s). Anal. Calcd for C<sub>33</sub>H<sub>40</sub>O<sub>9</sub>S<sub>2</sub>: C, 61.47; H, 6.25; Found: C, 61.62; H, 6.08.

**Crown Ether 11**. To a suspension of NaH (60% suspension in mineral oil, 675 mg, 2.7 mmol) in dry THF (15 mL) under argon was added dropwise with stirring a solution of **10** (200 mg, 1.35 mmol) in dry THF (45 mL), and the resulting mixture was refluxed with stirring during 0.5 h. To the reaction mixture was added drop-wise with stirring a solution of **1d** (350 mg, 1.35 mmol) in dry THF (75 mL) during 0.5 h. After the addition of **1d** had been completed, the resulting mixture was refluxed for 72 h. The reaction mixture was allowed to cool gradually to ambient temperature and then was quenched via addition of water (5 mL). The resulting aqueous suspension was extracted with CHCl<sub>3</sub> (4 × 25 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on neutral alumina by eluting with 50% EtOAc-hexane. Pure **11** (250 mg, 53%) was thereby obtained as a colorless

oil: IR (film) 3408 (br, s), 2987 (s), 1714 (m), 1597 (w), 1454 (m), 1257 (s), 1103 (s), 748  $\text{cm}^{-1}$  (s);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.40 (d,  $J = 10.5$  Hz, 1 H), 1.73–2.72 (m, 9 H), 3.40–3.73 (m, 4 H), 4.71 (m, 8 H), 7.12 (d,  $J = 8.1$  Hz, 2 H), 7.50 (t,  $J = 7.0$  Hz, 1 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  31.3 (t), 41.5 (d), 43.3 (t), 44.1 (d), 49.0 (d), 58.1 (d), 65.6 (t), 70.8 (t), 94.2 (s), 122.7 (d), 135.9 (d), 157.9 (s). Anal. Calcd for  $\text{C}_{22}\text{H}_{25}\text{NO}_3$ : C, 75.17; H, 7.17. Found: C, 74.85; H, 7.26. Exact mass (CI HRMS) Calcd for  $\text{C}_{22}\text{H}_{25}\text{NO}_3$ :  $[\text{M}_T + \text{H}]^+$  352.19127. Found:  $[\text{M}_T + \text{H}]^+$  352.19014.

**Crown Ether 12.** To a suspension of NaH (60% suspension in mineral oil, 46 mg, 1.79 mmol) in dry THF (14 mL) under argon was added dropwise with stirring a solution of **1b** (84 mg, 0.60 mmol) in dry THF (23 mL), and the resulting mixture was refluxed with stirring during 0.5 h. To the reaction mixture was added dropwise with stirring a solution of **10** (370 mg, 0.60 mmol) in dry THF (35 mL) during 0.5 h. After all of the reagent, **9**, had been added, the resulting mixture was refluxed for 56 h. The reaction mixture was allowed to cool gradually to ambient temperature and then was quenched via addition of water (20 mL). The resulting aqueous suspension was extracted with  $\text{CHCl}_3$  ( $4 \times 25$  mL). The combined organic layers were dried ( $\text{MgSO}_4$ ) 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 **12** (120 mg, 38%) was thereby obtained as a colorless oil: IR (film) 3350 (s), 2930 (s), 1730 (m), 1580 (m), 1456 (m), 1223 (s), 732  $\text{cm}^{-1}$  (s);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.40 (AB,  $J_{AB} = 10.1$  Hz, 1 H), 1.67 (AB,  $J_{AB} = 10.1$  Hz, 1 H), 1.95 (t,  $J = 6.8$  Hz, 4 H), 2.25 (s, 2 H), 2.35–2.48 (m, 6 H), 3.43–3.82 (m, 12 H), 4.73 (s, 4 H), 7.35 (d,  $J = 7.1$  Hz, 2 H), 7.76 (t,  $J = 7.8$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  32.3 (t), 41.5 (d), 43.3 (t), 44.1 (d), 47.9 (d), 58.9 (d), 67.6 (t), 69.5 (t), 69.7 (t), 73.8 (t), 94.2 (s), 120.7 (d), 136.9 (d), 157.9 (d). Anal. Calcd for  $\text{C}_{26}\text{H}_{33}\text{NO}_5$ : C, 71.05; H, 7.57. Found: C, 70.86; H, 7.60.

**Crown Ether 13.** To a mixture of **10** (190 mg, 0.30 mmol) and  $\text{Na}_2\text{CO}_3$  (160 mg, 1.5 mmol) in  $\text{CH}_3\text{CN}$  (15 mL) was added **1c** (98 mg, 0.3 mmol), and the resulting mixture was refluxed for 34 h. The reaction mixture was allowed to cool gradually to ambient temperature; the reaction mixture then was filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in  $\text{CHCl}_3$  (20 mL), and the resulting solution was washed with water ( $3 \times 20$  mL). The organic layer was dried ( $\text{MgSO}_4$ ) 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 **13** (48 mg, 27%) was thereby obtained as a colorless oil: IR (film) 3408 (br, s), 2950 (s), 1708 (m), 1610 (w), 1438 (m), 1247 (s), 1112 (s), 738 (m), 700  $\text{cm}^{-1}$  (m);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.51 (d,  $J = 11.0$  Hz, 1 H), 1.71–2.03 (m, 5 H), 2.32–2.61 (m, 12 H), 2.74 (t,  $J = 6.5$  Hz, 4 H), 3.45 (t,  $J = 5.4$  Hz, 8 H), 3.70 (s, 2 H), 3.85 (s, 2 H), 7.21–7.53 (m, 12 H), 7.64 (t,  $J = 8.0$  Hz 1 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  32.3 (t), 42.0 (d), 43.9 (t), 44.5 (d), 48.5 (d), 53.4 (t), 59.4 (d), 60.8 (t), 61.5 (t), 67.9 (t), 69.7 (t), 94.7 (s), 121.3 (d), 127.4 (d), 128.7 (d), 129.3 (d), 137.1 (d), 140.0 (s), 160.1 (s). Anal. Calcd for  $\text{C}_{40}\text{H}_{47}\text{N}_3\text{O}_3$ : C, 77.76; H, 7.67. Found: C, 77.51; H, 7.78.

**Li<sup>+</sup> Cryptate 15.** To a mixture of **5** (494 mg, 0.89 mmol) and  $\text{Li}_2\text{CO}_3$  (270 mg, 3.65 mmol) in  $\text{CH}_3\text{CN}$  (30 mL) was added **14<sup>23</sup>** (200 mg, 0.83 mmol), and the resulting mixture was refluxed for 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%  $\text{CH}_3\text{OH}-\text{CH}_2\text{Cl}_2$ . Pure Li<sup>+</sup> cryptate **15** (224 mg, 43%) was thereby obtained as a colorless, tacky semi-solid: IR ( $\text{CHCl}_3$ ) 3350 (br, s), 2963 (s), 1724 (w), 1585 (m), 1456 (m), 1223 (s), 1354 (w), 1008 (m), 751 (w), 732 (s), 680  $\text{cm}^{-1}$  (m);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.65 (d,  $J = 11.7$  Hz, 1 H), 2.14–2.25 (m, 5 H), 2.60 (s, 1 H), 2.76–2.90 (m, 8 H), 3.25–3.40 (m, 4 H), 3.70–3.83 (m, 4 H), 4.09–4.28 (m, 6 H), 6.80 (d,  $J = 8.0$  Hz, 4 H), 7.05 (AB,  $J_{AB} = 7.2$  Hz, 2 H), 7.30 (t,  $J = 8.4$  Hz, 2 H); 7.75 (AB,  $J_{AB} = 7.2$  Hz, 2 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.9 (q), 29.5 (t), 41.1 (d), 43.4 (t), 43.8 (d), 47.0 (d), 55.8 (t), 57.8 (d), 63.2 (t), 63.6 (t), 96.4 (s), 120.1 (d), 125.8 (d), 127.9 (d), 134.1 (s), 138.3 (d), 144.2 (s), 157.1 (s) Exact mass (CI HRMS) Calcd for  $\text{C}_{29}\text{H}_{32}\text{N}_4\text{OLi}$ :  $[\text{M}_T]^+$  459.27362. Found:  $[\text{M}_T]^+$  459.27432.



**Cryptand 16.** A solution of **15** (220 mg, 0.35 mmol) in CHCl<sub>3</sub> (50 mL) was placed in separatory funnel, placed on a mechanical shaker apparatus, and extracted with H<sub>2</sub>O (30 mL). The layers were separated after each 12 h interval, the water layer was replaced at that time with fresh water, and the extraction procedure was continued for a total of 5 days. The presence (or absence) of LiOTs was confirmed by withdrawing aliquots at 24 h intervals; each aliquot was then concentrated *in vacuo*, and the residue was analyzed via careful inspection of its <sup>1</sup>H NMR spectrum. After the lengthy water-extraction procedure had been completed, the layers in the separatory were separated. The organic layer then was filtered, and the filtrate was concentrated *in vacuo*. Pure **16** (98 mg, 62%) was thereby obtained as a colorless oil; IR (film) 3376 (br, s), 2938 (s), 1634 (m), 1603 (m), 1444 (m), 1200 (s), 1030 (m), 749 cm<sup>-1</sup> (s); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.40 (d, *J* = 11.7 Hz, 1 H), 1.65–1.80 (m, 5 H), 2.07–2.31 (m, 3 H), 2.63–2.90 (m, 5 H), 3.21–3.34 (m, 4 H), 3.73 (m, 4 H), 4.12–4.30 (m, 2 H), 7.40 (m, 4 H), 7.94 (m, 2 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 30.5 (t), 40.3 (d), 43.3 (t), 43.8 (d), 47.1 (d), 55.0 (t), 58.2 (d), 60.3 (t), 60.6 (t), 95.5 (s), 121.5 (d), 121.6 (d), 140.8 (d), 141.2 (d), 155.6 (s), 157.2 (s). Exact mass (CI HRMS) Calcd for C<sub>29</sub>H<sub>32</sub>N<sub>4</sub>O: [*M*<sub>r</sub> + H]<sup>+</sup> 453.26544. Found: *M*<sub>r</sub><sup>+</sup> 453.26628.

**Alkali Metal Picrate Extraction Experiments.** The extraction experiments were performed by using 5mM solutions of each compounds in CHCl<sub>3</sub>. The procedure that was used for this purpose has been described elsewhere.<sup>28</sup>

**X-ray Structure Determination of 6.** All data were collected at ambient temperature on a Rigaku AFC6S diffractometer with graphite monochromated Cu K $\alpha$  radiation ( $\lambda = 1.54178 \text{ \AA}$ ) by using the  $\theta$ – $2\theta$  scan technique with multiple scans for weak reflections. Pertinent X-ray data are given in Table 2. Data were corrected for Lorentz and polarization effects. Secondary extinction, and  $\psi$ -scan absorption corrections were applied. The structure was solved by direct methods (SIR92).<sup>29</sup> The model was refined by using full-matrix least-squares techniques. The non-hydrogen atoms were refined anisotropically; hydrogen atoms were included but were not refined. All calculations were performed by using TEXSAN.<sup>30</sup> Scattering factors were taken from Cromer and Waber.<sup>31</sup>

**Table 2.** X-ray data collection and processing parameters for **6**.

Compound	<b>6</b>	Z-value	4
		<i>D</i> <sub>calc</sub> (g·cm <sup>-3</sup> )	1.214
Formula	C <sub>28</sub> H <sub>28</sub> N <sub>4</sub>	$\mu$ (cm <sup>-1</sup> )	5.61
Size (mm)	0.10 x 0.20 x 0.20	T (K)	294
Space Group	P2 <sub>1</sub> /a (#14)	$2\theta_{\text{max}}$ (°)	156.9
a (Å)	11.991 (7)	Total reflections	4383
b (Å)	11.640 (3)	Unique reflections	4138 ( <i>R</i> <sub>int</sub> = 0.255)
c (Å)	16.503 (4)	Observed Reflections $I \geq 3\sigma(I)$	2043
$\alpha$ (°)	90	Parameters	290
$\beta$ (°)	92.39 (4)	<i>R</i> , <i>R</i> <sub>w</sub>	0.072; 0.088
$\gamma$ (°)	90	( $\Delta\sigma$ ) <sub>max</sub>	0.00
<i>V</i> (Å <sup>3</sup> )	2301 (1)	$\rho_{\text{max}}$ ; $\rho_{\text{min}}$ (eÅ <sup>-3</sup> )	0.30; -0.29

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