Diaza-18-Crown-6 Ligands Containing Two Aminophenol Side Arms: New Heterobinuclear Metal Ion Receptors

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Three diaza-18-crown-6 ligands substituted with two aminophenol side arms were synthesized as possible heterobinuclear metal ion receptors. Bis(*p*-aminophenol)-substituted diaza-18-crown-6 ligand (**13**) was prepared by treating the diazacrown with α-bromo-4-nitro-*o*-cresol in the presence of *N,N*-diisopropylethylamine followed by reduction of the nitro groups. Bis(*o*-aminophenol)-substituted diaza-18-crown-6 ligands (**11** and **12**) were prepared in two steps by the aminomethylation of either an *o*-nitrophenol or *o*-(trifluoroacetamido)phenol followed by reduction of the nitro groups or hydrolysis of the trifluoroacetamide groups. All new bisphenol-armed diazacrown ligands were purified by ultrasonication in MeOH followed by filtration and drying. Interaction of the ligands with Na⁺, K⁺, Ag⁺, and Cu²⁺ was evaluated by a calorimetric titration technique at 25 °C in MeOH. The complexes of Ag⁺ and Cu²⁺ are much more stable than those of Na⁺ and K⁺. Heterobinuclear complexes were observed for **11**-Cu²⁺- Na⁺ and **12**-Cu²⁺-Na⁺ but not for **13**-Cu²⁺-Na⁺ or for **12**-Cu²⁺-Ag⁺.

Introduction

Functionalization of crown ethers with additional ligating units is an effective way to increase metal ion complexing ability and selectivity.[1] Double-armed crown ethers have different, often better, metal ion complexing abilities than their mononuclear analogues.[2] Also, proton-ionizable phenol-containing azacrown ethers are effective complexing agents for transfer of metal cations from an aqueous to an organic phase.[1a,3] In some cases, these phenol-containing azacrown ethers display high selectivity and can be used for spectrophotometric determination of alkali and alkaline-earth metal cations.[1b,d,4] For the biscatechol-containing diazacrown ether,[5] an important application is its possible use as a heteronuclear metal ion receptor for simultaneous binding of soft transition and hard-alkali or alkaline-earth metal ions in one molecule. This type of ditopic receptors has received considerable attention in recent years because having two metal ions close together affects the redox properties of the complexed transition metal ions and they may be used for bimetalic catalysis and activation of small molecules such as O₂, CO, etc.[5] The negatively charged pseudocryptand, formed from the biscatechol-containing diazacrown ether and boron, can form neutral complexes with NH₄⁺ and K⁺.[5c,d]

A series of phenol-containing azacrown ethers with substituents such as Br, Cl, F, OH, CN, CH₃, OCH₃, Ph, C(CH₃)₃, NO₂, and CHO, which are *ortho* or *para* to the phenolic hydroxy group, have been prepared.[5–8] However, to our knowledge, no *ortho*- or *para*-aminophenol-substituted azacrown ethers have been reported. Double-armed aminophenol-substituted diaza-18-crown-6 ligands are expected to be interesting ionophores because the strongly electron donating amine group will make the phenol hydroxy group more electron rich and should influence its complexing ability. The amino group also has good complexing ability and may offer a competition or cooperation between amino and hydroxy groups in binding metal cations.

In this paper, we report the syntheses of seven new phenol-containing proton-ionizable diaza-18-crown-6 ligands (**6–9** and **11–13**, Scheme 1), including three new aminophenol-substituted diaza-18-crown-6 ligands (**11–13**). Compounds **11** and **12** are bis(*o*-aminophenol)-substituted diaza-18-crown-6 ligands, and compound **13** is a bis(*p*-aminophenol)-substituted diaza-18-crown-6

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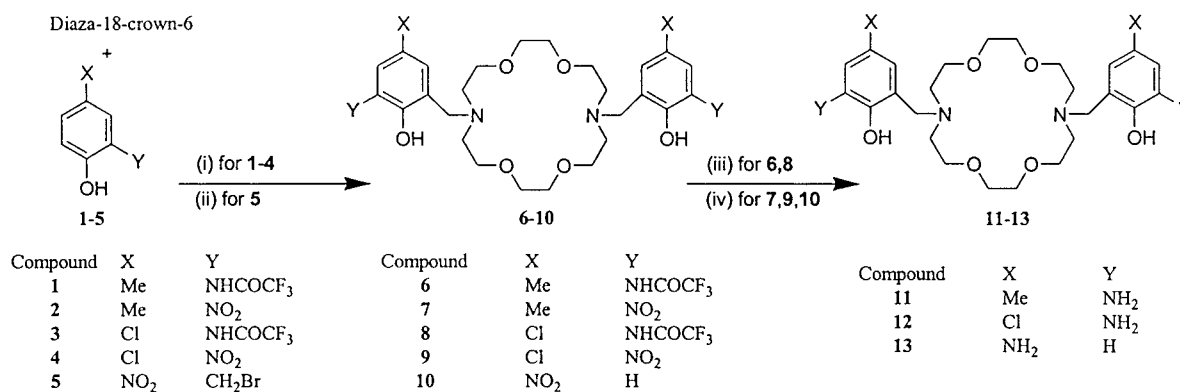(3) Nakamura, H.; Sakka, H.; Takagi, M.; Ueno, K. *Chem. Lett.* **1981**, 1305.

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Scheme 1. Syntheses of Bisphenol-Armed Diaza-18-Crown-6 Ligands[a]

Compound	X	Y
1	Me	NHCOCF$_3$
2	Me	NO$_2$
3	Cl	NHCOCF$_3$
4	Cl	NO$_2$
5	NO$_2$	CH$_2$Br

Compound	X	Y
6	Me	NHCOCF$_3$
7	Me	NO$_2$
8	Cl	NHCOCF$_3$
9	Cl	NO$_2$
10	NO$_2$	H

Compound	X	Y
11	Me	NH$_2$
12	Cl	NH$_2$
13	NH$_2$	H

[a] (i) (CH$_2$O)$_n$ and C$_6$H$_6$; (ii) N(i-Pr)$_2$Et and MeCN; (iii) 2.0 M NH$_3$ in MeOH; (iv) PtO$_2$/50−60 psi H$_2$.

ligand. We expected that the complexing ability of these three ligands would be affected by the position of the amino group relative to the hydroxy group—*ortho* or *para*. For compounds **11** and **12**, one or both of the two groups may take part in complexation with one metal ion. We also expected that compounds **11** and **12** would bind one transition metal ion among their amino and hydroxy groups and the resulting pseudocryptands[5,9] would bind another alkali metal ion. Compared to their biscatechol analogues,[5] the side arms of compounds **11** and **12** contain two soft donors (amino groups) and two hard donors (hydroxy groups). This arrangement was expected to make compounds **11** and **12** selective for soft metal ions. In contrast, compound **13** was not expected to form heterobinuclear complexes because only one of the two donating groups could take part in the complexation. Results from preliminary investigations demonstrate that ligands **11** and **12** do form binuclear complexes with Cu^{2+} and Na$^+$ while **13** does not.

Results and Discussion

The major methods for functionalizing azacrown macrocycles with proton-ionizable phenol groups include the following: (1) the Mannich reaction; (2) treatment of an azacrown ether with a benzyl or benzoyl halide; and (3) reductive amination with aromatic aldehydes.

The classical Mannich condensation reaction uses amines, formaldehyde, and an appropriate receptor for aminomethylation.[10] Many variations of this reaction have been developed. Methoxymethylamines, prepared quantitatively by treating the azacrown ethers with paraformaldehyde in MeOH, have been used successfully in functionalizing azacrown ethers.[8,11] This variation prevents the interaction of free formaldehyde with substances undergoing aminomethylation and possible side reactions between amine groups of the azacrown and functional groups such as carbonyls on the receptor

molecules. Preformation of the methoxymethylamines also allows the reaction to be performed in nonpolar solvents (CCl$_4$, C$_6$H$_6$, toluene, or xylene), which is important for some self-assembly cyclization processes.[12] A variety of phenol-, β-naphthol-, and amide-, sulfonamide-, imide- or azole-substituted monoaza-, diaza-, and pyridinoaza-crown ethers and cryptands have been prepared by this method.[8,11−17] One-pot Mannich reactions[6] of 4,-13-diaza-18-crown-6 with paraformaldehyde and a series of *para*-substituted phenols in refluxing benzene have been shown to give double-armed proton-ionizable crown ethers in good yields.[5] Solvent selection proved crucial for the successful synthesis of the Mannich base via this method.[6] Katritzky and co-workers have used bis(benzotriazolylmethyl)-substituted diaza-18-crown-6 as a versatile intermediate in the preparation of bislariat crown ethers.[18] Recently, the Einhorn reaction (amidomethylation) to construct anisole-containing building blocks for macrocyclization[19] was reported. The anisole-containing macrocycles were demethylated to form phenol-containing macrocycles.[19]

Treatment of the azacrown ether with benzyl halides or carboxylic acid derivatives in the presence of base is another method to prepare phenol-containing macrocycles. This method is not always convenient because of the difficulties in preparing the starting materials, the need to reduce the carbonyl group if carboxylic acid derivatives are used, and the need of the phenolic hydroxy group to be protected.[20,21]

Reductive amination is another convenient method to synthesize phenol-containing azacrown ethers. Treatment of the azacrown ethers with the appropriate alde-

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hydes in dichloroethane in the presence of sodium triacetoxyborohydride yields the proton-ionizable bis-lariat azacrown ethers in one step.[22,23]

We anticipated that the simplest route to synthesize compounds **11**−**13** would be via the Mannich reacction. However, this reaction with diaza-18-crown-6 and the aminophenols should lead to a mixture of regioisomers because both the OH and NH$_2$ groups would activate different substitution sites. In addition, byproducts with N−CH$_2$−N linkages[24,25] would also form. To avoid these problems, the amino group was either temporarily protected as a trifluoroacetamide group or obtained by hydrogenation of a nitro group after connection of the nitrophenol to the azacrown ether.

Our approaches to prepare compounds **6**−**13** are outlined in Scheme 1. For compound **10**, which was first synthesized by Nishida and co-workers and has been used to selectively determine the calcium ion concentration in blood serum,[4,21] method ii (Scheme 1) was used. In the presence of *N,N*-diisopropylethylamine, α-bromo-4-nitro-*o*-cresol (**5**) was refluxed with diaza-18-crown-6 in MeCN to give **10** in a 74% yield.[4,13] The yield is significantly higher than the 15% yield reported by Lagow's group using the one-pot Mannich reaction.[6] Thus, for electron deficient phenol compounds, this method may be the better choice if the appropriate benzyl halides are available. Method ii also works well for the reaction of diaza-18-crown-6 with 5,7-dichloro-2-iodo-methyl-8-quinolinol.[23] We found that adding a small amount of MeOH to the crude product and agitating it with ultrasound, followed by filtration and vacuum-drying, gave **10** in high purity. All of the crown ethers synthesized in this paper were purified by this method without the need for column chromatography or recrystallization.

Compounds **6**−**9** were synthesized by the one-pot Mannich reaction (Scheme 1).[6] Trifluoroacetamides **1** and **3**, needed to synthesize **6** and **8**, were prepared by treating the corresponding aminophenol with 2.2 equiv of trifluoroacetic anhydride and 3 equiv of pyridine in CH$_2$Cl$_2$. The trifluoroacetate was selectively hydrolyzed by stirring the resulting trifluoroacetate−trifluoroacetamide compounds in dry MeOH containing anhydrous K$_2$CO$_3$ at room temperature for 5 h.[26] For the one-pot Mannich reaction, 2-(trifluoroacetamido)-*p*-cresol (**1**) gave the highest yield (90%) presumably because it is more electron rich than its 4-chloro analogue **3** and compounds **2** and **4**.

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Table 1. log K, ΔH (kJ/mol), and $T\Delta S$ (kJ/mol) Values for Interactions of Macrocyclic Ligands with Metal Ions in Methanol Solution at 25.0 °C

ligand	cation	log K	ΔH	$T\Delta S$
6	Na$^+$	a		
	K$^+$	a	−70.0 ± 0.5	−39.7
	Cu^{2+}	5.30 ± 0.04		
8	K$^+$	2.72 ± 0.05	−12.1 ± 0.8	3.42
	Cu^{2+}	>5.5	−65 ± 3	>−33.6
11	Na$^+$	3.00 ± 0.05	−7.9 ± 0.8	9.22
	K$^+$	2.36 ± 0.08	−10.6 ± 0.7	2.87
	Cu^{2+}	>5.5	−69 ± 3	>−37.6
12	Na$^+$	3.42 ± 0.04	−12.4 ± 0.7	7.12
	K$^+$	a		
	Ag$^+$	>5.5	−47.9 ± 0.5	>−16.5
	Cu^{2+}	>5.5	−68 ± 3	>−36.7
13	Na$^+$	2.73 ± 0.06	−24.6 ± 0.7	−9.01
	K$^+$	2.81 ± 0.02	−34.8 ± 0.4	−18.8
	Cu^{2+}	>5.5	−65 ± 3	>−33.6
Cu^{2+}-**11**[b]	Na$^+$	1.41 ± 0.05	17.8 ± 0.6	25.8
Cu^{2+}-**12**	Na$^+$	1.86 ± 0.06	8.9 ± 0.4	19.5
Cu^{2+}-**13**	Na$^+$	a		

[a] No measurable heat other than heat of dilution indicating that ΔH or/and log K is small. *[b]* MeOH solutions of Cu^{2+} ligand (1:1) were titrated by an Na$^+$−MeOH solution.

Compounds **11** and **12** were prepared by removing the TFA groups of **6** and **8** with 2.0 M NH$_3$ in MeOH[27] or by hydrogenation of the nitro groups of **7** and **9** with 50−60 psi H$_2$ in the presence of PtO$_2$ as catalyst.[28] Both methods gave **11** and **12** in high yields. Compound **13** was only obtained by hydrogenation of **10**.

Interactions of the ligands **6**, **8**, and **11**−**13** with Na$^+$, K$^+$, Ag$^+$, and Cu^{2+} have been evaluated by a calorimetric titration technique[30] at 25.0 °C in absolute MeOH solution. The values of equilibrium constants (log K) and enthalpy (ΔH) and entropy changes ($T\Delta S$) for these interactions are listed in Table 1. In most cases, the ligands form stable complexes with the metal ions studied. The complexes of Cu^{2+} and Ag$^+$ are much more stable than those of Na$^+$ and K$^+$. Among the ligands studied, **6** shows weaker interaction with Na$^+$, K$^+$, and Cu^{2+} than the other ligands. The two *o*-nitrophenol-substituted compounds **7** and **9** have very low solubility in MeOH, and compound **9** (1 × 10^{-3} M in MeOH) forms a precipitate with K$^+$. Hence the thermodynamic quantities involving **7** and **9** were not evaluated.

Ligands **11**−**13** have been evaluated as heterobinuclear metal ion receptors. When MeOH solutions of **11**-Cu^{2+} and **12**-Cu^{2+} (1:1) were titrated by Na$^+$, appreciable interactions were observed as shown by log K values (1.41 and 1.86, respectively, see Table 1). These results indicate the formation of heterobinuclear complexes of **11**-Cu^{2+}-Na$^+$ and **12**-Cu^{2+}-Na$^+$. As expected, these log K values are smaller than those for direct **11**-Na$^+$ and **12**-Na$^+$ interactions (3.00 and 3.42, respectively). Interactions of Na$^+$ with **11**-Cu^{2+} and **12**-Cu^{2+} are endothermic (positive ΔH values) while the direct interactions of Na$^+$ with ligands **11** and **12** are exothermic. It is possible that a weak interaction between Cu^{2+} and the diaza-18-crown-6

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X = CH₃ **11**-Cu²⁺-Na⁺

X = Cl **12**-Cu²⁺-Na⁺

13-Cu²⁺
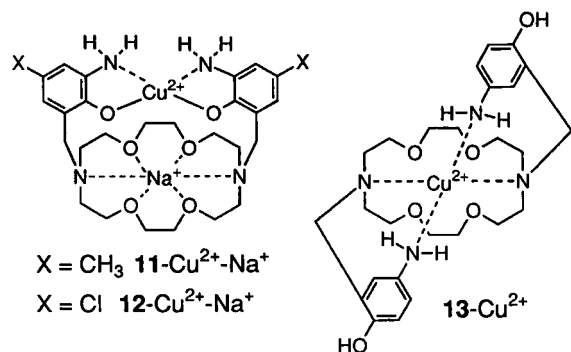
Figure 1.

macroring is present in the complexes of **11**-Cu²⁺ and **12**-Cu²⁺. As Na⁺ is titrated into the Cu²⁺ ligand solutions, this weak interaction is broken by the Na⁺ ion and Na⁺ is then complexed in the diaza-18-crown-6 macroring (see Figure 1). The elimination of Cu²⁺-macroring interactions by Na⁺ would be an energy-consuming process resulting in positive ΔH values for formation of the heterobinuclear complexes as was observed. The formation of heterobinuclear complexes of **11**-Cu²⁺-Na⁺ and **12**-Cu²⁺-Na⁺ originates from an increase in the entropy changes which arise from the liberation of organized solvent molecules in the solvation sphere of Na⁺ and those associated with the Cu²⁺ ligands. These favorable entropy changes overcome the energetically unfavorable enthalpy change arising from coordination of Na⁺ within the ligand cavity. The soft Cu²⁺ is probably strongly coordinated by both amino nitrogen and hydroxy oxygen atoms of two *o*-aminophenol side arms of **11** and **12**. Unfortunately, solid crystals of these binuclear complexes could not be isolated for X-ray analyses.

Although ligand **13** forms a very stable complex with Cu²⁺ and a stable complex with Na⁺, calorimetric titration shows no interaction between Na⁺ and the **13**-Cu²⁺ complex. This is not surprising since the two *p*-aminophenol side arms of **13** could not provide a stable coordination array for Cu²⁺. In this case, Cu²⁺ may be strongly coordinated by the ring nitrogen atoms and the two side arm amine nitrogen atoms and not with the hydroxy groups (see **13**-Cu²⁺ in Figure 1). This would place Cu²⁺ in the macrocycle cavity. Therefore, the hard Na⁺ would not be able to break the Cu²⁺−N bonds and no heterobinuclear complex would form.

We have also examined the interaction between Ag⁺ and the **12**-Cu²⁺ complex. Calorimetric titration of AgNO₃ into a Cu(NO₃)₂-**12** (1:1) solution (halogenide anions may not be used due to possible interactions with Ag⁺) showed a small endothermic effect but the log K value was too small to be accurately calculated. These results indicate that Ag⁺ probably does not form a heterobinuclear complex with the **12**-Cu²⁺ complex or the stability of **12**-Cu²⁺-Ag⁺ is too low to be determined by this method.

Conclusion

Three bis(aminophenol)-substituted diaza-18-crown-6 ligands (compounds **11**−**13**) were synthesized by reducing the nitro groups of the corresponding bis(nitrophenol)-containing ligands or hydrolyzing the trifluoroacetamide groups of bis(trifluoroacetamidophenol)-containing diazacrown ethers. The nitro- or trifluoroacetamido-containing diazacrown ethers were prepared via the one-

pot Mannich reaction of diaza-18-crown-6 with para-formaldehyde and the appropriate phenol (to form **6**−**9**) or reacting the diazacrown with benzyl halide **5** in the presence of *N,N*-diisopropylethylamine (to form **10**). Ligands **11** and **12** containing two *o*-aminophenol substituents form binuclear complexes with Cu²⁺ and Na⁺ as determined by log K values.

Experimental Section

The ¹H NMR spectra (300 MHz) and ¹³C NMR spectra (75 MHz) were recorded in DMSO-d_6 or CDCl₃. FAB ionization was used to record the high-resolution mass spectra. Solvents and starting materials were purchased from commercial sources where available.

7,16-Bis(2-hydroxy-5-nitrobenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (10) (Scheme 1). α-Bromo-4-nitro-*o*-cresol (**5**) (3.90 g, 16.8 mmol) and *N,N*-diisopropylethylamine (5.40 mL, 30.5 mmol) were added to a solution of 4,13-diaza-18-crown-6 (2.00 g, 7.18 mmol) in 200 mL of MeCN. The resulting mixture was refluxed for 12 h and cooled to room temperature. After standing overnight, the bright yellow deposit was filtered and dried. It was further purified by ultrasonication in a small amount of MeOH followed by filtration and drying to give 3.20 g (74%) of **10** as a bright yellow solid. The mp and NMR spectral data were identical to those reported.[6]

2-(Trifluoroacetamido)-*p*-cresol (1) (Scheme 1). To a solution of 2-hydroxy-5-methylaniline (10.0 g, 81.2 mmol) in 180 mL of CH₂Cl₂ were added trifluoroacetic anhydride (26.0 mL, 184 mmol) and anhydrous pyridine (20.0 mL, 244 mmol). The mixture was stirred at room temperature for 24 h, and the solvent was removed under vacuum. Anhydrous K₂CO₃ (16.8 g, 122 mmol) and 200 mL of dry MeOH were added, and the mixture was stirred at room temperature for another 5 h. The solvent was evaporated, and the resulting solid was washed with H₂O and CHCl₃ to give 16.9 g (95%) of **1** as a light green solid: mp 193−194 °C; ¹H NMR (DMSO-d_6) δ 2.20 (s, 3 H), 6.83 (d, J = 8.4 Hz, 1 H), 6.93 (dd, J = 1.8, 8.1 Hz, 1 H), 7.16 (d, J = 1.8 Hz, 1 H), 9.65 (s, 1 H), 10.41 (s, 1 H); ¹³C NMR (DMSO-d_6) δ 20.06, 116.04, 116.84 (q, J_{CF} = 288.5 Hz), 122.03, 126.61, 127.81, 128.44, 148.95, 155.05 (q, J_{CF} = 36.3 Hz); HRMS calcd for C₉H₈F₃NO₂ (M + H)⁺ 220.0586, found 220.0582. A satisfactory elemental analysis was obtained for macrocycle **6**, a derivative of **1**.

4-Chloro-2-trifluoroacetamidophenol (3) (Scheme 1). Compound **3** was synthesized as above from 5-chloro-2-hydroxyaniline (10.0 g, 69.6 mmol), trifluoroacetic anhydride (22.0 mL, 153 mmol), anhydrous pyridine (17.0 mL, 209 mmol), and K₂CO₃ (14.4 g, 104 mmol) to give 16.3 g (98%) of **3** as a light yellow solid: mp 184−185 °C; ¹H NMR (DMSO-d_6) δ 6.97 (d, J = 8.4 Hz, 1 H), 7.20 (dd, J = 2.4, 9.0 Hz, 1 H), 7.455 (d, J = 2.4 Hz, 1 H), 10.38 (bs, 1 H), 10.65 (s, 1 H); ¹³C NMR (DMSO-d_6) δ 111.81 (q, J_{CF} = 288.6 Hz), 113.35, 117.82, 119.43, 121.71, 123.55, 146.20, 151.00 (q, J_{CF} = 36.7 Hz); HRMS calcd for C₈H₅ClF₃NO₂ (M + H)⁺ 240.0040, found 240.0041. A satisfactory elemental analysis was obtained for macrocycle **8**, a derivative of **3**.

General Procedure for the One-Pot Syntheses of Compounds 6−9 Using the Mannich Reaction (Scheme 1).[6] An anhydrous C₆H₆ solution (180 mL) of 4,13-diaza-18-crown-6 (1.0 g, 3.81 mmol), paraformaldehyde (280 mg, 9.30 mmol), and the appropriate phenol (9.10 mmol) was refluxed at 80 °C for 20 h. The solvent was evaporated under reduced pressure, and a small amount of MeOH was added. The mixture was ultrasonicated for 20−30 min. The resulting solid was collected by filtration and dried.

7,16-Bis(2-hydroxy-5-methyl-3-trifluoroacetamido-benzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (6) (Scheme 1). Compound **6** was prepared by the above procedure from **1** to give a white solid; mp 155−157 °C; yield 90%; ¹H NMR (DMSO-d_6) δ 2.20 (s, 6 H), 2.74 (t, J = 4.8 Hz, 8 H), 3.51 (s, 8 H), 3.59 (t, J = 4.8 Hz, 8 H), 3.80 (s, 4 H), 6.83 (d, J = 1.5 Hz, 2 H), 7.12 (d, J = 1.5 Hz, 2 H); ¹³C NMR (DMSO-d_6) δ

20.04, 52.98, 57.21, 67.95, 69.89, 116.03 (q, J_{CF} = 289.1 Hz), 121.80, 123.24, 124.91, 126.93, 127.81, 148.99, 154.70 (q, J_{CF} = 36.3 Hz); HRMS calcd for $C_{32}H_{42}F_6N_4O_8$ (M$^+$) 724.2907, found 724.2899. Anal. Calcd for $C_{32}H_{42}F_6N_4O_8$: C, 53.04; H, 5.84. Found: C, 53.23; H, 6.05.

7,16-Bis(2-hydroxy-5-methyl-3-nitrobenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (7) (Scheme 1). Compound **7** was prepared by the above procedure from **2** to give a yellow solid: mp 146−148 °C; yield 36%; ^{1}H NMR (CDCl$_3$) δ 2.29 (s, 6 H), 2.88 (t, J = 5.4 Hz, 8 H), 3.60 (s, 8 H), 3.69 (t, J = 5.4 Hz, 8 H), 3.90 (s, 4 H), 7.14 (s, 2 H), 7.66 (s, 2 H); ^{13}C NMR (CDCl$_3$) δ 20.43, 53.91, 57.73, 69.00, 70.99, 124.55, 126.39, 127.91, 135.41, 136.82, 151.85; HRMS calcd for $C_{28}H_{40}N_4O_{10}$ (M + Na)$^+$ 615.2624, found 615.2636. Anal. Calcd for $C_{28}H_{40}N_4O_{10}$: C, 56.75; H, 6.80. Found: C, 56.74; H, 6.90.

7,16-Bis(5-chloro-2-hydroxy-3-trifluoroacetamido-benzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (8) (Scheme 1). Compound **8** was prepared by the above procedure from **3** to give a light yellow solid: mp 136−137 °C; yield 64%; ^{1}H NMR (DMSO-d_6) δ 2.77 (t, J = 4.5 Hz, 8 H), 3.51 (s, 8 H), 3.59 (t, J = 4.5 Hz, 8 H), 3.88 (s, 4 H), 7.14 (d, J = 2.4 Hz, 2 H), 7.40 (d, J = 2.4 Hz, 2 H); ^{13}C NMR (DMSO-d_6) δ 52.92, 56.54, 67.74, 69.86, 115.87 (q, J_{CF} = 288.6 Hz), 121.12, 123.29, 124.08, 125.33, 126.78, 150.65, 154.85 (q, J_{CF} = 36.3 Hz); HRMS calcd for $C_{30}H_{36}Cl_2F_6N_4O_8$ (M$^+$) 764.1814, found 764.1823. Anal. Calcd for $C_{30}H_{36}Cl_2F_6N_4O_8$: C, 47.07; H, 4.74. Found: C, 47.07; H, 5.01.

7,16-Bis(5-chloro-2-hydroxy-3-nitrobenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (9) (Scheme 1). Compound **9** was prepared by the above procedure from **4** to give a light yellow solid: mp 152−153 °C; yield 41%; ^{1}H NMR (CDCl$_3$) δ 2.88 (t, J = 5.4 Hz, 8 H), 3.59 (s, 8 H), 3.70 (t, J = 5.4 Hz, 8 H), 3.95 (s, 4 H), 7.30 (d, J = 2.7 Hz, 2 H), 7.84 (d, J = 2.4 Hz, 2 H); ^{13}C NMR (CDCl$_3$) δ 54.01, 57.72, 68.66, 71.03, 122.58, 124.31, 128.30, 133.87, 137.22, 153.34; HRMS calcd for $C_{26}H_{34}Cl_2N_4O_{10}$ (M + H)$^+$ 633.1731, found 633.1749. Anal. Calcd for $C_{26}H_{34}Cl_2N_4O_{10}$: C, 49.30; H, 5.41. Found: C, 49.52; H, 5.24.

General Method for Synthesizing Compounds 11, 12, and 13 from 7, 9, and 10 by Reduction with H$_2$ (Scheme 1). To a solution of the corresponding nitrophenol-containing crown ether (2 mmol) in 50 mL of MeOH was added PtO$_2$ (40 mg). The reaction mixture was shaken under 50−60 psi of H$_2$ until the absorption of H$_2$ ceased (about 5 h). The mixture was filtered to remove the catalyst, and the solvent was evaporated. Ultrasonification of the resulting solid in a small amount of MeOH for 20−30 min followed by filtration and drying gave the corresponding aminophenol-containing crown ether in almost quantitative yield.

7,16-Bis(3-amino-2-hydroxy-5-methylbenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (11) (Scheme 1). Compound **11** was prepared by the above procedure from **7** to give a yellow solid: mp 131−132 °C; yield 98%; ^{1}H NMR (CDCl$_3$) δ 2.17 (s, 6 H), 2.84 (t, J = 5.4 Hz, 8 H), 3.61 (s), 3.66 (t, J = 5.4 Hz), 3.71 (s), the peak for four amine hydrogen atoms merged into the peaks at 3.61, 3.66, and 3.71 as proved by the total intergration of those peaks (24 H), 6.22 (s, 2 H), 6.47 (s, 2 H); ^{13}C NMR (CDCl$_3$) δ 20.90, 53.95, 58.80, 69.42, 70.93, 115.58, 119.09, 121.75, 128. 45, 135.01, 143.21; HRMS calcd for

$C_{28}H_{44}N_4O_6$ (M + Na)$^+$ 555.3159, found 555.3149. Anal. Calcd for $C_{28}H_{44}N_4O_6$: C, 63.13; H, 8.33. Found: C, 62.97; H, 8.21.

7,16-Bis(3-amino-5-chloro-2-hydroxybenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclo-octadecane (12) (Scheme 1). Compound **12** was prepared by the above procedure from **9** to give a dark yellow solid: mp 126−127 °C; yield 98%; ^{1}H NMR (CDCl$_3$) δ 2.84 (t, J = 5.4 Hz, 8 H), 3.61 (s, 8 H), 3.66 (t, J = 5.4 Hz, 8 H), 3.71 (s, 4 H), 3.84 (bs, 4 H); 6.38 (d, J = 2.4 Hz, 2 H), 6.61 (d, J = 2.4 Hz, 2 H); ^{13}C NMR (CDCl$_3$) δ 54.01, 58.36, 69.21, 70.94, 114.20, 117.77, 122.94, 123.78, 136.60, 144.03; HRMS calcd for $C_{26}H_{38}N_4O_6$ (M + H)$^+$ 573.2247, found 573.2229. Anal. Calcd for $C_{26}H_{38}N_4O_6$: C, 54.45; H, 6.68. Found: C, 54.60; H, 6.75.

7,16-Bis(5-amino-2-hydroxybenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (13) (Scheme 1). Compound **13** was prepared by the above procedure from **10** to give a light yellow solid: mp 142−143 °C; yield 98%; ^{1}H NMR (CDCl$_3$) δ 2.84 (t, J = 5.4 Hz, 8 H), 3.31 (bs, 4 H), 3.60 (s, 8 H), 3.65 (t, J = 5.4 Hz, 8 H), 3.71 (s, 4 H), 6.38 (d, J = 2.7 Hz, 2 H), 6.54 (dd, J = 2.7, 8.4 Hz, 2 H), 6.65 (d, J = 8.1 Hz, 2 H); ^{13}C NMR (CDCl$_3$) δ 53.90, 58.88, 69.35, 70.91, 116.07, 116.41, 116.93, 123. 29, 138. 45, 150.81; HRMS calcd for $C_{26}H_{40}N_4O_6$ (M + Na)$^+$ 527.2846, found 527.2836. Anal. Calcd for $C_{26}H_{40}N_4O_6$: C, 61.88; H, 7.99. Found: C, 61.94; H, 7.75.

General Method for Synthesizing Compounds 11 and 12 from 6 and 8 by Hydrolyzing the TFA Groups (Scheme 1). The corresponding trifluoroacetamidophenol-containing crown ether (3 mmol) was added to 20 mL of 2.0 M NH$_3$ in MeOH and stirred for 20 h. The solvent was removed under vacuum, and the residue was treated as before to give **11** (95%) and **12** (97%) which had the same spectra as reported above.

Determination of Thermodynamic Quantities. Values of log K, ΔH, and $T\Delta S$ were determined as described[29] in absolute MeOH solutions at 25.0 ± 0.1 °C by titration calorimetry using a Tronac Model 450 calorimeter equipped with a 20-mL reaction vessel. For single metal ion−ligand interactions, a metal ion solution was titrated into the macrocyclic ligand solution and the titrations were carried out to a 2−2.5-fold excess of the metal ions. In general, concentrations of the ligands were 2.0×10^{-3} to 3.0×10^{-3} M and those of the metal ions were 0.1 M (Na$^+$ and Ag$^+$) and 7.1×10^{-2} M (K$^+$). In the case of Cu^{2+}, concentrations of the ligands were 1.2×10^{-3} M and that of Cu^{2+} was 4.0×10^{-2} M. For the interactions of Na$^+$ and Ag$^+$ with the Cu^{2+} ligand complexes, the Na$^+$ or Ag$^+$ solution was titrated into the Cu^{2+} ligand solutions and the titrations were carried out to a 2-fold excess of the Na$^+$ or Ag$^+$. Concentrations of Na$^+$ and Ag$^+$ were 0.1 M, and those of the Cu^{2+} ligand (1:1) complex were 3.0×10^{-3} M. For the titrations involving Ag$^+$, Cu(NO$_3$)$_2$, instead of CuCl$_2$, was used. The method used to process the calorimetric data and to calculate the log K and ΔH values has been described.[30] Reagant grade inorganic chemicals were obtained from commercial sources and used without further purification.