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-α cresol in the presence of N,N-disopropylethylamine followed by reduction of the nitro groups. Bis(α-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-(trifluoroacetamide)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⁺.
OFFICE OF NAVAL RESEARCH

Grant N00014-98-1-0485

Technical Report No. 12

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

by

Ning Su, Jerald S. Bradshaw, Xian Xin Zhang, Paul B. Savage, Krzysztof E. Krakowiak, and Reed M. Izatt

Department of Chemistry and Biochemistry
Brigham Young University, Provo, UT 84602-4678

September 30, 1999

Reproduction in whole or in part is permitted for any purpose of the United States Government

This document has been approved for public release and sale; its distribution is unlimited
Diaza-18-Crown-6 Ligands Containing Two Aminophenol Side Arms: New Heterobinuclear Metal Ion Receptors

Ning Su, Jerald S. Bradshaw,† Xian Xin Zhang, Paul B. Savage, Krzysztof E. Krakowiak,‡ and Reed M. Izatt

Department of Chemistry & Biochemistry, Brigham Young University, Provo, Utah 84602

Received August 10, 1998 (Revised Manuscript Received January 21, 1999)

Three diaza-18-crown-6 ligands substituted with two aminophenol side arms were synthesized as possible heterobinuclear metal ion receptors. Bis(2-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-disopropylethylamine 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-nitrophenoI or o-(trifluoroacetamido)phenol followed by reduction of the nitro groups or hydrolysis of the trifluoroacetamide groups. All new biphenol-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-iodizable phenol-containing azacrown ethers are effective complexing agents for transfer of metal cations from an aqueous to an organic phase.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.5 For the bis(biscatechol-containing diaza-crown ether), 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 bimetallic catalysis and activation of small molecules such as O₂, CO, etc.6 The negatively charged pseudocryptand, formed from the bis(catechol-containing diaza-crown ether) and boron, can form neutral complexes with NH₄⁺ and K⁺.5,c,d

A series of phenol-containing azacrown ethers with substituents such as Br, CI, 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,e-g 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 amino 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

1 Fax: 801-376-3474; E-mail: jerald_bradshaw@byu.edu.
2 Current address for K.E.K., IBC Advanced Technologies, Inc., P.O. Box 98, American Fork, UT 84003.
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 pseudocryptand5,9 would bind another alkali metal ion. Compared to their bissalicylaldehyde analogues,9 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 Cu2+ and Na+ while 13 does not.

**Results and Discussion**

The major methods for functionalizing azacrown macrocycles with proton-ionicizable 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 (CCl4, C6H6, 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 pyridinoazacrown ethers and cryptands have been prepared by this method.8,11-17 One-pot Mannich reactions8 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.8 Solvent selection proved crucial for the successful synthesis of the Mannich base via this method.8 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 aniso-containing building blocks for macrocyclization19 was reported. The aniso-containing macrocycles were demethylated to form phenol-containing macrocycles.18

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

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

---

Diazao-Crown 18 Ligands with Aminophenol Side Arms

hydnes 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 reaction.

However, this reaction with diaza-18-crown-6 and the aminophenols should lead to a mixture of regioisomers

because both the OH and NH2 groups would activate different substitution sites. In addition, byproducts with

N–CH2–N linkages24,25 would also form. To avoid these problems, the amino group was either temporarily pro-
tected 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 concentra-
tion in blood serum,4,5 method II (Scheme 1) was used. In the presence of N,N-dilsopropylethylamine, 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.4

Thus, for electron deficient phenol compounds, this method may be the better choice if the appropriate benzy-

l 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 recrys-
tallization.

Compounds 6–9 were synthesized by the one-pot Mannich reaction (Scheme 1).4 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 CH2Cl2. The trifluoroacetate was selectively hydrolyzed by

stirring the resulting trifluoroacetate—trifluoroacetamide compounds in dry MeOH containing anhydrous

K2CO3 at room temperature for 5 h.28 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.

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

<table>
<thead>
<tr>
<th>ligand</th>
<th>cation</th>
<th>log K</th>
<th>ΔH</th>
<th>TΔS</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Na+</td>
<td>a</td>
<td>-70.0 ± 0.5</td>
<td>-39.7</td>
</tr>
<tr>
<td>K+</td>
<td>K+</td>
<td>a</td>
<td>-12.1 ± 0.8</td>
<td>3.42</td>
</tr>
<tr>
<td>Cu2+</td>
<td>Cu2+</td>
<td>5.30 ± 0.04</td>
<td>-65 ± 3</td>
<td>&gt;33.6</td>
</tr>
<tr>
<td>8</td>
<td>Na+</td>
<td>&gt;5.5</td>
<td>-7.9 ± 0.8</td>
<td>9.22</td>
</tr>
<tr>
<td>K+</td>
<td>K+</td>
<td>5.3 ± 0.05</td>
<td>-60.7 ± 0.3</td>
<td>2.87</td>
</tr>
<tr>
<td>Cu2+</td>
<td>Cu2+</td>
<td>&gt;5.5</td>
<td>-68 ± 3</td>
<td>&gt;37.6</td>
</tr>
<tr>
<td>11</td>
<td>Na+</td>
<td>3.42 ± 0.04</td>
<td>-12.4 ± 0.7</td>
<td>7.12</td>
</tr>
<tr>
<td>K+</td>
<td>K+</td>
<td>a</td>
<td>-47.9 ± 0.5</td>
<td>&gt;16.5</td>
</tr>
<tr>
<td>Cu2+</td>
<td>Cu2+</td>
<td>&gt;5.5</td>
<td>-68 ± 3</td>
<td>&gt;36.7</td>
</tr>
<tr>
<td>13</td>
<td>Na+</td>
<td>2.73 ± 0.06</td>
<td>-24.6 ± 0.7</td>
<td>-9.01</td>
</tr>
<tr>
<td>K+</td>
<td>K+</td>
<td>2.81 ± 0.02</td>
<td>-34.8 ± 0.4</td>
<td>-18.8</td>
</tr>
<tr>
<td>Cu2+</td>
<td>Cu2+</td>
<td>&gt;5.5</td>
<td>-65 ± 3</td>
<td>&gt;33.6</td>
</tr>
<tr>
<td>Cu2+−11b</td>
<td>Na+</td>
<td>1.41 ± 0.05</td>
<td>17.8 ± 0.6</td>
<td>25.8</td>
</tr>
<tr>
<td>Cu2+−12</td>
<td>Na+</td>
<td>1.86 ± 0.06</td>
<td>8.9 ± 0.4</td>
<td>19.5</td>
</tr>
<tr>
<td>Cu2+−13</td>
<td>Na+</td>
<td>a</td>
<td>-48.8 ± 0.5</td>
<td>&gt;36.7</td>
</tr>
</tbody>
</table>

*No measurable heat other than heat of dilution indicating that ΔH or log K is small. MeOH solutions of Cu2+ 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 NH3 in MeOH27 or by
hydrogenation of the nitro groups of 7 and 9 with 50–60 psi H2 in the presence of PdO2 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 11−3 with Na+, K+, Ag+, and Cu2+ have been evaluated by a calorimetric
titration technique30 at 25.0°C in absolute MeOH solution. The values of equilibrium constants (log K) and enthalpy (ΔH) and entropy changes (TΔS) for these interactions are listed in Table 1. In most cases, the ligands form stable complexes with the metal ions studied. The complexes of Cu2+ and Ag+ are much more stable than those of Na+ and K+; among the ligands studied, 6 shows weaker interaction with Na+, K+, Cu2+, and Cu2+ than the other ligands. The two α-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-Cu2+ and 12-Cu2+ (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-Cu2+−
Na+ and 12-Cu2+−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-Cu2+ and 12-Cu2+ 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 Cu2+ and the diaza-18-crown-6


J. Org. Chem., Vol. 64, No. 11, 1999 3827
macroring is present in the complexes of 11-Cu^{2+} and 12-Cu^{2+}. As Na^+ is titrated into the Cu^{2+} 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 Cu^{2+}-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-Cu^{2+}Na^+ and 12-Cu^{2+}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 Cu^{2+} ligands. These favorable entropy changes overcome the energetically unfavorable enthalpy change arising from coordination of Na^+ within the ligand cavity. The soft Cu^{2+} is probably strongly coordinated by both amino nitrogen and hydroxyl oxygen atoms of two α-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 Cu^{2+} and a stable complex with Na^+, calorimetric titration shows no interaction between Na^+ and the 13-Cu^{2+} complex. This is not surprising since the two p-aminophenol side arms of 13 could not provide a stable coordination array for Cu^{2+}. In this case, Cu^{2+} may be strongly coordinated by the ring nitrogen atoms and the two side arm amine nitrogen atoms and not with the hydroxyl groups (see 13-Cu^{2+} in Figure 1). This would place Cu^{2+} in the macrocycle cavity. Therefore, the hard Na^+ would not be able to break the Cu^{2+}–N bonds and no heterobinuclear complex would form.

We have also examined the interaction between Ag^+ and the 12-Cu^{2+} complex. Calorimetric titration of AgNO_3 into a Cu(NO_3)_2·12 (1:1) solution (halogenide anions may Cu^2+ cannot 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-Cu^{2+} complex or the stability of 12-Cu^{2+}Ag^+ is too low to be determined by this method.

**Experimental Section**

The 1H NMR spectra (300 MHz) and 13C NMR spectra (75 MHz) were recorded in DMSO-d_6 or CDCl_3. 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-dilisopropyl ethylamine (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.

2-(Trifluoroacetamido)-p-cresol (11) (Scheme 1). A solution of 2-hydroxy-5-methylaniline (10.0 g, 81.2 mmol) in 180 mL of CH_2Cl_2 was added dropwise to a solution of trifluoroacetic anhydride (26.0 mL, 264 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 K_2CO_3 (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 H_2O and CH_2Cl_2 to give 16.9 g (95%) of 11 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 (ddd, 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, 144.95, 155.05 (q, J_CF = 36.3 Hz); HRMS calculated for C_9H_8F_2NO_3 (M + H)^+ 220.0586, found 220.0582. A satisfactory elemental analysis was obtained for macrocycle 6, a derivative of 1.

4-Mono[3-chloro-2-hydroxyacetamidophenol] (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 K_2CO_3 (14.4 g, 104 mmol) to give 16.3 g (88%) 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 calculated for C_9H_6ClF_2NO_3 (M + H)^+ 240.0400, found 240.0414. 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). An anhydrous CaH_2 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-trifluoroacetamidobenzyl]-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), 7.12 (d, J = 1.5 Hz, 2 H), 13C NMR (DMSO-d_6) δ

**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 and hydrolyzing the trifluoroacetamide groups of bis(trifluoroacetamidophenol)-containing diazacrown ethers. The nitro- trifluoroacetamido-containing diazacrown ethers were prepared via the one-pot Mannich reaction of diaza-18-crown-6 with paraformaldehyde and the appropriate phenol (to form 6–9) or reacting the diazacrown with benzyl halide 5 in the presence of N,N-dilisopropylethylamine (to form 10). Ligands 11 and 12 containing two α-aminophenol substituents form binuclear complexes with Cu^{2+} and Na^+ as determined by log K values.
Diaza-18-Crown-6 Ligands with Aminophenol Side Arms

20.04, 52.98, 57.21, 67.95, 69.89, 116.03 (q, JCF = 289.1 Hz), 121.80, 123.24, 124.91, 126.93, 127.81, 148.99, 154.70 (q, JCF = 36.3 Hz); HRMS calcd for C18H24N2O6 (M+Na+) 724.2907, found 724.2899. Anal. Calcd for C18H24N2O6: C, 53.30; H, 6.05.

7.16-Bis(2-hydroxy-3-methyl-1-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%; 1H NMR (CDCl3) δ 2.29 (s, 6 H), 2.88 (t, J = 5.4 Hz, 8 H), 3.60 (s, 8 H), 3.89 (t, J = 5.4 Hz, 8 H), 3.90 (s, 4 H), 7.14 (s, 2 H), 7.16 (s, 2 H); 13C NMR (CDCl3) δ 20.43, 53.91, 57.73, 69.00, 79.99, 124.55, 126.39, 127.91, 135.41, 136.82, 151.85; HRMS calcd for C20H21NO10 (M+Na+) 615.2624, found 615.2636. Anal. Calcd for C20H21NO10: C, 56.75; H, 6.80. Found: C, 56.74; H, 6.90.

7.16-Bis(3-chloro-2-hydroxy-3-trifluoroacetamidobenzyl)-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%; 1H NMR (CDCl3) δ 2.77 (t, J = 4.5 Hz, 8 H), 3.51 (s, 4 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); 13C NMR (CDCl3) δ 52.92, 56.54, 67.74, 69.86, 115.87 (q, JCF = 288.6 Hz), 121.12, 123.29, 124.08, 125.33, 126.78, 150.65, 154.85 (q, JCF = 36.3 Hz); HRMS calcd for C20H18Cl3N2O2 (M+) 764.1814, found 764.1823. Anal. Calcd for C20H18Cl3N2O2: C, 47.07; H, 4.74.

General Method for Synthesizing Compounds 11 and 12 from 1 and 6 by Heating the TFA Groups (Scheme 1). The corresponding trifluoroacetamidobenzyl containing crown ether (3 mmol) was added to 20 mL of 2.0 M NaOH 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 ΔS were determined as described24 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 × 10−2 M and those of the metal ions were 0.1 M (Na+ and Ag+) and 7.1 × 10−4 M (K+). In the case of Cu2+, concentrations of the ligands were 1.2 × 10−3 M and that of Cu2+ was 4.0 × 10−2 M. For the interactions of Na+ and Ag+ with the Cu2+ ligand complexes, the Na+ or Ag+ solution was titrated into the Cu2+ 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 Cu4+ ligand (1:1) complex were 3.0 × 10−3 M. For the titrations involving Ag+, Cu(NO3)2, instead of CuCl2, was used. The method used to process the calorimetric data and to calculate the log K and ΔH/ΔS values has been described.30 Reagent grade inorganic chemicals were obtained from commercial sources and used without further purification.

Acknowledgment. This work was supported by the Office of Naval Research.

J. Org. Chem., Vol. 64, No. 11, 1999 3829