Pergamon

Tetrahedron, Vol. 52, No. 27, pp. 8979-8988, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00446-2

Syntheses of Bis- and Tetra-Crowned Clefts and Studies of Their Selectivities in Metal Ion Complexation

Richard A. Bartsch* and Mark D. Eley
Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX 79409-1061

Alan P. Marchand,* Rajesh Shukla, Kaipenchery A. Kumar, and G. Madhusudhan Reddy
Department of Chemistry, University of North Texas, Denton, TX 76203-0068

Abstract: A novel "tetra[benzo(18-crown-6)]-crowned cleft" (**2**) and two new "bis[benzo(15-crown-5)]-crowned clefts" (**3** and **4**) have been synthesized. Their respective selectivities in (i) alkali metal picrate extraction into chloroform and (ii) alkali metal perchlorate transport across bulk chloroform membranes have been determined relative to those of appropriate model compounds in each case. The observed picrate extraction selectivity order for **2**, *i. e.* $Cs^+ > Rb^+ > K^+ > Na^+ > Li^+$, strongly suggests the existence of "sandwich" complexes which result from cooperativity between two spatially proximate benzo(18-crown-6) units in **2** and a guest alkali metal cation. Interestingly, the corresponding extraction selectivity order for **3** and **4** suggests that only 1:1 metal ion-crown ether complexes are formed. For bulk chloroform membranes, bis- and tetra-crowned clefts exhibit much more efficient transport of certain alkali metal perchlorates than do model mono-crown ether compounds.

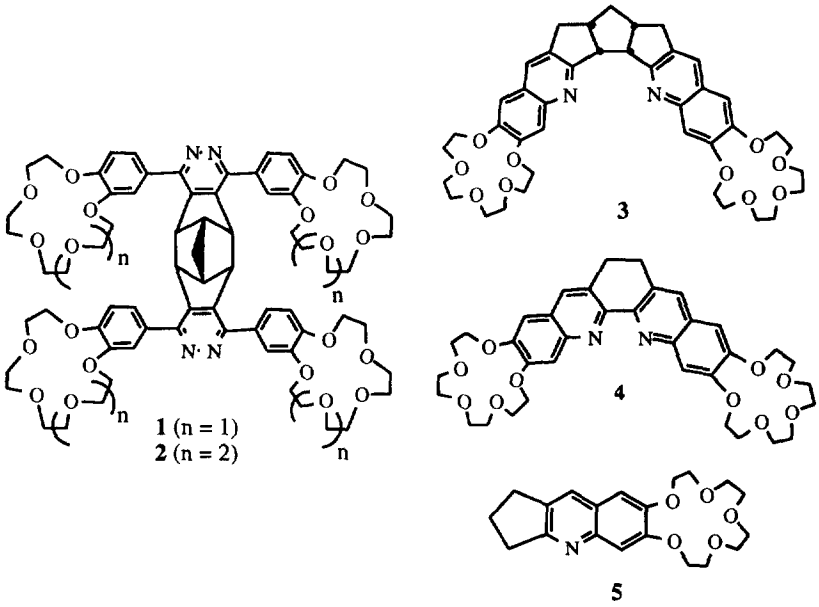
Introduction: As part of a study that involves the synthesis of new molecular clefts,[1] we recently reported the synthesis of the novel "tetra-crowned cleft" **1** (Scheme 1), which consists of a *syn*-orthocyclophane that contains four benzo(15-crown-5) moieties arrayed in two "sets" of spatially proximate crown ethers.[2] Alkali metal picrate extraction studies revealed that each "set" of crown ethers displays cooperativity as a host system, thereby forming a "sandwich" complex with the guest cation.[2] Thus, **1** was found to display marked selectivity for K^+ and Rb^+ complexation in these experiments. In the present study, we report the syntheses and the alkali metal picrate extraction profiles for three additional host systems, *i. e.*, a new "tetra-crowned cleft (**2**, Scheme 1), along with two "bis-crowned clefts" (**3** and **4**) and an appropriate model system, **5** (*vide infra*). In addition, transport of alkali metal perchlorates across bulk chloroform membranes which contain bis- and tetra-crowned clefts as carriers has been explored.

Syntheses of Crown Ether-containing Compounds 2, 3, 4, and 5. The procedure used to synthesize **2** is shown in Scheme 2. As in the case of our earlier preparation of **1**[2], a key step in this synthesis involves inverse electron demand Diels-Alder cycloaddition[3] of the substituted 3,6-diaryl-1,2,4,5-tetrazine **9** to the electron-rich enolate anion derived from tetracyclo[6.3.0.$0^{4,11}$.$0^{5,9}$]undecane-2,7-dione (**10**).[4]

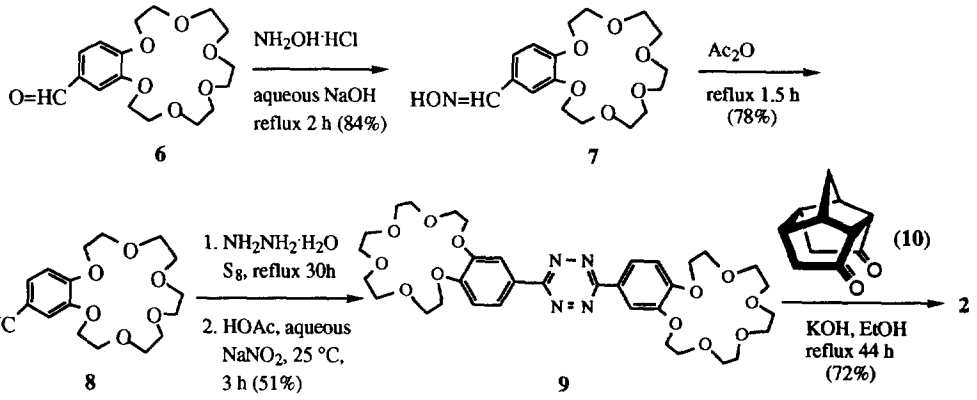
The procedures used to prepare **3**, **4**, and **5** are shown in Scheme 3. A key feature in the synthesis of **3** is a base-promoted Friedländer condensation[1] of the crown-functionalized *ortho*-amino-benzaldehyde **13** with

cis,cisoid,cis-tricyclo[6.3.0.0^{2,6}]undecane-3,11-dione (**14**).[5] Similarly, base-promoted Friedländer condensation[1] of cyclohexane-1,2-dione and cyclopentanone with **13** afforded **4** and **5**, respectively, each in 72% yield.

Scheme 1



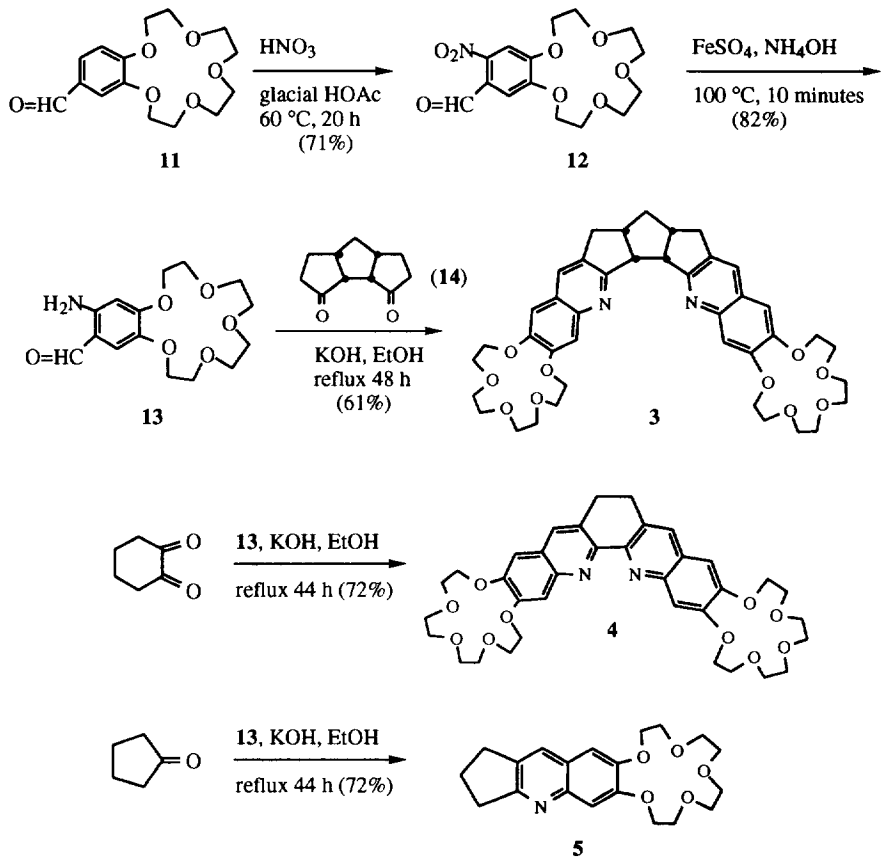
Scheme 2



Alkali Metal and Alkaline Earth Metal Picrate Extractions. The alkali metal cation complexing abilities of (i) the tetra-crowned clefts **1**[2] and **2**, (ii) the bis-crowned clefts **3** and **4**, and (iii) three model compounds [*i. e.*, benzo-(15-crown-5), benzo(18-crown-6), and **5**] were assessed by solvent extraction of alkali metal picrates from aqueous solutions into chloroform.[6] The picrate extraction results are presented in Table 1.

In order to provide a suitable comparison, it was necessary to utilize the model compounds [benzo(15-crown-5) and benzo(18-crown-6), respectively] at four times the concentration of **1** and **2**. In this manner, equimolar concentrations of crown ether units could be compared among all systems

Scheme 3



Whereas selective extraction of Na^+ normally would be anticipated on the basis of the 15-crown-5 ring size,[7] the data in Table 1[2] indicate that benzo(15-crown-5) exhibits selectivity toward K^+, suggestive of the formation of a 2:1 host-guest "sandwich" complex.[7,8] The observed extraction selectivity order for benzo(15-crown-5) is $K^+ > Na^+ > Rb^+ > Cs^+ > Li^+$.[2]

When the alkali metal picrate extraction capability of **1** is compared with that of benzo(15-crown-5) (4 equivalents), it is observed that **1** extracts all five alkali metal picrates more efficiently than does an equivalent concentration of the model system.[2] Furthermore, the extraction selectivity order for **1** is $K^+ >> Rb^+ > Cs^+ > Na^+ > Li^+$.[2] This result is consistent with our earlier suggestion[2] that the efficacious juxtaposition of pairs of crown ether moieties which is present in **1** results in the formation of host-guest "sandwich" complexes with K^+ and the larger alkali metal cations.

Like **1**, compound **2** also is a tetra-crowned cleft; it contains four benzo(18-crown-6) units per molecule. Thus, it was necessary once again to employ four equivalents of the model host molecule benzo(18-crown-6) in the alkali metal picrate extraction experiments.

Table 1. Alkali metal picrate extractions from aqueous solutions into chloroform by **1**[2], **2**, **3**, **4**, and by relevant model compounds.

	Percent of Picrate Extracted (%)				
Host Molecule	Li^+	Na^+	K^+	Rb^+	Cs^+
1[a]	20.1 ± 1.4[b]	26.3 ± 1.4	97.0 ± 1.8	55.9 ± 1.6	44.0 ± 1.7
Benzo(15-crown-5)[a]	BDL[c]	11.8 ± 1.8	19.3 ± 1.9	5.9 ± 1.2	4.1 ± 1.4
2	18.7 ± 0.1	24.9 ± 0.1	67.5 ± 0.1	71.5 ± 0.1	88.6 ± 0.1
Benzo(18-crown-6)	7.1 ± 0.3	25.9 ± 0.4	65.4 ± 0.1	45.4 ± 0.1	40.6 ± 0.3
3	22.1 ± 0.7	25.7 ± 0.3	19.9 ± 0.6	10.0 ± 0.8	6.4 ± 0.6
4	ppt[d]	ppt[d]	ppt[d]	ppt[d]	ppt[d]
5	5.8 ± 0.1	8.6 ± 0.4	17.5 ± 0.3	16.7 ± 0.3	7.6 ± 0.2

[a]Data taken from ref. 2. [b]Average and standard deviation for five samples. [c] BDL = below detection limit.
[d]A precipitate formed at the interface.

Like **1**, compound **2** also is a tetra-crowned cleft; it contains four benzo(18-crown-6) units per molecule. Thus, it was necessary once again to employ four equivalents of the model host molecule benzo(18-crown-6) in the alkali metal picrate extraction experiments.

Selective extraction of K^+ normally would be anticipated on the basis of the 18-crown-6 ring size.[7] In agreement, the data in Table 1 show the following order of alkali metal picrate extraction for benzo(18-crown-6): $K^+ > Rb^+ > Cs^+ > Na^+ > Li^+$. The extraction efficiencies of **2** and benzo(18-crown-6) toward Na^+ and K^+ were found to be quite similar. However, **2** diplayed particularly high avidity toward complexation of Cs^+ and Rb^+; the observed extraction selectivity order for **2** toward alkali metal picrates is $Cs^+ > Rb^+ > K^+ > Na^+ > Li^+$ (see Table 1). Since both Cs^+ and Rb^+ are too large to fit within the cavity of a single benzo(18-crown-6) moiety,[7] the extraction selectivity data strongly suggests the existence of "sandwich" complexes which result from cooperativity between two spatially proximate benzo(18-crown-6) units in **2** and a guest alkali metal cation.

In order to compensate for the two 6,7-quinolino(15-crown-5) moieties that are present in bis-crowned cleft **3**, it was necessary to utilize twice the concentration of model compound **5** to allow direct comparison of its behavior in the alkali metal picrate extraction experiments with that of **3**. Model compound **5** displayed the following selectivity order in picrate extraction: $K^+ \sim Rb^+ > Na^+ \sim Cs^+ > Li^+$ (see Table 1). The observed selectivity order is consistent with the formation of 2:1 "sandwich"-type complexes of model compound **5** with K^+ and Rb^+. However, for bis-crowned cleft **3**, the corresponding selectivity order was observed to be $Na^+ > Li^+ > K^+ > Rb^+ > Cs^+$ (see Table 1). This result suggests that **3** forms only 1:1 alkali metal cation-crown ether complexes, *i. e.*, there is *no evidence* for cooperativity between crown ether moieties in **3** in its complexes with al-

kali metal cations. It was not possible to confirm a similar tendency for formation of 1:1 complexes with the bis-crowned cleft **4** due to precipitate formation at the aqueous-organic interface in picrate extraction experiments.

Data obtained for alkaline earth metal picrate extractions by bis-crowned hosts **3** and **4** and the corresponding extraction data obtained by using model compound **5** are presented in Table 2. Extraction efficiencies are observed to be low in all cases, and the bis-crowned hosts and corresponding model compound display the same picrate extraction selectivity, *i. e.*, $Sr^{2+} > Ba^{2+} > Ca^{2+}$. Although the extraction percentage for Mg^{2+} observed with bis-crowned clefts **3** and **4** is somewhat higher than that for the relevant model compound **5**, the overall similarity of extraction results among all three host systems strongly suggests that there is no appreciable difference in the mode of alkaline earth metal cation complexation. Therefore, it appears that even the enhanced charge-dipole interactions anticipated for divalent metal ions are insufficient to produce cooperativity between the crown ether units in bis-crowned clefts **3** and **4**.

Table 2. Alkaline earth metal picrate extractions from aqueous solutions into chloroform by using **3**, **4**, and **5**.

	Percent of Picrate Extracted (%)[a]			
Host Molecule	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
3	3.4 ± 0.1	3.1 ± 0.1	6.2 ± 0.1	4.3 ± 0.1
4	3.9 ± 0.1	3.7 ± 0.1	5.7 ± 0.1	5.0 ± 0.1
5	1.8 ± 0.1	3.2 ± 0.1	4.2 ± 0.1	3.8 ± 0.1

[a]Average and standard deviation for five samples.

Attempts to investigate potential interactions of Ag^+ with the quinoline nitrogen atoms in bis-crowned clefts **3** and **5** via the picrate extraction method were thwarted by formation of precipitates at the aqueous-organic interface.

Alkali Metal Perchlorate Transport Across Liquid Membranes. To further compare the nature and extent of host-guest interactions of our crowned clefts and appropriate model compounds with alkali metal cations, these ionophores were utilized as metal ion carriers to transport these ions across bulk chloroform membranes. These studies were conducted by using cells that were configured as a "hollow tube within a vial".[9,10] In this system, the alkali metal perchlorate is transported out of an aqueous source phase (inside the hollow glass tube) through a lower chloroform phase that contains the carrier and into the aqueous receiving phase which is located outside of the hollow glass tube. In this transport system, the concentration gradient of the alkali metal perchlorate provides the driving force for carrier-facilitated ion transport from the source phase into the receiving phase. For such bulk liquid membranes, the metal salt flux is usually controlled by the rate of diffusion of the metal salt-ionophore complex through the membrane.

Results for alkali metal perchlorate transport across bulk chloroform membranes by crowned-cleft compounds **1**-**4** and appropriate model compounds as carriers are presented in Table 3. For these transport

experiments, alkali metal perchlorates were utilized rather than alkali metal picrates to allow for determination of the alkali metal cation concentrations in the aqueous receiving phase by ion chromatography.

Table 3. Alkali metal perchlorate transport across bulk chloroform membranes by **1**[2], **2**, **3**, and **4** and by relevant model compounds.

	Moles of alkali metal perchlorate (x 10^7) transported in 24 hours				
Host Molecule	Li^+	Na^+	K^+	Rb^+	Cs^+
1[a]	BDL[b]	5.6 ± 0.4	120 ± 20	130 ± 20	36 ± 4
Benzo(15-crown-5)[a,c]	BDL[b]	3.8 ± 1.8	4.3 ± 0.5	1.4 ± 0.2	1.8 ± 0.2
2	BDL[b]	2.0 ± 0.1	66 ± 1	3.0 ± 0.1	1.1 ± 0.1
Benzo(18-crown-6)[c]	BDL[b]	1.3 ± 0.1	4.5 ± 0.1	2.5 ± 0.1	2.1 ± 0.1
3	3.0 ± 0.1	8.9 ± 0.8	3.4 ± 0.7	0.9 ± 0.4	0.4 ± 0.1
4	1.4 ± 0.1	9.7 ± 0.7	2.0 ± 0.3	0.3 ± 0.1	0.8 ± 0.1
5	BDL[b]	0.1 ± 0.1	0.4 ± 0.1	0.2 ± 0.1	0.1 ± 0.1

[a]Data taken from ref. 2. [b]BDL = below detection limit. [c]Average and standard deviation for three samples.

As noted previously,[2] transport of certain alkali metal perchlorates by tetra-crowned cleft **1** is significantly more efficient that that for four equivalents of the model compound benzo(15-crown-5).[2] Thus, relative to benzo(15-crown-5), Rb^+ transport by **1** is *ca.* 90 times faster, and K^+ and Cs^+ transport are *ca.* 20 times more rapid. The order of alkali metal perchlorate transport selectivity of **1** is $Rb^+ \sim K^+ > Cs^+ > Na^+ > Li^+$ (Table 3).[2] Preference for alkali metal cations that are too large to fit within the cavity of the benzo(15-crown-5) moieties in **1**[7] strongly suggests that transport of alkali metal perchlorates by **1** proceeds via "sandwich" complexes that involve two spatially proximate crown ether units.[2]

Comparison between the results for the tetra-crowned cleft **2** and four equivalents of the model compound benzo(18-crown-6) (Table 3) reveals similar transport efficiencies for Li^+, Na^+, Rb^+, and Cs^+ by the two carrier species. However, tetra-crowned cleft **2** transports K^+ much more rapidly than the other alkali metal cations and *ca.* 15 times faster than do four equivalents of benzo(18-crown-6). Thus, cleft **2** exhibits marked selectivity for K^+ transport.

When comparing alkali metal perchlorate transport across liquid membranes by the bis-crowned clefts **3** and **4** and by two equivalents of the model compound **5** (Table 3), it is noted that the monocyclic model compound is a very poor metal ion carrier. Both **3** and **4** exhibit modest selectivity for Na^+ transport, but the transport rates are much lower than those for the preferred metal ion transport by the tetra-crowned clefts **1** and **2**.

Results of Molecular Mechanics (MM3) Calculations.[11] The energetics of **1-4** each were minimized via application of molecular mechanics methods (MM3 force-field).[11b] Adjacent pairs of benzo(crown ether) moieties are roughly parallel in **1** and **2**. The closest nonbonded O···O distances between adjacent crown ethers in these compounds are 3.69 Å and 3.93 Å, respectively. This arrangement is suitable for promoting "sandwich" complex formation between spatially proximate crown ether moieties in **1** and **2** with a guest metal cation.

By way of contrast, the results of MM3 calculations reveal that the two crown ether moieties in **3** roughly occupy planes which intersect at an angle of 23.4°. Accordingly, nonbonded O···O distances between the crown ether moieties are large, the closest approach being 5.20 Å. The crown ether units in **4** are divergent; the molecule possesses only a slight deviation from planarity, but this may be sufficient to interfere with stacking, thereby effectively preventing "sandwich" complex formation with a guest metal cation. These results suggest that the crown ether units in either **3** or **4** are not well situated to participate in either intra- or intermolecular cooperative interactions with a guest metal cation

Summary and Conclusions. The alkali metal picrate extraction selectivities for the tetra[benzo(15-crown-5)]crowned cleft **1** and tetra[benzo(18-crown-6)]crowned cleft **2** provide strong evidence for cooperativity between two spatially proximate crown ether units of the host with a guest metal cation. On the other hand, the picrate extraction results do not support the formation of "sandwich" complexes of alkali metal cations with the crown ether units in the bis[benzo(15-crown-5)]-crowned clefts **3** and **4**. For transport of alkali metal perchlorates across bulk chloroform membranes, the tetra[benzo(18-crown-6)]crowned cleft **2** exhibits efficient and selective transport of K^+.

Experimental Section

Melting points are uncorrected. Proton NMR spectra at 200 MHz and ^{13}C NMR spectra at 50 MHz were obtained by using a Varian Gemini-200 NMR spectrometer. Chemical shifts are reported in ppm (δ) downfield from internal Me_4Si. Infrared spectra were obtained by using a Micac Fourier transform IR spectrophotometer. A Shimadzu Model 260 UV-visible spectrophotometer was used to measure absorbances at 375 nm in connection with the picrate extraction experiments described below. A Dionex Model 100 ion chromatograph was used in connection with the membrane transport studies described below. Microanalytical data were obtained by personnel at Galbraith Laboratries, Inc., Knoxville, TN and at M-H-W Laboratories, Phoenix, AZ. High-resolution EI mass spectra of **8** and **14** were obtained by personnel at the Midwest Center for Mass Spectrometry, University of Nebraska, Lincoln, NE and by Dr. P. Sharma, Department of Chemistry, Ohio State University, respectively.

2,3-[4'-(Oximinomethyl)benzo]-1,4,7,10,13,16-hexaoxacyclooctadecane (7). To a solution of **6**[12] (580 mg, 1.74 mmol) in EtOH (4 mL) was added sequentially a solution of hydroxylamine hydrochloride (1.21 g, 16.4 mmol) in water (10 mL) and NaOH (516 mg, 12.9 mmol), and the resulting mixture was refluxed for 2 h and then was extracted with $CHCl_3$ (4 x 30 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue, a colorless solid (518 mg, 84%), was recrystallized from aqueous ethanol to give pure **7** (518 mg, 84%) as a colorless, microcrystalline solid: mp 122-123 °C; IR (KBr) 3120 (w), 2978 (s), 1625 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 3.58-4.32 (m, 21 H), 6.81-7.59 (m, 3 H), 8.04 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 68.92 (t), 69.47 (t), 70.59 (t), 70.62 (t), 70.65 (t), 70.71 (t), 70.74 (t), 70.81 (t), 70.88 (t), 70.91 (t), 110.54 (d), 113.04 (d), 121.75 (d), 125.25 (s), 149.07 (s), 150.07 (d), 150.62 (s). Anal. Calcd for $C_{17}H_{25}NO_7$: C, 57.65; H, 7.09. Found: C, 57.49; H, 7.23.

2,3-(4'-Cyanobenzo)-1,4,7,10,13,16-hexaoxacyclooctadecane (8). A solution of **7** (280 mg, 0.81 mmol) in acetic anhydride (Ac_2O, 1 mL, excess) was refluxed vigorously for 1.5 hr and then was poured into cold water (5 mL) with stirring. The resulting mixture was stirred until hydrolysis of the excess Ac_2O was com-plete (*ca.* 0.5 h). The mixture was extracted with $CHCl_3$ (4 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue purified by column chromatography on neutral alumina by eluting with CH_2Cl_2. After the eluate was concentrated *in vacuo*, the residue was recrystallized from CH_2Cl_2-hexane, thereby affording pure **8** (213 mg, 78%) as a colorless, microcrystal-line solid: mp 75-76 °C; IR (film) 2930 (s), 2280 cm^{-1} (w); ^1H NMR ($CDCl_3$) δ 3.62-4.24 (m, 20 H), 6.88 (d, J =

8.0 Hz, 1 H), 7.06 (d, J =1.0 Hz, 1 H), 7.22 (dd, J = 8.0, 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 68.94 (t), 69.07 (t), 69.17 (t), 69.21 (t), 69.26 (t), 70.64 (t), 70.66 (t), 50.58 (t), 70.81 (t), 70.93 (t), 103.98 (s), 112.98 (d), 116.33 (d), 119.16 (s), 126.62 (d), 148.89 (s), 152.87 (s). Anal. Calcd for $C_{17}H_{23}NO_6$: M_r^+ 337.1525. Found: (high-resolution mass spectrometry): M_r^+ 337.1526.

3.6-Bis[4'-(2,3-benzo-1,4,7,10,13,16-hexaoxacyclooctadecyl)]-1,2,4,5-tetrazine (9).[13] To a solution of **8** (130 mg, 0.39 mmol) in *t*-BuOH (1 mL) under argon was added hydrazine hydrate (1.0 g, 20 mmol) and sulfur (50 mg, 1.6 mmol). The resulting mixture was refluxed gently for 30 h. Water (2 mL) was added to the cooled reaction mixture, and the resulting aqueous suspension was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue (crude dihydrotetrazine) was used directly in the next synthetic step.

To a solution of the residue in 1:6 HOAc-CH_2Cl_2 (10 mL) was added a solution of $NaNO_2$ (400 mg, 5.8 mmol) in water (1 mL). The reaction mixture was stirred at ambient temperature for 3 h. The organic layer was separated and then was washed sequentially with water (5 mL), 10% aqueous $NaHCO_3$ (2 mL), and water (5 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. The residue was recrystallized from EtOAc-CH_2Cl_2 to provide pure **9** (70 mg, 51%) as a bright red, microcrystalline solid: mp 178-179 °C; IR (nujol) 2980 (s), 1635 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 3.70-4.34 (m, 40 H), 7.04 (d, J =7.8 Hz, 2 H), 8.22 (d, J =0.8 Hz, 2 H), 8.46 (dd, J =7.8, 0.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 69.02 (t), 69.10 (t), 69.24 (t), 69.31 (t), 69.41 (t), 69.48 (t), 70.65 (t), 70.73 (t), 70.83 (t), 71.00 (t), 112.04 (d), 113.35 (d), 121.87 (d), 124.58 (s), 149.39 (s), 152.82 (s), 163.04 (s). Anal. Calcd for $C_{34}H_{46}N_4O_{12}$: C, 58.09; H, 6.60. Found: C, 57.92; H, 6.75.

Base-Promoted Reaction of 9 with Tetracyclo[6.3.0.0^{4,11}.0^{5,9}]undecane-2,7-dione (10). To a solution of **9** (395 mg, 0.56 mmol) in THF (40 ml) was added **10** (50 mg, 0.28 mmol). The solution was heated to reflux, and 10% aqueous methanolic KOH (4 mL) was added dropwise. The resulting mixture was refluxed for an additional 1 h and then was concentrated *in vacuo*. Water (10 mL) was added to the residue, and the resulting aqueous suspension was extracted with CH_2Cl_2 (4 x 20 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was recrystallized from CH_2Cl_2-hexane, thereby affording pure **2** (140 mg, 34%) as a colorless, microcrystalline solid: mp 179-180 °C; IR (KBr) 2980 (s), 1165 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 1.24 (m, 2 H), 1.88-2.30 (m, 6 H), 3.52-4.36 (m, 80 H), 6.52 (d, J =5.0 Hz, 4 H), 6.68 (d, J = 5.0 Hz, 4 H), 7.32 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 28.90 (t), 49.70 (d), 63.34 (d), 68.90 (t), 69.00 (t), 68.49 (t), 69.14 (t), 69.60 (t), 69.99 (t), 70.14 (t), 70.53 (t), 70.72 (t), 70.83 (t), 112.81 (d), 114.18 (d), 121.71 (d), 128.92 (s), 145.19 (s), 149.08 (s), 149.75 (s), 153.77 (s). Anal. Calcd for $C_{79}H_{100}N_4O_{24}$: C, 63.70; H, 6.78. Found: C, 63.53; H, 6.89.

2,3-(4'-Nitro-5'-formylbenzo)-1,4,7,10,13-pentaoxacyclopentadecane (12). To a solution of **11**[14] (2.8 g, 9.3 mmol) in $CHCl_3$ (35 mL) and glacial HOAc (35 mL) was added dropwise 70±1% aqueous HNO_3 (17 mL) during 0.5 h. After the addition of nitrating agent had been completed, the reaction mixture was heated at 60 °C for 20 h. The cooled reaction mixture was neutralized via careful addition of saturated aqueous $NaHCO_3$ (500 mL). The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (4 x 30mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue, a pale yellow oil, was triturated with 1:3 $CHCl_3$-EtOH mixed solvent until crystallization occurred. The resulting solid was recrystallized from $CHCl_3$-EtOH, thereby affording pure **12** (2.3 g, 71%) as a pale yellow, microcrystalline solid: mp 131-132 °C; IR (KBr) 2891 (s), 1678 (s), 1571 (s), 1352 (s), 1301 (s), 1240 (s), 1154 (s), 1095 (s), 959 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 3.50-4.02 (m, 12 H), 4.14-4.36 (m, 4 H), 7.29 (s, 1 H), 7.51 (s, 1 H), 10.35 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 68.55 (t), 68.90 (t), 69.10 (t), 69.90 (t), 70.97 (t), 108.3 (d), 110.7 (d), 125.5 (s), 143.6 (s), 152.1 (s), 153.0 (s), 187.6 (d). Anal. Calcd for $C_{15}H_{19}NO_8$: C, 52.79; H, 5.61. Found: C, 52.53; H, 5.57.

2,3-(4'-Amino-5'-formylbenzo)-1,4,7,10,13-pentaoxacyclopentadecene (13). To a solution of ferrous sulfate heptahydrate (10 g, 36 moles) in boiling water (60 mL) was added **12** (1.00 g, 2.94 mmol), and the resulting solution was stirred for one minute. To this boiling solution was added concentrated aqueous NH_4OH (28% NH_3 w/w, 16 mL, excess) dropwise with stirring, and the resulting mixture was heated at 100 °C for 10 minutes. The hot reaction mixture was filtered rapidly, and the residue was washed with hot water (40 mL). The filtrate was cooled and then was extracted with EtOAc (3 x 50 mL). The organic layer was dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. Crude **13** (750 mg, 82%) was thereby obtained as a tan microcrystalline solid: mp 98-100 °C; IR (KBr) 3420 (m), 3316 (m), 2871 (s), 1622 (s), 1596 (s) , 1209 (m), 1444 (m), 1262 (s), 1154 (s), 962 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 3.50-4.10 (m, 16 H), 5.92 (s, 1 H), 6.24 (s, 2 H), 6.75 (s, 1 H), 9.46 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 67.69 (t), 68.54 (t), 69.28 (t), 69.68 (t), 70.17 (t), 70.32 (t), 70.55 (t), 98.79 (d), 111.1 (s), 120.3 (d), 139.9 (s), 148.1 (s), 156.7 (s), 191.1 (d). This material was used in the next step without further purification.

Friedländer Condensation of 13 with *cis,cisoid,cis*-Tetracyclo[6.3.0.0^{2,6}]undecane-3,11-dione (14).[1] To a refluxing solution of **13** (311 mg, 1.00 mmol) and **14**[5] (89 mg, 0.50 mmol) in absolute EtOH (20 mL) under argon was added a solution of KOH (75 mg, 1.3 mmol) in absolute EtOH (1.5 mL). The resulting mixture was refluxed for 48 h and then was concentrated *in vacuo*. The residue was diluted with water (40 mL), and the resulting aqueous suspension was extracted with $CHCl_3$ (3 x 50 mL). The combined organic layers were washed with water (2 x 30 mL), dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo*, and the residue was recrystallized from EtOAc to give pure **3** (216 mg, 61%) as a pale yellow, microcrystalline solid: mp 167-168 °C; IR (KBr) 2935 (s), 2862 (s), 1618 (m), 1506 (s), 1457 (s), 1397 (m), 1262 (s), 1161 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 1.06-1.45 (m, 1 H), 1.90-2.64 (m, 3 H), 2.82-3.30 (m, 4 H), 3.50-4.22 (m, 34 H), 6.74 (s, 4 H), 7.30 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 37.05 (t), 39.67 (t), 44.41 (t), 55.85 (d), 67.70 (t), 68.39 (t), 68.88 (t), 69.12 (t), 69.95 (t), 70.07 (t), 70.91 (t), 71.02 (t), 106.5 (d), 109.3 (d), 122.4 (s), 128.4 (d), 133.6 (s), 144.0 (s), 148.3 (s), 150.6 (s), 164.7 (s). Anal. Calcd for $C_{41}H_{48}N_2O_{10}$: C, 67.03; H, 6.70. Found: C, 67.24; H, 6.66; Calcd for $C_{41}H_{48}N_2O_{10}$: M_r^+ 728.3309. Found: (high-resolution mass spectrometry): M_r^+ 728.3336.

Friedländer Condensation of 13 with Cyclohexane-1,2-dione.[1] To a refluxing solution of **13** (300 mg, 0.97 mmol) and cyclohexane-1,2-dione (50 mg, 0.45 mmol) in absolute EtOH (25 mL) under argon was added a solution of KOH (50 mg, 0.89 mmol) in absolute EtOH (2.5 mL). The resulting mixture was refluxed for 44 h and then was concentrated *in vacuo*. The residue was diluted with water (40 mL), and the resulting aqueous suspension was extracted with $CHCl_3$ (3 x 50 mL). The combined organic layers were washed with water (2 x 30 mL), dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo*, and the residue was recrystallized from $CHCl_3$-EtOAc, thereby affording pure **4** (212 mg, 72%) as a pale yellow microcrystalline solid: mp 269-270 °C; IR (KBr) 2871 (s), 1619 (s), 1458 (m), 1258 (s), 1150 (s), 966 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 3.07 (s, 4 H), 3.60-4.04 (m, 24 H), 4.12-4.40 (m, 8 H), 6.90 (s, 2 H), 7.65 (s, 2 H), 7.75 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 28.26 (t), 68.02 (t), 68.42 (t), 69.06 (t), 69.18 (t), 70.11 (t), 70.18 (t), 71.24 (t), 105.5 (d), 110.4 (d), 124.1 (s), 130.6 (s), 132.8 (d), 145.2 (s), 150.1 (s), 150.5 (s), 151.7 (s). Anal.Calcd. for $C_{36}H_{42}N_2O_{10}$: M_r^+ 662.2839. Found: (high-resolution mass spectrometry): M_r^+ 662.2845.

Friedländer Condensation of 13 with Cyclopentanone.[1] . To a refluxing solution of **13** (220 mg, 0.71 mmol) and cyclopentanone (59 mg, 0.70 mmol) in absolute EtOH (25 mL) under argon was added a solution of KOH (50 mg, 0.89 mmol) in absolute EtOH (2.5 mL). The resulting mixture was refluxed for 48 h and then was concentrated *in vacuo*. The residue was diluted with water (40 mL), and the resulting aqueous suspension was extracted with $CHCl_3$ (3 x 50 mL). The combined organic layers were washed with water (2 x 30 mL), dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo*, and the residue was recrystallized from CH_2Cl_2-EtOAc, thereby affording pure **5** (80 mg, 31%) as an ivory-colored, microcrystalline solid: mp 120-121 °C; IR (nujol) 2923 (s), 2870 (s), 1466 (s), 1376 (s), 1260 (s), 1155 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 2.00-2.30 (m, 2 H), 2.90-3.20 (m, 4 H), 3.85-4.30 (m, 16 H), 6.95 (s, 1 H), 7.35 (s, 1 H), 7.70 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.10 (t), 30.97 (t), 34.91 (t), 68.65 (t), 69.23 (t), 69.71 (t), 69.89 (t), 70.76 (t), 70.85 (t), 71.72 (t), 71.78 (t), 107.7 (d), 109.3 (d), 123.1 (s), 129.5 (d), 134.1 (s), 144.8 (s), 149.1 (s), 151.7 (s), 165.8 (s). Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.84; H, 7.01. Found: C, 66.97; H, 7.22.

Procedure for Extraction of Metal Picrates into Chloroform. Reagent grade $CHCl_3$ was washed with distilled, deionized water and then was utilized to prepare a 5.00 mM solution of **2-4** in ethanol-free $CHCl_3$. In the case of the model host systems, *i. e.*, benzo(15-crown-5), benzo(18-crown-6), and **5**, the concentrations of the host in ethanol-free $CHCl_3$ utilized in this study were 20.00, 20.00, and 10.00 mM, respectively. An aqueous solution was prepared which was 5.00 mM in the alkali metal or alkaline earth metal picrate and 50.00 mM in the alkali metal or alkaline earth metal chloride.

Into a 5 mL glass centrifuge tube were placed the $CHCl_3$ solution of the host (0.50 mL) and the aqueous solution of the alkali metal or alkaline earth metal picrate and chloride (0.50 mL). The centrifuge tube was stoppered, agitated on a vortex mixer at ambient temperature for 4 minutes, and then centrifuged for 4 minutes to complete phase separation. A 10.0 μL aliquot of the aqueous phase was removed with a microsyringe, and the aliquot was diluted in a volumetric flask via addition of CH_3CN to a total volume of 5.0 mL. Another portion of the metal picrate solution was extracted by $CHCl_3$ which contained no host and then was diluted similarly with CH_3CN. UV-visible spectra were obtained for the two solutions, and the percent of picrate extracted in each case was calculated from the absorbance measured at 375 nm. For each combination of host and alkali metal picrate, the picrate extraction was conducted on five different samples, and the average value of percent picrate extracted, with standard deviation, was calculated. In the absence of host, no metal ion picrate extraction was detected.

Procedure for Transport of Alkali Metal Perchlorates Across Bulk Chloroform Membranes. The transport studies were conducted at 25 ± 1 °C in "hollow-tube-within-a-vial" cells.[9,10] A hollow glass tube (7 mm ID) was suspended vertically within a glass vial (23 mm ID) such that the bottom of the

glass tube extended below the surface of the $CHCl_3$ membrane. Thus configured, the $CHCl_3$ membrane separated the aqueous receiving phase (6.50 mL of distilled, deionized water, located outside the hollow glass tube) from the aqueous source phase (1.00 mL of a 7.00 mM aqueous solution of the alkali metal perchlorate inside the hollow glass tube). The liquid membrane consisted of 4.00 mL of a 10.00 mM solution of the host molecule (or a 40.00 mM solution of model hosts: benzo(15-crown-5) or benzo(18-crown-6), or a 20.00 mM solution of model host **5**) in $CHCl_3$ which had previously been washed with distilled, deionized water. The area of the source phase-$CHCl_3$ phase interface was 38.5 mm^2, and the area of the $CHCl_3$ phase-receiving phase interface was 352 mm^2. The organic phase was stirred at 120 rpm by means of an internal small magnetic stirring bar and an external magnet which was attached to a constant speed stirring motor. After 24 h, an aliquot of the aqueous phase was with-drawn, and the concentration of the alkali metal perchlorate was determined by ion chromatography. Triplicate runs were conducted for each combination of ionophore and alkali metal perchlorate. From the results of the three runs, the average amount of alkali metal perchlorate transported, with standard deviation, was calculated. In the absence of host, no alkali metal perchlorate transport was detected.

Acknowledgment. We thank the Office of Naval Research (Grant N00014-94-1-1039 to A. P. M.), the United States Air Force (Contract F29601-92-K-0018 to A. P. M.), and the Robert A. Welch Foundation (Grants B-963 to A. P. M., D-775 to R. A. B.) for financial support of this study.

References and Footnotes

1. (a) Marchand, A. P.; Annapurna, P.; Flippen-Anderson, J. L.; Gilardi, R.; George, C. *Tetrahedron Lett.* **1988,** *29*, 6681. (b) Marchand, A. P.; Annapurna, P.; Watson, W. H.; Nagl, A. *J. Chem. Soc., Chem. Commun.* **1989**, 271. (c) Marchand, A. P.; Annapurna, P.; Taylor, R. W.; Simmons, D. L.; Watson, W. H.; Nagl, A.; Flippen-Anderson, J. L.; Gilardi, R.; George, C. *Tetrahedron* **1990**, *46*, 5077.

2. Marchand, A. P.; Reddy, G. M.; Zaragoza, F.; Bartsch, R. A.; Eley, M. D. *Tetrahedron Lett.* **1993**, *34*, 5377.

3. Boger, D. L. *Chem. Rev.* **1986**, *86*, 781.

4. The synthesis of **10** is described by Wenkert, E.; Yoder, J. E. *J. Org. Chem.* **1970**, *35*, 2986.

5. Mehta, G.; Srikrishna, A.; Reddy, A. V.; Nair, M. S. *Tetrahedron* **1981**, *37*, 4543.

6. (a) Moore, S. S.; Tarnowski, T. L.; Newcomb, M.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6398. (b) Nolte, R. J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1984**, *106*, 1416.

7. Hiraoka, M. *Crown Compounds. Their Characteristics and Application*; Elsevier: New York, 1982; Chapter 3.

8. Kimura, K.; Maeda, R.; Tamura, H.; Shono, T. *J. Electroanal. Chem. Interfacial Electrochem.* **1979**, *95*, 91.

9. Izatt, R. M.; Deardon, D. V.; Brown, P. R.; Bradshaw, J. S.; Lamb, J. D.; Christensen, J. J. *J. Am. Chem. Soc.* **1983**, *105*, 1785.

10. Izatt, R. M.; LindH, G. C.; Bruening, R. L.; Huszthy, P.; McDaniel, C. W.; Bradshaw, J. S.; Christensen, J. J. *Anal. Chem.* **1988**, *60*, 1694.

11. (a) Molecular mechanics calculations were performed by using SPARTAN® computer software, version 4.0.3 (MM3 force-field[11b]) on an SGI INDIGO2 computer workstation. SPARTAN® software was purchased from Wavefunction, Inc., 18401 Von Karman, Suite 370, Irvine, CA. (b) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551, 8566, 8576. The MM3 program is available to all users from the Technical Utilization Corporation, Inc., 235 Glen Village Court, Powell, OH 43065.

12. Ungaro, R.; El Haj, B.; Smid, J. *J. Am. Chem. Soc.* **1976**, *98*, 5198.

13. (a) Abdel-Rahman, M. O.; Kira, M.A.; Tolba, M. N. *Tetrahedron Lett.* **1968**, 3871; (b) Geldard, J. F.; Lions, F. *J. Org. Chem.* **1965**, *30*, 318. (c) Lin, C.-H.; Liever, E.; Horwitz, J. P. *J. Am. Chem. Soc.* **1954**, *76*, 427.

14. Hyde, E. M.; Shaw, B. L.; Shepherd, I. *J. Chem. Soc., Dalton Trans.* **1978**, 1696.

(*Received in USA* 18 *March* 1996; *revised* 29 *April* 1996; *accepted* 6 *May* 1996)