Structure-cation complexation relationships for *ortho-*, *meta-*, and *para*-substituted bis(oxymethylcrown)benzenes and α,α'-xylenes

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Abstract

New bis(crown ether) compounds are synthesized by attaching two (hydroxymethyl)crown ether units to a benzene or α,α'-xylene framework. Bis(15-crown-5) polyether substitution patterns are varied from ortho to meta to para. *ortho*-Bis(18-crown-6) polyethers are prepared together with mono(crown ether) analogs, as well as *ortho*-bis(12-crown-4) polyethers. Complexation abilities of these compounds for alkali metal cations are evaluated by picrate extraction allowing the influence of structural modifications in the ligands on extraction constants (K_{ex}) and association constants (K_a) for alkali metal cations to be assessed.

Keywords: Host-guest chemistry, bis(crown ethers), alkali metal cations, complexation, picrate extraction
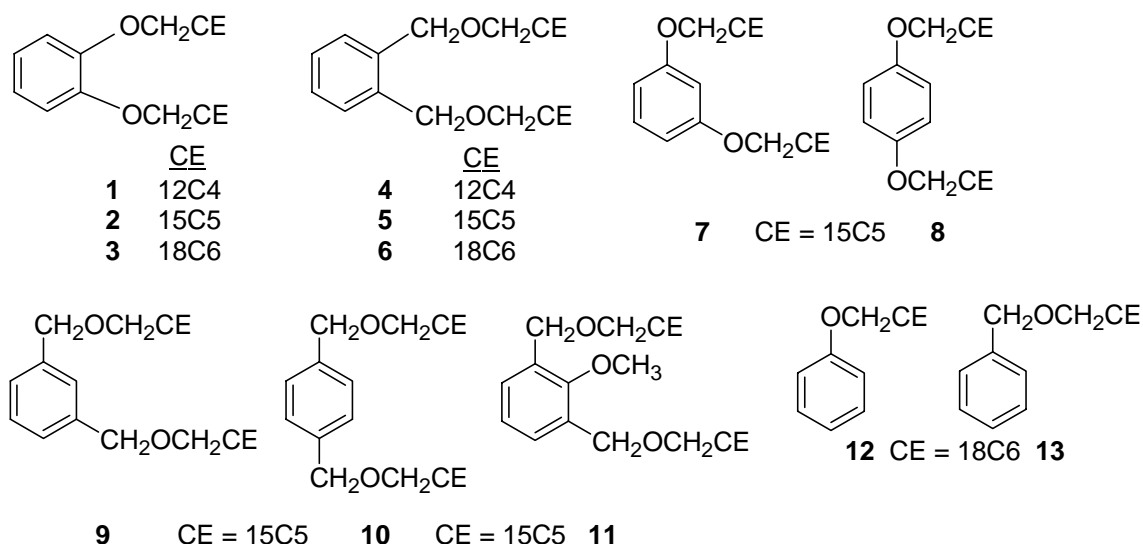
Introduction

Early in the investigation of crown ether-cation interactions it was determined that crown ethers can form 2:1 (host:guest) "sandwich" complexes with cations that are too large to fit into the macrocyclic cavity.[1-5] This led to the synthesis of new compounds in which two or more crown ether units were covalently linked in a fashion to promote formation of intramolecular 2:1 (crown ether:cation) complexes.[6] Subsequently, bis(crown ethers) have found a variety of applications and their enhanced binding properties and greater selectivities than mono(crown ethers) have been well-established.[7-13]

We now report the results of a systematic study of structural variations in bis(crown ethers) formed by attaching two (hydroxymethyl)crown ether units to a benzene or α,α'-xylene framework. The influence of these structural variations (crown ether ring size and length of the spacer between the crown ether ring and the central benzene ring) upon alkali metal cation complexation are assessed by picrate extraction.

Results and Discussion

Synthesis

Bis[(oxymethyl)crown] ethers **1-3**, **7**, and **8** and the analogous mono(oxymethyl)crown ether **12** were prepared by reaction of the appropriate dihydroxybenzene (or phenol for **12**) with NaH or KH in THF and then with the appropriate (tosyloxymethyl)crown ether. Refluxing the mixture for 48 hours and workup with purification of the crude product by column chromatography gave these polyether ligands as oils in 65-85% yields.

α,α'-Bis-[(oxymethyl)crown] xylenes **4-6** and **9-11** were synthesized by reaction of the appropriate (hydroxymethyl)crown ether with NaH in THF and then with the appropriate α,α'-dibromoxylene. Refluxing the mixture overnight and workup with purification of the crude product by column chromatography produced these polyether ligands as oils in 50-77% yields.

For bis(crown ethers) **1-3** and **4-6**, the systematic structural variation is changing the crown ether ring size from 12-crown-4 to 15-crown-5 to 18-crown-6. For the two series of bis(crown ethers) **2, 7, 8** and **5**, **9**, **10**, there is a common 15-crown-5 ring size and the attachment of the two crown ether-containing substituents to the central benzene unit is varied from ortho to meta to para. The series of bis(crown ethers) **1-3**, **7**, **8** differs from the series **4-6**, **9**, **11** in the former has a -CH$_2$O- linkage between the crown ether ring and benzene ring and for the latter this linkage is -CH$_2$OCH$_2$-. For *meta*-bis(15-crown-5) ethers **9** and **11**, the hydrogen on the benzene ring between the two crown ether-containing substituents in the former is replaced by a methoxy group in the latter.

The alkali metal ion complexing properties of bis(crown ether) ligands **1-11** and their mono(crown ether) analogs **12** and **13** were evaluated by alkali metal picrate extractions from

aqueous solutions into deuteriochloroform. Extraction constants (K_{ex})[14] and association constants (K_a)[15] were calculated by reported procedures. The stoichiometry of each extraction complex was ascertained from the position of the absorption maximum for the picrate anion in the organic phase after dilution with THF.[5] A maximum in the range of 375-385 nm indicates a separated ion pair and is consistent with formation of a sandwich complex involving two crown ether units and one metal ion. A maximum in the range of 355-365 nm reveals a tight ion pair and association of the alkali metal cation with a single polyether ring. Hereafter, we will refer to the former as a 2:1 complex [even though both crown ether rings are provided by a bis(crown ether) ligand] and the former as a 1:1 complex.

Bis(12-crown-4) hosts 1 and 4

Picrate extraction data and association constants (K_a) for complexation of alkali metal picrates by bis(crown ethers) **1** and **4**, which each have two 12-crown-4 rings, are presented in Table 1.

Table 1. Alkali metal picrate extraction from aqueous solution into deuteriochloroform by bis(12-crown-4) ligands **1** and **4**

Ligand	M^+	Percent extraction	log K_{ex}	log K_a	λ_{max}(nm)
1	Li	0.4	1.02	3.86	383
	Na	3.2	1.89	4.65	367
	K	1.2	1.42	4.01	378
	Rb	1.0	1.39	3.73	379
	Cs[a]	ND[b]	-----	-----	----
4	Li	0.8	1.25	4.10	380
	Na	5.6	2.16	4.92	365
	K	1.3	1.44	4.03	380
	Rb	0.8	1.25	3.58	380
	Cs[a]	0.3	1.71	3.97	380

[a]Cesium picrate extractions were conducted using a different concentration. [b]Not detected.

Complexation of Li^+ by 12-crown-4 hosts has been the subject of earlier investigations.[16-18] Although at least one X-ray crystal structure has appeared showing Li^+ in a 12-crown-4 sandwich complex,[19] this is probably a rare occurrence, especially in solution. The λ_{max} values observed for extractions of lithium picrate by bis(crown ethers) **1** and **4** indicate separated ion pairs. However, it is postulated that this is the result of water in the Li^+ solvation sphere of the extraction complex, rather than formation of a sandwich complex.

Although the association constants for all of the alkali metal cations are small, both bis(12-crown-4) ligands **1** and **4** exhibit their greatest extraction capacity for Na^+. The λ_{max} values for sodium picrate extraction are intermediate between those for tight and separated ion pairs indicating that the extraction complexes are a mixture of Na^+ associated with one and both crown

ether rings in the bis(crown ether) host. The association constant for complexation of sodium picrate is higher for **4**, which has a longer spacer between the polyether ring and the central benzene ring, than for **1**. The λ_{max} values for complexes formed in potassium, rubidium, and cesium picrate extractions are consistent with 2:1 complexes.

The association constants in deuteriochloroform decrease in the order $Na^+>K^+>Li^+>Rb^+>Cs^+$ for **1** and $Na^+>Li^+>K^+,Cs^+>Rb^+$ for **4**.

Bis(15-crown-5) hosts

The influence of two different structural modifications were probed with bis(15-crown-5) ethers: i) attachment of the two crown ether-containing substituents ortho, meta, and para on the central benzene ring; and, ii) changing the length of the spacer between the crown ether unit and the central benzene ring.

Bis(oxymethyl-15-crown-5)benzenes 2, 7, and 8

Picrate extraction data and association constants (K_a) for complexation of alkali metal picrates by bis(crown ethers) **2**, **7**, and **8**, which each have two $-OCH_2$(15-crown-5) substituents, are presented in Table 2.
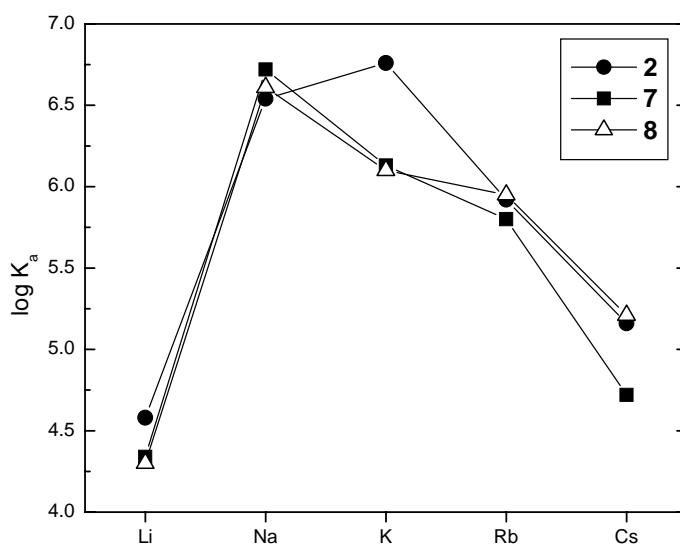
Table 2. Alkali metal picrate extraction from aqueous solution into deuteriochloroform by bis(15-crown-5) ligands **2**, **7**, and **8**

Ligand	M^+	Percent extraction	log K_{ex}	log K_a	λ_{max}(nm)
2	Li	2.2	1.73	4.58	358
	Na	50.2	3.76	6.54	354
	K	62.4	4.11	6.76	380
	Rb	43.4	3.94	5.92	380
	Cs[a]	3.2	2.94	5.16	380
7	Li	1.3	1.50	4.34	355
	Na[b]	56.6	3.97	6.72	----
	K[b]	41.6	3.53	6.13	----
	Rb[b]	39.0	3.46	5.80	355
	Cs[a]	1.3	2.48	4.72	353
8	Li	1.2	1.48	4.30	353
	Na[b]	52.6	3.85	6.61	351
	K[b]	40.6	3.51	6.10	354
	Rb[b]	44.2	3.62	5.95	355
	Cs[a,b]	3.5	2.95	5.21	357

[a]Cesium picrate extractions were conducted using a different concentration. [b]Calculated from aqueous phase absorbance readings (see Experimental Section).

Extractions of Li$^+$ and Cs$^+$ were uniformly inefficient throughout the series. Association constants for complexation of sodium picrate by **2**, **7**, and **8** are high and show little variation as the attachment of the crown ether-containing substitutents is varied from ortho to meta to para. The λ_{max} values are consistent with 1:1 complexation of Na$^+$. On the other hand, the λ_{max} values reveal 2:1 complexation with the *ortho*-substituted ligand **2** and K$^+$, as well as Rb$^+$ and Cs$^+$. The association constants for complexation of alkali metal picrates by ligand **2** decrease in the order of K$^+$>Na$^+$>Rb$^+$>Cs$^+$>Li$^+$. The *meta*-substituted isomer **7** formed a precipitate when the deuteriochloroform solution obtained by extraction of the aqueous potassium picrate solution was diluted with THF, rendering determination of the stoichiometry by UV-visible absorbance impossible (see Experimental Section). However, the 1:1 complex stoichiometry evident for K$^+$ with the *para*-substituted isomer **8** and the similarity of association constants for complexation of K$^+$ with **7** and **8** strongly suggests formation of a 1:1 complex for **7** with K$^+$ as well. The λ_{max} values for complexes of Rb$^+$ and Cs$^+$ with **7** and **8** are also consistent with 1:1 complexation.

Association constants for complexation of alkali metal picrates by the *meta*- and *para*-substituted isomers **7** and **8**, respectively, decrease in the order Na$^+$>K$^+$>Rb$^+$>Cs$^+$>Li$^+$, which is a reversal of the relative positions for Na$^+$ and K$^+$ in the ordering observed for the *ortho*-substituted isomer **2**. The enhanced complexation of K$^+$ by **2** is clearly evident from the graphical presentation of the association constant data for isomers **2**, **7**, and **8** in Figure 1.

Figure 1. Association constants for complexation of alkali metal picrates by bis(15-crown-5) compounds **2**, **7**, and **8** in deuteriochloroform.

α,α'-Bis(oxymethyl-15-crown-5)xylenes 5 and 9-11

Picrate extraction data and association constants (K_a) for complexation of alkali metal picrates by bis(crown ethers) **5**, **9**, and **10**, which each have two -CH_2OCH_2(15-crown-5) substituents, are presented in Table 3. For **5**, **9**, and **10**, the structural variation is attachment of the two crown ether-containing substituents ortho, meta, and para, respectively on the central benzene ring.

Table 3. Alkali metal picrate extraction from aqueous solution into deuteriochloroform by bis(15-crown-5) ligands **5**, **9**, **10** and **11**
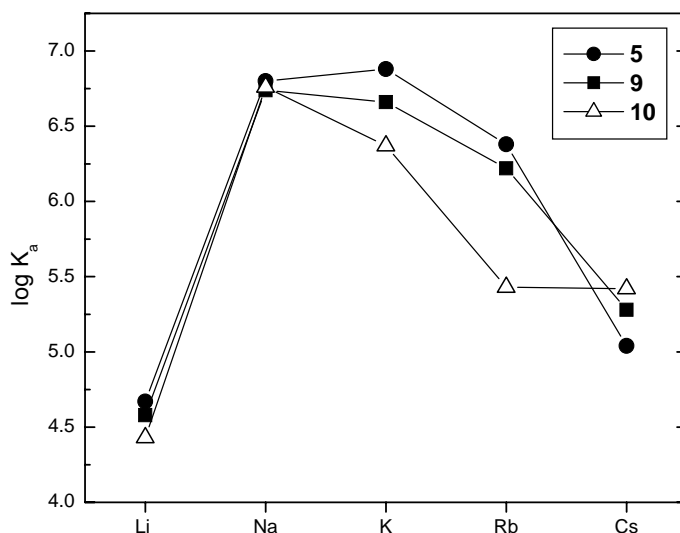
Ligand	M^+	Percent extraction	$\log K_{ex}$	$\log K_a$	λ_{max}(nm)
5	Li	2.8	1.83	4.67	356
	Na	58.8	4.00	6.80	354
	K	66.4	4.22	6.88	379
	Rb	58.8	4.04	6.38	379
	Cs[a]	2.5	2.84	5.04	363
9	Li	2.3	1.73	4.58	356
	Na	57.0	3.99	6.74	354
	K	59.6	4.03	6.66	380
	Rb[b]	53.6	3.88	6.22	380
	Cs[a]	3.9	3.05	5.28	367
10	Li	1.6	1.59	4.43	355
	Na	57.6	4.04	6.76	352
	K[b]	50.0	3.78	6.37	357
	Rb	26.4	3.11	5.43	359
	Cs[a,b]	5.0	3.16	5.42	360
11	Li	14.3	2.67	5.52	350
	Na	53.0	3.84	6.62	353
	K	35.4	3.36	5.96	360
	Rb	27.8	3.15	5.48	359
	Cs[a]	10.2	3.27	5.54	360

[a]Cesium picrate extractions were conducted using a different concentration. [b]Calculated from aqueous phase absorbance readings (see Experimental Section).

In almost every case, association constants for complexation of the alkali metal picrates were increased by lengthening of the spacer between the crown ether unit and central benzene ring in bis(15-crown-5) analogues **2**, **7**, and **8**. Only the association constants of **5** with Cs^+ and **10** with Rb^+ showed decreases compared with **7** and **8**.

Extraction efficiencies of these hosts for Li^+ were again uniformly low. Association constants for Na^+ remain constant as the attachment sites for the two crown ether-containing substituents are varied from ortho to meta to para. Once again the λ_{max} values show that the ortho isomer (**5**) forms 2:1 complexes with K^+ and Rb^+. The extraction complex for Cs^+ and **5** appears to have mixed stoichiometry.

Although some propensity for complexation of the larger metal ions is lost in going from *ortho*-isomer **5** to *meta*-isomer **9**, the λ_{max} values reveal that the latter continues to form 2:1 complexes with K^+ and Rb^+. The *para*-isomer **10** does not form 2:1 complexes with any of the alkali metal cations. Differences in the nature of K^+ and Rb^+ complexation by **5** and **9** versus **10** is responsible for the markedly enhanced affinities of **5** and **9** for these alkali metal cations, especially for Rb^+ (see Figure 2). Small, but steady, increases in association constants for Cs^+ complexation in going from **5** to **9** to **10** may be due to easier formation of intermolecular complexes of the 2:1 type or could reflect enhanced interaction of this soft cation with the π-electron cloud of the benzene ring during complexation.[20] However, preliminary ^{1}H NMR studies of **10** in d_6-acetone showed no downfield shift of the aromatic protons upon addition of cesium nitrate to the sample, indicating little or no π-cloud interaction.

Figure 2. Association constants for complexation of alkali metal picrates by bis(15-crown-5) compounds **5**, **9**, and **10**.

1-Methoxy-2,6-bis(α,α'-oxymethyl-15-crown-5)xylene (11)
Replacement of the hydrogen on the central benzene ring between the two crown ether-containing substituents in *meta*-isomer **9** gives bis(15-crown-5) **11**. Picrate extraction data and association constants (K_a) for complexation of alkali metal picrates by **9** and **11** are given in Table 3. From the λ_{max} values for alkali metal picrate extraction by **11**, only 1:1 complexation is

evident. In agreement, Na^+, which provides the best match with the cavity size of a single 15-crown-5 unit, has the largest association constant. Association constants for complexation of alkali metal picrates decrease in the order $Na^+>K^+>Li^+, Rb^+, Cs^+$.

Bis(18-crown-6) hosts 3 and 6 and mono(18-crown-6) hosts 12 and 13

Bis(18-crown-6) hosts

Picrate extraction data and association constants (K_a) for complexation of alkali metal picrates by bis(crown ethers) **3** and **6** are presented in Table 4.

Table 4. Alkali metal picrate extraction from aqueous solution into deuteriochloroform by bis(18-crown-6) ligands **3** and **6**

Ligand	M^+	Percent extraction	$\log K_{ex}$	$\log K_a$	λ_{max}(nm)
3	Li	3.2	1.87	4.72	380
	Na	24.2	3.04	5.79	366
	K	95.2	6.04	8.85	366
	Rb	82.4	5.06	7.34	366
	Cs[a]	19.6	4.37	6.67	370
6	Li	3.4	1.92	4.76	380
	Na	21.0	2.95	5.68	364
	K	93.2	5.71	8.51	366
	Rb	83.8	5.08	7.42	365
	Cs[a]	19.0	4.34	6.62	370

[a]Cesium picrate extractions were conducted using a different concentration.

For the bis(18-crown-6) ligands **3** and **6**, λ_{max} values for all of the alkali metal picrates except Li^+ are consistent with 1:1 complexes. In agreement, K^+, which provides the best match with the cavity size of a single 18-crown-6 unit, has the largest association constant. Association constants for complexation of alkali metal picrates decrease in the order $K^+>Rb^+>Cs^+>Na^+>Li^+$. Although the λ_{max} values for Li^+ might suggest 2:1 complexes, they are attributed instead to the ability of Li^+ to carry waters of solvation into its complexes with large ring crown ethers.[21]

Comparison of bis(18-crown-6) hosts 3 and 6 with mono(18-crown-6) hosts 12 and 13

In the extraction studies of K^+ with bis(18-crown-6) compounds **3** and **6**, the association constants were so high that it was necessary to conduct separate extractions at a host:guest ratio of 1:2 (ligand:alkali metal picrate). Extraction data and association constants for bis(18-crown-6) ligands **3** and **6** determined under these conditions are compared with those for mono(18-crown-6) model compounds **12** and **13** obtained with the customary 1:1 host:guest ratio are presented in Table 5. The differing ratios correct for the fact that each bis(crown ether) ligand provides two 18-crown-6 units, while each mono(crown ether) molecule has a single 18-crown-6 ring.

Comparison of the data for bis(crown ether) **3** with mono(crown ether) **12** and of bis(crown ether) **6** with mono(crown ether) **13** reveals no substantial differences between the extraction data and association constants obtained under these conditions. This is consistent with formation of only 1:1 complexes (one crown ether unit per metal ion) and is supported by the λ_{max} values for the four ligands.

Table 5. Alkali metal picrate extraction from aqueous solution into deuteriochloroform by bis(18-crown-6) ligands **3** and **6** and mono(18-crown-6) ligands **12** and **13**

Ligand	M^+	Percent extraction	$\log K_{ex}$	$\log K_a$	λ_{max}(nm)
3[a]	Na	32.7	3.10	5.84	359
	K	85.7	5.60	8.12	367
6[a]	Na	25.8	2.87	5.60	359
	K	69.6	4.63	7.03	367
12[b]	Na	24.9	2.81	5.57	351
	K	81.5	5.09	7.73	365
	Rb	63.4	4.78	7.10	361
13[b]	Na	24.3	2.80	5.56	358
	K	66.8	4.27	6.90	367
	Rb	64.4	4.83	7.14	362

[a]Extractions performed with 15 mM bis(crown ether) and 30 mM metal picrate. [b]Extractions performed with 30 mM crown ether and 30 mM metal picrate.

Summary
The new biscrown ethers **1-10** provide a series with systematic structural variations of the ring size, the positioning of the two crown ether rings on a central benzene unit and the length of the tether that connects each crown ether unit to the benzene ring. Alkali metal picrate extraction results reveal that these structural variations affect the efficiency with which a particular metal ion is extracted, as well as its interaction with one or both crown ether rings.

In **1** and **4**, the two 12-crown-4 rings are attached ortho on the benzene ring by -OCH$_2$- and -CH$_2$OCH$_2$- units, respectively. Compared with the other biscrown ether compounds, **1** and **4** are only weak extractants for alkali metal cations. Both ligands give strongest complexation of Na$^+$ with formation of mixed complexes in which the metal ion interacts with one and both polyether rings. For K$^+$ and Rb$^+$, both crown ether units interact with the complexed metal ion.

The most complete structural effect study includes the five bis(15-crown-5) compounds **2**, **5**, and **7-9**. In the alkali metal picrate extractions, all of these ligands are weak extractants of Li$^+$ and Cs$^+$. For **2**, **7**, and **8**, the two crown ether rings are positioned ortho, meta and para, respectively, with -OCH$_s$- tethers between the 15-crown-5 rings and the central benzene ring. The association constant orders are K$^+$ > Na$^+$ > Rb$^+$ for **2** and Na$^+$ > K$^+$ > Rb$^+$ for **7** and **8**. This differing ordering for *ortho*-substituted ligand **2** results from interaction of K$^+$ with both crown

ether rings; whereas the complexed metal ion interacts with only one cyclic polyether unit in **7** and **8**. With alteration of the tether to -CH_2OCH_2-, the extraction selectivity is K^+, $Na^+ > Rb^+$ for **5** and **9**, but $Na^+ > K^+ > Rb^+$ for **10** with K^+ complexed by two crown ether rings in **5** and **9**, but only one in **10**. For the two *ortho*-substituted bis(18-crown-6) compounds **3** and **6**, the stability constant order is $K^+ > Rb^+ > Na^+ > Cs^+ > Li^+$ and only interactions of the complexed metal ion with a single crown ether unit are evident.

Experimental Section

General Procedures. IR spectra were obtained on neat samples with a Nicolet MX-S spectrometer and are recorded in wavenumbers. ^{1}H NMR spectra were recorded with a Varian EM 360 spectrometer in $CDCl_3$ and chemical shifts are reported in parts per million (δ) downfield from TMS. UV-visible spectra were recorded with a Perkin-Elmer Lambda 5 spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Inc. of Knoxville, Tennessee. Unless specified otherwise, reagent-grade reactants and solvents were obtained from commercial suppliers and were used as received. THF was purified by distillation from $LiAlH_4$ under nitrogen. Hydroxymethyl-12-crown-4, hydroxymethyl-15-crown-5, and hydroxymethyl-18-crown-6 and their tosylates were prepared by literature methods.[22-25] Ligand **13** was prepared by a reported method.[23] The 2,6-bis(bromomethyl)anisole was obtained from 2,6-dimethylanisole by bromination with *N*-bromosuccinimide.

General procedure for synthesis of bis(oxymethylcrown)benzenes 1-3, 7, and 8
Under nitrogen, KH (22% suspension in mineral oil, 11.0 mmol) was suspended in 8 mL of THF. (In some cases NaH was used as the base.) To this mixture, a solution of the appropriate dihydroxybenzene (3.1 mmol) in THF (10 mL) was added dropwise at room temperature. After 1 h, a solution of the appropriate (tosyloxymethyl)crown ether (6.2 mmol) in THF (10 mL) was added and the mixture was refluxed for 48 h. The solvent was evaporated *in vacuo*. Water (30 mL) was added to the residue and the mixture was extracted with CH_2Cl_2 (2 X 20 mL). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated *in vacuo* to give the crude product that was purified by column chromatography on neutral alumina.
1,2-Bis(oxymethyl-12-crown-4)benzene (1). Coupling of catechol (0.34 g, 3.1 mmol) and tosyloxymethyl-12-crown-4 (2.24 g, 6.2 mmol) was conducted by the general procedure. After chromatography with EtOAc as eluent, 1.05 g (70%) of **1** was obtained as a very hygroscopic, pale yellow oil: IR (neat): 1126 (C-O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.50-4.20 (m, 34H), 6.88 (s, 4H). Analysis calculated for $C_{24}H_{38}O_{10}$: C, 59.24; H, 7.87. Found: C, 59.05; H, 7.77.
1,2-Bis(oxymethyl-15-crown-5)benzene (2). On a reduced scale, catechol (0.28 g, 2.5 mmol) was reacted with tosyloxymethyl-15-crown-5 (2.02 g, 5.0 mmol) under conditions of the general procedure. Chromatography with EtOAc-MeOH (15:1) as eluent gave **2** (1.17 g, 81%) as an extremely hygroscopic, colorless liquid. IR (neat): 1126 (C-O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.52-

4.32 (s+m, 42H), 6.88 (s, 4H). Analysis calculated for $C_{28}H_{46}O$: C, 58.52; H, 8.07. Found: C, 58.62; H, 8.12.

1,2-Bis(oxymethyl-18-crown-6)benzene (3). On a reduced scale, catechol (0.27 g, 2.4 mmol) was coupled with tosyloxymethyl-18-crown-6 (2.19 g, 4.9 mmol) using NaH (0.26 g of 50% suspension in mineral oil, 5.4 mmol, with mineral oil removed by washing with pentane). Chromatography with EtOAc-MeOH (20:1) as eluent gave **3** (1.05 g, 65%) as an extremely hygroscopic, colorless oil. IR (neat): 1128 (C-O) cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 3.50-4.32 (s+m, 50H), 6.89 (s, 4H). Analysis calculated for $C_{32}H_{54}O_{14}$: C, 57.99; H, 8.21. Found: C, 57.83; H, 8.23.

1,3 Bis(oxymethyl-15-crown-5)benzene (7). Under the same conditions that were used for the synthesis of **2**, but replacing catechol with resorcinol, tosyloxymethyl-15-crown-5 (2.02 g, 5.0 mmol) and resorcinol (0.275 g, 2.5 mmol) were combined. After chromatography of the crude product with EtOAc-MeOH (40:1) as eluent, **7** (1.17 g, 81%) was obtained as a colorless, viscous, hygroscopic oil. IR (neat): 1130 (C-O) cm^{-1}. ^{1}1H NMR (CDCl$_3$): δ 3.50-4.32 (m, 42H), 6.31-6.65 (m, 3H); 6.90-7.32 (m, 1H). Analysis calculated for $C_{28}H_{46}O_{12}$: C, 58.52; H, 8.07. Found: C. 58.54; H, 8.12.

1,4-Bis(oxymethyl-15-crown-5)benzene (8). Hydroquinone (0.275 g, 2.5 mmol) and tosyloxymethyl-15-crown-5 (2.02 g, 5.0 mmol) were combined under the same conditions as described above. Chromatography with EtOAc-MeOH (40:1) as eluent gave 1.25 g (85%) of **8** as a hygroscopic, colorless oil. IR (neat): 1126 (C-O) cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 3.45-4.11 (m, 42H), 6.80 (s, 4H). Analysis calculated for $C_{28}H_{46}O_{12}$: C, 58.52; H, 8.07. Found: C, 58.31; H, 8.12.

General procedure for the synthesis of α,α'-bis(oxymethylcrown)xylenes 4-6, **9**, **and 10** NaH (50% in mineral oil, 0.21 g, 4.4 mmol) was washed with pentane under nitrogen and suspended in THF (5 mL). A solution of the (hydroxymethyl)crown ether (4.0 mmol) in THF (2 mL) was added dropwise. After stirring at room temperature for 1 h, a solution of the appropriate dibromide (2.0 mmol) in THF was added and the mixture was refluxed overnight. The solvent was evaporated *in vacuo* and the crude product was chromatographed on alumina.

α,α'-Bis(oxymethyl-12-crown-4)-*ortho*-xylene (4). The reaction of hydroxymethyl-12-crown-4 (0.82 g, 4.0 mmol) with α,α'-dibromo-*o*-xylene (0.52 g, 2.0 mmol) was conducted using the general procedure. Chromatography with EtOAc and then EtOAc-MeOH (40:1) as eluents gave **4** (0.75 g, 73%) as an extremely hygroscopic, pale yellow oil. IR (neat): 1126, 1095 (C-O) cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 3.35-4.05 (s+m, 34H), 4.59 (s, 4H), 7.32 (s, 4H). Analysis calculated for $C_{26}H_{42}O_{10}$•0.5H$_2$O: C, 59.64, H 8.28; Found: C, 59.76; H, 8.03.

α,α'-Bis(oxymethyl-15-crown-5)-*ortho*-xylene (5). On a larger scale, hydroxymethyl-15-crown-5 (1.25 g, 5.0 mmol) was reacted with α,α'-dibromo-*o*-xylene (0.66 g, 2.5 mmol) using the general procedure. After chromatography with EtOAc and then EtOAc-MeOH (20:1) as eluents, 1.26 g (71%) of **5** was obtained as a viscous, hygroscopic, pale yellow oil. IR (neat): 1124 (C-O)

cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 3.35-4.02 (s+m, 42H), 4.60 (s, 4H), 7.33 (br s, 4H). Analysis calculated for C$_{30}$H$_{50}$O$_{12}$: C, 59.78; H, 8.36. Found: C, 59.72; H, 8.47.

α,α'-Bis(oxymethyl-18-crown-6)-*ortho*-xylene (6). On a reduced scale, hydroxymethyl-18-crown-6 (0.64 g, 2.2 mmol) was combined with α,α'-dibromo-*o*-xylene (0.25 g, 0.95 mmol) using the general procedure. Chromatography with EtOAc and then EtOAc-MeOH (40:1) as eluents gave **6** (0.46 g, 70%) as a viscous, very hygroscopic, pale yellow oil. IR (neat): 1116 (C-O) cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 3.65 (br s, 50H), 4.60 (s, 4H), 7.32 (s, 4H). Analysis calculated for C$_{34}$H$_{58}$O$_{14}$•0.5H$_2$O: C, 58.35; H, 8.50. Found: C, 58.48; H, 8.35.

α,α'-Bis(oxymethyl-15-crown-5)-*meta*-xylene (9). On an increased scale, hydroxymethyl-15-crown-5 (1.25 g, 5.0 mmol) was reacted with α,α'-dibromo-*m*-xylene (0.66 g, 2.5 mmol) using the general procedure. Chromatography with EtOAc and then EtOAc-MeOH (20:1) as eluents gave **9** (0.85 g, 56%) as a viscous, pale yellow oil. IR (neat): 1124 (C-O) cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 3.65 (br s, 42H), 4.52 (s, 4H), 7.23 (s, 4H). Analysis calculated for C$_{32}$H$_{50}$O$_{12}$: C, 59.78; H, 8.36. Found: C, 59.63; H, 8.42.

α,α'-Bis(oxymethyl-15-crown-5)-*para*-xylene (10). With the general procedure, hydroxymethyl-15-crown-5 (1.25 g, 5.0 mmol) and α,α'-dibromo-*p*-xylene (0.66 g, 2.5 mmol) were combined. Chromatography with EtOAc and then EtOAc-MeOH (40:1) as eluents gave 0.75 g (50%) of **10** as a hygroscopic, colorless, heavy oil. IR (neat): 1126 (C-O) cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 3.30-4.00 (m, 42H), 4.53 (s, 4H), 7.28 (s, 4H). Analysis calculated for C$_{30}$H$_{50}$O$_{12}$×H$_2$O: C, 58.90; H, 8.40. Found: C, 58.54; H, 8.41.

2-Methoxy-1,3-bis-(α,α'-oxymethyl-15-crown-5)-*meta*-xylene (11). Under nitrogen, NaH (50% suspension in mineral oil; 0.60 g, 12.5 mmol) was washed with pentane and suspended in THF (10 mL). A solution of hydroxymethyl-15-crown-5 (2.50 g, 10.0 mmol) in THF (10 ml) was added dropwise and the mixture was stirred for 1 h at room temperature. A solution of 2,6-bis(bromomethyl)anisole (1.47 g, 5.0 mmol) in THF (5 mL) was added and the resulting mixture was refluxed for 36 h. The solvent was removed *in vacuo* and the residue was chromatographed on alumina with EtOAc and then EtOAc-MeOH (40:1) as eluents to give **11** (1.68 g, 53%) as a colorless, viscous oil. IR (neat): 1128 (C-O) cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 3.30-4.00 (m, 45H), 4.58 (s, 4H), 6.90-7.50 (m, 3H). Analysis calculated for C$_{31}$H$_{52}$O$_{13}$: C, 58.85; H, 8.28. Found: C, 58.66; H, 8.50.

Phenoxymethyl-18-crown-6 (12). NaH (50% suspension in mineral oil, 0.09 g, 1.9 mmol) was washed with pentane under nitrogen and suspended in THF (10 mL). A solution of phenol (0.17 g, 1.8 mmol) in THF (20 mL) was added slowly. After stirring for 1 h at room temperature, a solution of tosyloxymethyl-18-crown-6 (0.79 g, 1.8 mmol) in THF (20 mL) was added and the mixture was refluxed for 48 h. The solvent was removed *in vacuo* and the residue was chromatographed on alumina with CHCl$_3$-EtOH (50:3) as eluent to give **12** (0.64 g, 96%) as a pale yellow, viscous liquid. IR (neat): 1122 (C-O) cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 3.50-4.15 (m, 25H); 6.70-7.40 (m, 5H). Analysis calculated for C$_{19}$H$_{30}$O$_7$: C, 61.60; H, 8.16. Found: C, 61.46; H, 8.36.

Preparation of alkali metal picrates. The alkali metal picrates were prepared by dissolving picric acid in a minimum amount of boiling distilled water and slowly adding a stoichiometric amount of the alkali metal carbonate. The solution was cooled to room temperature and placed in an ice bath to facilitate crystallization. The precipitate was filtered and recrystallized once from distilled water. After filtration and extensive air drying, the salt was carefully heated to dryness in a vacuum oven at 100° C for 3 h. (Although we have never experienced any difficulty with this step, caution must be exercised in drying any metal picrate salt. Heating should not exceed 100° C and the salt should be allowed to cool to room temperature under vacuum before handling.) The anhydrous metal picrate was stored in the dark in a vacuum desiccator.

Procedure for picrate extractions. Except where noted (Table II), extractions of alkali metal picrates with bis(crown ether) hosts were performed by placing 0.50 mL of a 15 mM solution of the metal picrate in deionized water and 0.50 mL of a 15 mM solution of the bis(crown ether) in deuteriochloroform into a 15-mL centrifuge tube and mixing the solutions on a vortex mixer for 60 sec. Five samples were prepared for each picrate extraction experiment. The tubes were centrifuged for 10 min and then allowed to stand for 10 min to assure complete separation of the layers. Aliquots were taken from each phase of the sample in the tube and the concentration of metal picrate in each phase was determined by UV-visible absorbance scanning from 550 nm to 320 nm. In some cases, the organic phase concentration was determined by difference from the aqueous phase readings before and after extraction because of turbidity or formation of complexes insoluble in THF. The extraction constants (K_{ex})[14] and association constants (K_a)[15] were calculated according to previously developed methods. Standard deviations from the analysis of the five samples were less than 10% of the K_{ex} and K_a values. All extractions of cesium involved 5 mM cesium picrate and 15 mM bis(crown ether) due to the lower solubility of cesium picrate.

Acknowledgments

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