Colorless prisms were deposited and were washed with Et_2O and dried in vacuo: mp (hexane–CH_2Cl_2) 108–109 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.73 (1 H, m), 2.97 (2 H, m), 2.07–1.15 (26 H, m), 1.15 (3 H, d, J = 6.1), 1.08 (3 H, s), 0.86 (3 H, t, J = 7.4). Anal. Calcd for $C_{21}H_{41}NO_3$: C, 70.94; H, 11.62; N, 3.94. Found: C, 71.12; H, 11.55; N, 4.03.

Compound **26** crystallized in space group $P1$ with a = 9.698 (2) Å, b = 11.001 (2) Å, c = 11.074 (4) Å, α = 71.61 (2) °, β = 104.21 (2)°, γ = 95.43 (2)°, V = 1086 Å^3, Z = 2, d_{calc} = 1.09 g/cm^3, and d_{obsd} = 1.08 g/cm^3. All nonequivalent reflections in the range 3° < 2θ < 42° were measured by the 0–2θ technique on a Syntex P1 diffractometer with graphite-monochromated Mo Kα radiation. A total of 1680 independent reflections having $F^2 > 3\sigma(F^2)$ afforded R = 10.2% and R_w = 12.8%.

Determination of the Configuration of Lactones 9, 10, and 11. Comparison of the lactones from degradation with synthetic lactones **9**, **20**, and **22** was carried out as follows. A solution of the pair of naturally derived and synthetic lactones (1–2 mg) in 0.5 mL of $CDCl_3$ was treated with successive quantities of Eu(hfc)$_3$, and the 400-MHz ^1H NMR spectra were recorded. This procedure was then repeated using the enantiomerically pure synthetic lactone. Increasing induced shifts of the methyl signals were observed for stereochemically unmatched lactones in each case. The configuration of **9** was thus determined as *S*. Lactones **10** and **11** were likewise shown to be homochiral with (2*R*,5*S*)-**22** and (2*R*,5*S*)-**24**, respectively.

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Synthesis and Complexation Properties of Suitcase-Shaped Macrotricyclic and Butterfly-Shaped Macrobicyclic Polyether Ligands

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Ten suitcase-shaped macrotricyclic polyethers (**1–10**) containing nitrogen and carbon bridgehead atoms have been synthesized. These new cage compounds were prepared by connecting together two hydroxymethyl-substituted or two secondary amine-containing butterfly-shaped macrobicyclic polyethers by means of linear bifunctional connecting groups. Intermediate bis(hydroxymethyl)-substituted butterfly-shaped macrobicyclic polyether **14** was prepared by treating *N*,*N*′-bis(2-hydroxyethyl)ethylenediamine with 5-methylene-3,7-dioxanonane-1,9-diyl ditosylate to give bislariat 1,4-diaza-13-crown-4 (**11**) which was cyclized with 3-chloro-2-(chloromethyl)-1-propene followed by hydroboration. Intermediate bissecondary amine-containing butterfly-shaped macrobicyclic polyethers **18** and **19** were prepared by treating *N*,*N*′-bis(2-hydroxyethyl)ethylenediamine with 6-tosyl-3,9-dioxa-6-aza-1,11-undecanediyl ditosylate (**33**) to give *N*-tosyl-*N*′,*N*″-bis(2-hydroxyethyl)triaza-15-crown-5 (**12**). Lariat crown ether **12** was cyclized with **33** followed by reduction with $LiAlH_4$ to give **18**, or with 4-tosyl-4-aza-1,7-heptanediyl ditosylate (**36**) to give **19**. Some of the suitcase-shaped macrotricycles interacted with various cations. One was selective for Pb^{2+} ions and another interacted strongly with Hg^{2+}. A crystal structure for the **13**–$NaClO_4$ complex also is reported.

Introduction

The successful design, synthesis, and use of macropolycyclic compounds capable of the selective recognition of metal cations and other species are of great interest to workers in catalysis, separations, extraction, enzyme functions, and other areas of chemistry. A variety of macrocyclic,[1] macrobicyclic,[2–4] macrotricyclic,[5–13] macrotetracyclic,[13,14] and macropentacyclic[15,16] polyethers have been synthesized in a search for preorganized synthetic host molecules. Basket-shaped macrotricyclic host mole-

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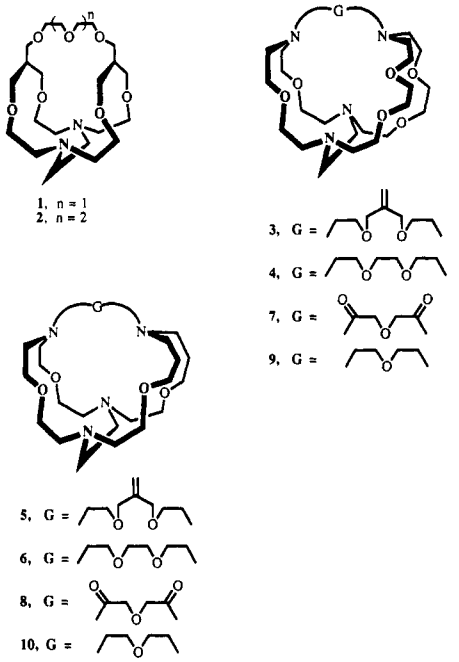


Figure 1. Suitcase-shaped macrotricyclic polyethers.

cules[17] and picnic basket-shaped porphyrin host molecules[18] also have been synthesized. Macrobicyclic polyethers generally form stable complexes with certain metal cations by means of the cooperative effect of the polyether units.[2-4] Some macrotricyclic polyethers form stable complexes with certain metal cations,[6,7] while some others form inclusion complexes with bis(primary alkyl)ammonium salts.[10] Macrotetracyclic and macropentacyclic polyethers generally do not form stable complexes with single metal cations because of their large cavities and lack of effective cooperation among the polyether units. The synthesis and properties of the macropolycyclic polyethers have been reviewed.[19]

Although many examples of macropolycyclic synthetic ligands capable of complexing metal cations are known, there is an active search for new preorganized receptors having even greater complex stabilities or higher selectivities for certain cations and neutral molecules. The reported examples of macrotricyclic polyethers have spherical, cylindrical, basket, and folder shapes.[19] It seems that nitrogen atoms are essential for the more complicated molecules to coordinate with transition and alkali metal ions even though the nitrogen atoms do not interact strongly with alkali metal cations. Nitrogen atoms are frequently used to build preorganized macropolycycles. Cryptands, with nitrogen atoms at the bridgeheads, have 10^5–10^6 times greater association constants for certain cations than those with carbon atoms at bridgehead positions.[20]

In the present paper, we describe the synthesis of 10 suitcase-shaped macrotricyclic polyethers (1–10, see Figure 1) with nitrogen bridgeheads and reasonable cavities for certain metal cations. These macrocycles provide cooperation of the connected polyether units for complexation,

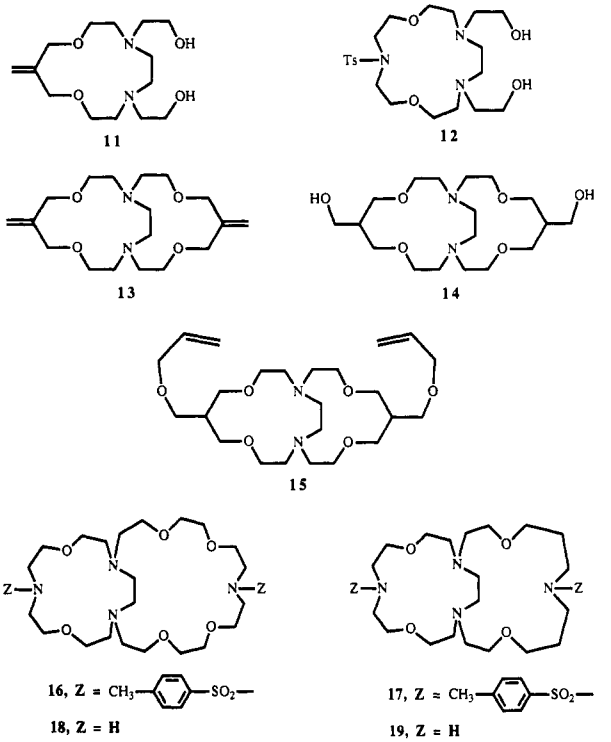
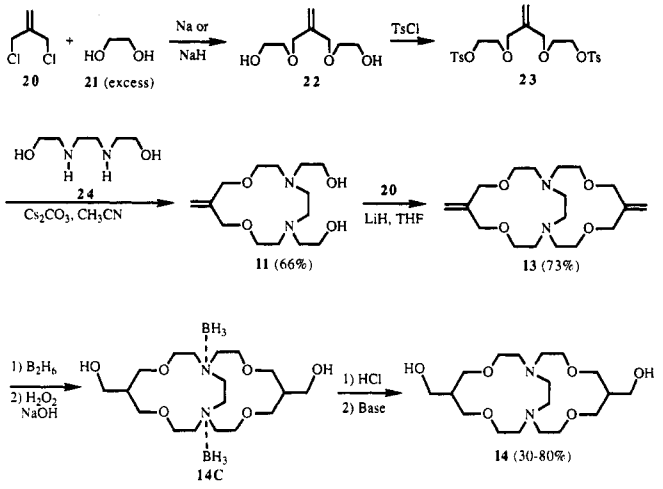


Figure 2. Intermediate lariat crown ethers and butterfly-shaped macrobicyclic ligands.

Scheme I. Synthesis of Lariat Crown Ether 11 and Macrobicyclic Polyethers 13 and 14



thus allowing the formation of mononuclear inclusion complexes. The preparation of new intermediate dipivot lariat crown ethers **11** and **12** (Figure 2) and butterfly-shaped macrobicyclic polyethers **13–19** is also described. The metal ion complexing properties of some of these suitcase-shaped molecules also are reported in this work. In addition, the crystal structure of the complex of macrobicycle **13** with $NaClO_4$ is reported.

Results and Discussion

We previously synthesized a series of butterfly-shaped macrobicyclic polyethers containing nitrogen bridgeheads.[2] Complexation properties of one of those macrobicyclic polyethers with potassium and sodium cations were also studied.[21] The X-ray crystal structure of the complex of one of those macrobicyclic polyethers, namely 4,7,10,13,19,22,25-heptaoxa-1,16-diazabicyclo[14.11.2]nonacosane, with potassium iodide showed that the bicyclic ligand coordinated with the potassium cation with all nine

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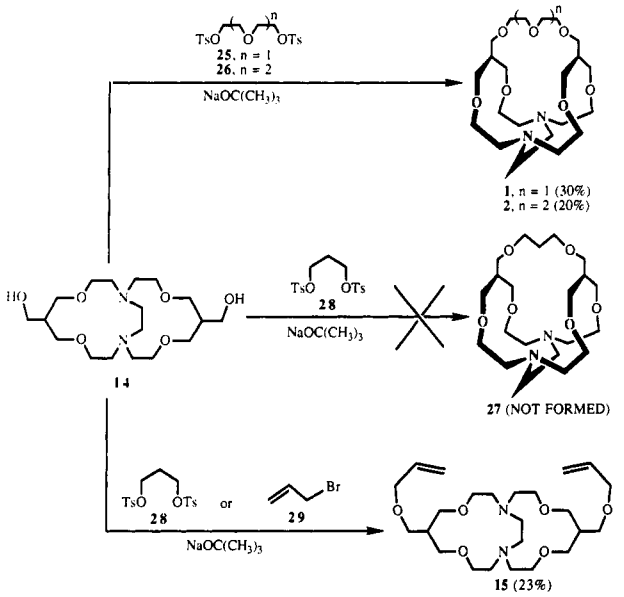
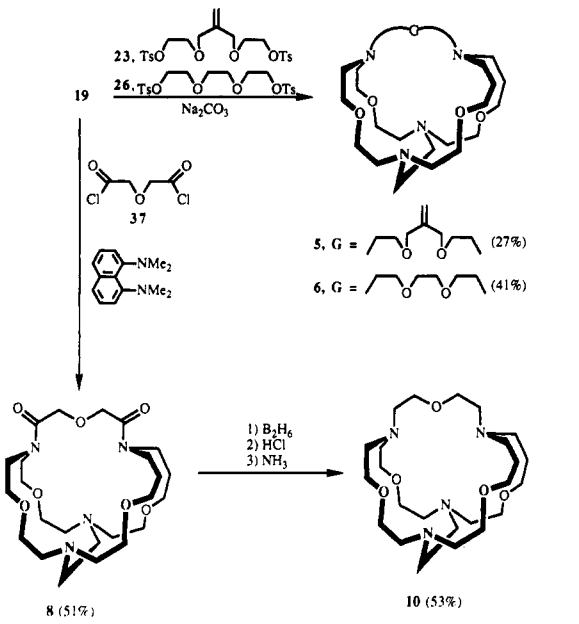
Scheme II. Synthesis of Suitcase-Shaped Macrotricyclic Polyethers 1 and 2 and the Formation of Unexpected Dipivot Macrobicyclic Polyether 15



Scheme III. Synthesis of Protected Lariat Crown 12 and Macrobicyclic Polyethers 16–19



donor atoms through nearly the same distances.[21] The selectivity of macropolycyclic ligands for certain metal cations is primarily based on the preorganization and size of the cavity. In order to prepare other preorganized macropolycyclic ligands with improved complexation properties, the two subunits of several butterfly-shaped macrobicyclic polyethers were connected together by different linear bifunctional compounds to form suitcase-shaped macrotricyclic polyethers 1–10.

First, the butterfly-shaped macrobicycles 13 and 14 were prepared (see Scheme I). 3-Chloro-2-(chloromethyl)-1-propene (20) was treated with an excess of ethylene glycol (21) using sodium metal[22] or sodium hydride as the base to give intermediate glycol 22. Ditosylate 23 was prepared by a method similar to that reported.[23] Under weak carbonate base conditions, the secondary amine groups of *N,N'*-bis(2-hydroxyethyl)ethylenediamine (24) reacted as nucleophiles with ditosylate 23 to form *N,N'*-dipivot lariat 1,4-diaza-13-crown-4 (11) in a yield of 66%. Cesium carbonate was used as the base in this reaction because the crown ether forms an extremely stable complex with the sodium cations of sodium carbonate making isolation of the product more difficult.[2] Under lithium hydride base conditions, 11 reacted with 20 to close the second ring, giving butterfly-shaped macrobicyclic polyether 13 in a yield of 73%. Ligand 13 was obtained by using sodium hydride as the base, but at a lower yield. Hydroboration–oxidation of the two methylene groups of 13 gave the bisborane complex 14C which was not purified and characterized. Strong complexation of the tertiary amines by BH_3 probably protects these functions from oxidation by hydrogen peroxide. The borane complex was decomposed under heating in hydrochloric acid to give bis(hydroxymethyl)-substituted macrobicyclic polyether 14 in a yield of 30–80% (Scheme I). Hydroboration–oxidation of methylene-substituted crown ethers which do not contain nitrogen atoms previously has been reported.[22,24] Macrobicyclic polyether 14 was obtained in only a 10% yield using the reported procedure for converting methylene-substituted aza-crowns to the hydroxymethyl derivatives.[25] We improved the reported procedure by changing the dropping sequence of starting materials, changing the ratio of diborane to substrate, changing the reaction temperature and time, and increasing the pH. A small amount of the tertiary alcohol isomer of 14 (hydroxy attached to the ring carbon atom) was also observed in this synthesis.

Suitcase-shaped macrotricyclic ligands 1 and 2 were obtained by cyclization of 14 with glycol ditosylates 25 and 26, respectively, using sodium *tert*-butoxide as the base (Scheme II). An attempt to synthesize macrotricyclic polyether 27, containing a propylene bridge, by cyclization of 14 with ditosylate 28 was unsuccessful. Dipivot lariat macrobicyclic polyether 15 was obtained in the latter reaction. It is likely that the length of the carbon chain in ditosylate 28 is not long enough to connect the two hydroxyl groups of 14. Presumably, under strong base, one tosyl group of ditosylate 28 was eliminated to form allyl tosylate which then reacted with 14 to give 15. Elimination of a tosylate from ethylene glycol ditosylate in these types of reactions previously has been reported.[26] Ethylene glycol ditosylate and ditosylate 28 can be used to prepare aza-crown ethers only by connecting nitrogen atoms together under carbonate base conditions.[7,26–28] In order to confirm this elimination, macrobicyclic ligand 15 was prepared by the reaction of 14 with allyl bromide (29) (Scheme II).

Butterfly-shaped macrobicyclic polyethers 18 and 19, precursors to suitcase-shaped macrotricycles 3–10, were prepared by another synthetic route (Scheme III). 6-Tosyl-3,9-dioxa-6-aza-1,11-undecanediol (32)[7,29] was tosy-

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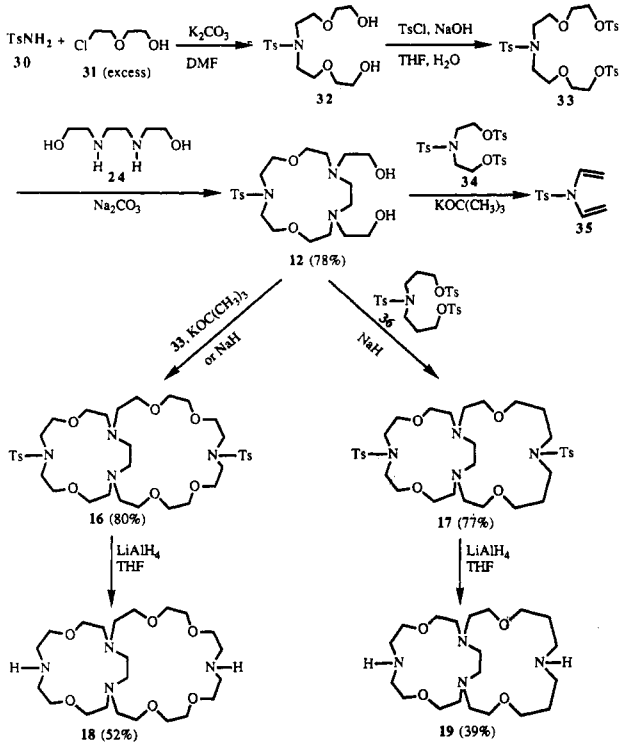
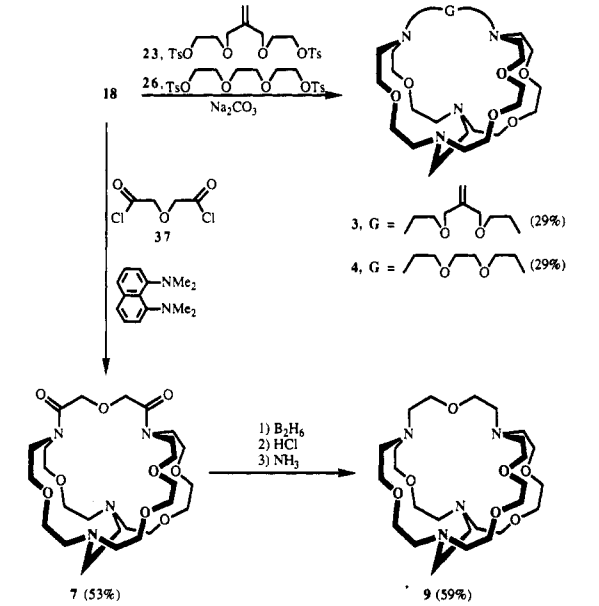
Scheme IV. Synthesis of Suitcase-Shaped Macrotricyclic Polyethers 3, 4, 7, and 9



Scheme V. Synthesis of Suitcase-Shaped Macrotricyclic Polyethers 5, 6, 8, and 10



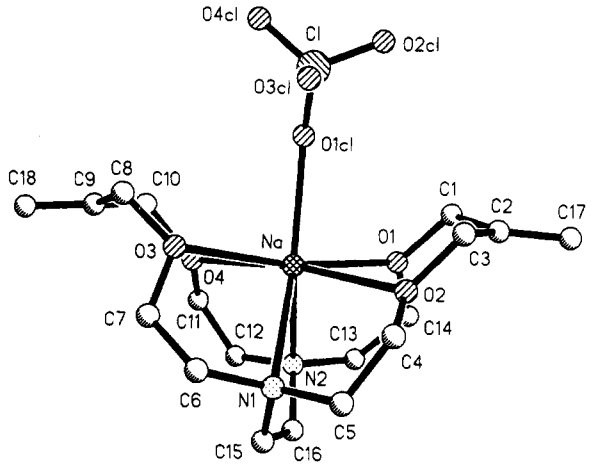


Figure 3. Computer drawing of the X-ray results of the **13**–$NaClO_4$ complex calculated from average atomic coordinates with hydrogens omitted for clarity.

lated by treatment with tosyl chloride in the presence of sodium hydroxide to form tritosylate **33**. As in the preparation of dipivot lariat crown **11**, dipivot lariat **12** was synthesized in a yield of 78% from tritosylate **33** and diamino diol **24** under carbonate base conditions. When lariat crown **12** was treated with the ditosylate of 3-tosyl-3-aza-1,5-pentanediol (**34**),[28] elimination product **35** was obtained rather than the expected macrobicyclic polyether. This elimination product also was observed by others under similar conditions.[1d] Under strong basic conditions, protected dipivot lariat crown **12** was reacted with tritosylate **33**, giving diprotected macrobicyclic polyether **16** in a yield of 80%. Similarly, protected macrobicyclic polyether **17** was obtained in a yield of 77% by the reaction of **12** with tritosylate **36**. Deprotection of macrobicyclic polyethers **16** and **17** was accomplished by reduction with $LiAlH_4$ in THF[30] to give key intermediate tetraza macrobicyclic polyethers **18** and **19**, respectively.

Suitcase-shaped macrotricyclic polyethers **3**–**10** were prepared from **18** and **19** (Schemes IV and V). Cyclization of **18** with ditosylates **23** and **26** under carbonate base conditions gave **3** and **4**, respectively (Scheme IV). Similarly, macrotricyclic polyethers **5** and **6** were synthesized from intermediate **19** (Scheme V). Acylation of **18** with diglycolyl dichloride[31] in the presence of a proton sponge, 1,8-bis(dimethylamino)naphthalene, gave macrotricyclic diamide **7** in a yield of 53%. Suitcase-shaped macrotricyclic polyether **9** was obtained by the diborane reduction of diamide **7** followed by hydrolysis of the borane complex. Macrotricycles **8** and **10** were similarly obtained from macrobicycle **19** (Scheme V). The structures of suitcase-shaped macrotricycles **1**–**10**, butterfly-shaped ligands **13**–**19**, and lariat intermediates **11** and **12** were consistent with spectral and elemental analyses.

A variety of *N*-pivot lariat polyethers with side arms on opposite sides of the macroring have been reported.[32] However, *N,N'*-1,4-dipivot lariat polyethers were just recently synthesized in our laboratory by a new method.[2,33] *N,N'*-Dipivot lariat-crowns **11** and **12** are expected to have high selectivity for sodium and potassium cations, respectively, because each of the two hydroxyethyl side chains can interact with the crown ether cavity from opposite sides. Butterfly-shaped macrobicyclic polyethers **13**–**19** could have specific complexing properties for certain metal cations. Indeed, butterfly-shaped macrobicyclic ligands, similar to **17** but with oxygen atoms substituted for the *N*-tosyl groups at the center of each polyether chain, exhibited excellent recognition for potassium over

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Table I. log β Values for the Interaction of Five Macrotricycles with Protons and Several Metal Cations[a]

ions	3	4	6	9	10
$H^+(1)$	8.25 (7)	5.67 (6)	8.47 (7)	8.85 (6)	9.06 (8)
$H^+(2)$	12.87 (8)	9.68 (7)	12.83 (8)	14.37 (9)	13.75 (1)
$H^+(3)$	17.0 (2)			18.40 (1)	
Cs^+		1.40 (2)		NR	0.50 (3)
Sr^{2+}	NR	NR	0.80 (1)	2.50 (8)	2.40 (6)
Ba^{2+}	NR	1.50 (1)	1.80 (9)	4.50 (5)	3.40 (5)
Nd^{3+}	2.80 (4)	3.12 (6)	2.96 (5)	3.30 (5)	3.77 (6)
Eu^{3+}				3.60 (6)	
Er^{3+}				3.70 (6)	
Pb^{2+}				12.90 (7)	
Hg^{2+}					10.10 (9)
Cd^{2+}				6.57 (8)	
Cu^{2+}				6.32 (8)	

[a] Interactions were carried out in aqueous solution at 25 °C with an ionic strength of 0.1 M Me_4NNO_3. The uncertainties of the log β values are given in parentheses.

sodium ions.[21] Some of them also can be used as key intermediates to synthesize more highly preorganized macropolycyclic ligands. Polyether **13** formed a stable complex with sodium ion as described below. The oxygen atoms on the side arms of ligands **14** and **15** may also coordinate to the metal cation together with the crown ring. Some hydroxy-substituted crown ethers have specific complexing properties.[22] Methylene and allyl groups in polyethers **13** and **15** also can be used to attach the parent crown ether onto silica gel.[26,34]

The X-ray crystal structure of the **13**-$NaClO_4$ complex along with atom labels is shown in Figure 3. Several atoms of the macroring are disordered. It was not possible to resolve all of the disorder and so the average structure is reported. It is clear from the figure that the Na^+ is coordinated to seven donor atoms, four ether oxygens, and two nitrogens of the macrocyclic ligand and an oxygen from the ClO_4^-. The Na–O interatomic distances range from 2.389 (7) Å, the perchlorate oxygen, to 2.484 (9) Å, O4 of the ligand, and the two Na–N interatomic distances are 2.543 (9) Å and 2.532 (7) Å. The average Na–O interatomic distance is 2.447 (40) Å. The bond lengths and angles involving sodium and the heteroatoms are included in the supplementary material. The coordination scheme can be described as a distorted octahedral with the four oxygens of the ligand forming a nearly planar pseudorectangle, the ClO_4^- oxygen being at one apex and the two nitrogen atoms of the ligand being at the other apex (see Figure 3). The four ligand oxygens deviate from their least-square plane by –0.187 Å, O1; 0.175 Å, O2; –0.178 Å, O3; and 0.179 Å, O4. The Na^+ is 0.018 Å above the plane. The line joining N1 to N2 makes an angle of 88.9° with the normal to the least-square plane. The result is a cup-shaped molecule with the Na^+ lying in the plane of the heteroatoms at the top of the cup. Experimental details, positional and thermal parameters, and bond lengths and angles are included in the supplementary material. The disorder of the ligand mentioned earlier is apparent from an examination of the thermal parameters and the bond lengths.

log β values for the interaction of five ligands with protons, metal ions, and anions are listed in Table I. It was found that each of the five ligands was able to bind at least two protons. Binding of a third proton was possible for two of the ligands (**3** and **9**), but binding of the fourth proton was not observed for any of the five ligands. Binding constants for the first and second protonations were determined accurately, while that for the third protonation was hard to determine and the constant was greater uncertainty. It is possible that the first and second protonations occur on the two all-ethereal bridgehead nitrogen atoms which are isolated from each other. Since the other two bridgehead nitrogens are separated by only an ethylene linkage, protonation of each of them should be unlikely due to charge repulsion. The third protonation would occur to either of these close linked bridgehead nitrogen atoms, but the four protonation would be less likely because of the close proximity of the positive charges.

Ligands **3**, **4**, **6**, **9**, and **10** exhibited a variety of interactions with the metal cations studied (Table I). Ligands **9** and **10** have appreciable interactions with Sr^{2+} and Ba^{2+} with both favoring Ba^{2+}. Ligand **4**, with a large cavity, exhibited a stronger interaction with Cs^+ than did ligands **9** and **10**. The "size-match" rule seems to hold true in this case. The rest of the metal cations studied are significantly smaller in size as compared to the cavities of the ligands. Because of the high positive charge of the Nd^{3+}, Eu^{3+}, and Er^{3+} ions, the ligands have appreciable interactions with these cations through enhanced charge–dipole attractions. Ligand **9** forms very strong complexes with Pb^{2+}, Cd^{2+}, and Cu^{2+} while **10** complexes strongly with Hg^{2+}. These complexation properties are mainly due to the high affinities of these cations for nitrogen donor atoms.

Experimental Section

Proton and carbon NMR spectra were obtained at 200 MHz in $CDCl_3$. Molecular weights were determined by electron-impact HRMS. Starting materials were used as purchased from Aldrich Chemical Co. Ditosylates **25**,[23] **26**,[23] and **28**;[23] tritosylates **34**[28] and **36**;[28] and diol **32**[7,29a] were prepared as reported. Diglycolyl dichloride **37** was prepared from diglycolic acid.[31] Other starting materials were prepared as reported below. The nitrate salts of Cs^+ and $(CH_3)_4N^+$ (Alfa); Cd^{2+} and Ba^{2+} (Baker); and Sn^{2+}, Cu^{2+}, Pb^{2+}, and Hg^{2+} (Fisher) and $(CH_3)_4NOH{\cdot}5H_2O$ (Aldrich) were used as purchased for complexation studies. Deionized distilled water was used for the preparation of all solutions.

Preparation of 5-Methylene-3,7-dioxanonane-1,9-diol (22) (Scheme I). NaH (10 g, 0.42 mol) was added in portions to stirred glycol **21** (400 mL) under N_2. The mixture was stirred and heated to 60 °C. 3-Chloro-2-(chloromethyl)-1-propene (**20**) (26 g, 0.2 mol) was added at 40–50 °C, and the mixture was stirred at 80–90 °C for 15 h. The cooled mixture was neutralized with acetic acid. The product was distilled under reduced pressure to give 19.3 g (54%) of **22** as a colorless liquid: bp 115–118 °C (0.05 mm); ^1H NMR δ 2.87 (t, 2 H, J = 5.7 Hz, disappeared in D_2O), 3.52 (t, 4 H, J = 4.7 Hz), 3.65–3.76 (m, 4 H), 4.10 (s, 4 H), 5.18 (s, 2 H); IR 3390 (b), 1650, 1470, 1100 cm^{-1}; MS m/e 176 (M^+).

Preparation of 5-Methylene-3,7-dioxa-1,9-nonanediyl Ditosylate (23) (Scheme I). NaOH (17 g, 0.43 mol) dissolved in 100 mL of water and 19 g (0.11 mol) of diol **22** in 100 mL of THF were mixed together. Tosyl chloride (46 g, 0.24 mol) in 140 mL of THF was added dropwise to the stirred mixture at 0 °C over a period of 2 h. The mixture was stirred at 0 °C for 2 h and poured into 10% HCl at 0 °C. The mixture was extracted with benzene, and the extract was washed with water, dilute aqueous $NaHCO_3$, and then water. The benzene extract was dried ($MgSO_4$) and evaporated to give a white solid which was recrystallized from ethyl alcohol to give 46 g (86%) of **23**: mp 90–91 °C; ^1H NMR δ 2.42 (s, 6 H), 3.57 (t, 4 H, J = 4.9 Hz), 3.87 (s, 4 H), 4.13 (t, 4 H, J = 4.9 Hz), 5.08 (s, 2 H), 7.31 (d, 4 H, J = 7.8 Hz), 7.77 (d, 4 H, J = 7.8 Hz); MS m/e 484 (M^+).

Preparation of 6-Tosyl-3,9-dioxa-6-aza-1,11-undecanediyl Ditosylate (33) (Scheme III). A solution of NaOH (40 g, 1.00 mol) in 150 mL of water and a solution of **32** (43 g, 0.123 mol) in 150 mL of THF were mixed together at rt. A solution of tosyl chloride (142 g, 0.747 mol) in 250 mL of THF was added dropwise to the stirred mixture at 0 °C over a period of 2 h. The mixture was stirred for 4 h at 0 °C and poured into a mixture of 350 mL of ice water and 180 mL of 37% HCl at 0 °C. The mixture was extracted with benzene, and the extract was washed with water,

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dilute aqueous $NaHCO_3$, and then water. The benzene extract was dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel using CH_2Cl_2 as eluent. Evaporation of the solvent gave 70.3 g (87%) of **33** as a pale yellow oil: ^1H NMR δ 2.41 (s, 3 H), 2.43 (s, 6 H), 3.31 (t, 4 H, J = 5.2 Hz), 3.48–3.62 (m, 16 H), 3.95 (t, 4 H, J = 5.2 Hz), 7.23–7.36 (m, 6 H), 7.68 (d, 2 H, J = 7.8 Hz), 7.79 (d, 4 H, J = 7.8 Hz); IR 1734, 1597, 1451, 1095 cm^{-1}; MS m/e 655 (M^+). **33** also was prepared by other methods.[29a,b]

Preparation of 4-Tosyl-4-aza-1,7-heptanediyl Ditosylate (36) (Scheme III). Tritosylate **36** was prepared as above for **33** from NaOH (40 g, 1.00 mol), 4-tosyl-4-aza-1,7-heptanediol (37.4 g, 0.13 mol), and tosyl chloride (140 g, 0.74 mol) in the appropriate amounts of water and THF. Purification by chromatography on silica gel using CH_2Cl_2 as eluent and recrystallization from ethanol gave 36.2 g (47%) of **36** as white crystals: mp 78–79 °C (lit.[35] mp 79–80 °C); ^1H NMR δ 1.89 (m, 4 H), 2.43 (s, 3 H), 2.46 (s, 6 H), 3.08 (t, 4 H, J = 6.2 Hz), 4.02 (t, 4 H, J = 5.7 Hz), 7.25–7.39 (m, 6 H), 7.60 (d, 2 H, J = 7.8 Hz), 7.78 (d, 4 H, J = 7.8 Hz); IR 1600, 1350, 1150 cm^{-1}; MS (CI) m/e 595 (M^+). 1,3-Propanediyl ditosylate (20 g) also was isolated as a byproduct.

3-Methylene-8,11-bis(2-hydroxyethyl)-1,5-dioxa-8,11-diazacyclotridecane (11) (Scheme I). A mixture of 5.2 g (0.035 mol) of *N,N'*-bis(2-hydroxyethyl)ethylenediamine (**24**), 17.0 g (0.035 mol) of **23**, 500 mL of CH_3CN, and 20 mg of anhyd Cs_2CO_3 was stirred under reflux for 3 days. The cooled mixture was filtered, and the solid was washed with $CHCl_3$. The filtrate was evaporated, and 100 mL of $CHCl_3$ was added to the residue to dissolve the product. After mixing, the suspended solid was filtered and washed two times with $CHCl_3$. The combined organic solution was evaporated to give a pale yellow oil. The oil was purified by chromatography on neutral alumina using toluene/ethanol, 70/1, 20/1, and 10/1, as eluents. Evaporation of the solvent gave 6.7 g (66%) of 11 as a colorless oil: ^1H NMR δ 2.48–2.66 (m, 12 H), 3.50 (m, 8 H), 4.03 (s, 4 H), 4.55–4.92 (b, 2 H, disappeared in D_2O), 5.09 (s, 2 H); IR 3324, 1445, 1359, 1099 cm^{-1}; MS m/e 271 ($M^+ - 17$). Anal. Calcd for $C_{14}H_{28}N_2O_4$: C, 58.31; H, 9.78. Found: C, 58.12; H, 9.99.

4-Tosyl-10,13-bis(2-hydroxyethyl)-1,7-dioxa-4,10,13-triazacyclopentadecane (12) (Scheme III). Lariat ligand **12** was synthesized as above for 11 from 13.6 g (0.02 mol) of **33**, 2.96 g (0.02 mol) of **24**, 50 g of anhyd Na_2CO_3, and 750 mL of CH_3CN. Purification by chromatography on neutral alumina using toluene/ethanol, 60/1, 20/1, and 10/1, as eluents gave 7.08 g (78%) of **12** as a colorless oil which solidified on standing: ^1H NMR δ 2.42 (s, 3 H), 2.53 (t, 4 H, J = 5.2 Hz), 2.65 (s, 8 H), 3.37 (t, 4 H, J = 5.2 Hz), 3.48–3.59 (m, 8 H), 3.70 (t, 4 H, J = 5.2 Hz), 4.76 (b, 2 H, disappeared in D_2O), 7.30 (d, 2 H, J = 7.8 Hz), 7.68 (d, 2 H, J = 7.8 Hz); IR 3416, 1598, 1453, 1089 cm^{-1}; MS m/e 458 ($M^+ - 1$), 442 ($M^+ - 17$), 359 ($M^+ - 100$, base peak). Anal. Calcd for $C_{21}H_{37}N_3SO_6$: C, 54.88; H, 8.11. Found: C, 54.80; H, 7.91.

6,16-Dimethylene-4,8,14,18-tetraoxa-1,11-diazabicyclo[9.9.2]docosane (13) (Scheme I). A solution of 6.69 g (0.023 mol) of 11 in 200 mL of THF was added to a stirred mixture of 2 g of LiH in 100 mL of THF. The resulting mixture was stirred for 2 h under reflux and N_2. A solution of **20** (3 g, 0.023 mol) in 200 mL of THF was slowly dropped into the stirred mixture at 60 °C, and the reaction mixture was stirred under reflux for 12 h. The cooled mixture was filtered, and the solid was washed with THF. The filtrate was evaporated. The residue was purified by chromatography on silica gel using CH_3OH/30% aqueous NH_4OH, 30/1, 10/1, and 8/1, as eluents or on neutral alumina using toluene/ethanol, 80/1, as the eluent. Evaporation of the solvent gave 5.77 g (73%) of 13 a a pale yellow oil: ^1H NMR δ 2.60 (t, 8 H, J = 4.7 Hz), 2.68 (s, 4 H), 3.56 (t, 8 H, J = 4.7 Hz), 4.13 (s, 8 H), 5.07 (s, 4 H); IR 3045, 1650, 1450, 1348, 1106 cm^{-1}; MS m/e 340 (M^+). Anal. Calcd for $C_{18}H_{32}N_2O_4$: C, 63.50; H, 9.47. Found: C, 63.77; H, 9.25.

6,16-Bis(hydroxymethyl)-4,8,14,18-tetraoxa-1,11-diazabicyclo[9.9.2]docosane (14) (Scheme I). A solution of 2 g (5.8 mmol) of **13** in 100 mL of THF was added dropwise to a stirred mixture of 120 mL of 1 M BH_3–THF solution and 40 mL of THF under N_2 at 0 °C. The mixture was stirred for 2 h at 0 °C and then for 3 h at rt while a white solid formed. H_2O (8 mL) was added very carefully to decompose the excess BH_3. Aqueous NaOH (90 mL, 3 M) was added, followed by 10 mL of 30% H_2O_2. The resulting mixture was stirred at 60–70 °C for 2 h. The cooled mixture was saturated with NaCl. The THF layer was separated. The aqueous layer was extracted with THF and then CH_2Cl_2. The combined organic solution was evaporated, and 60 mL of THF and 2 mL of H_2O were added to dissolve the residue. Concentrated HCl (80 mL) was added over 30 min at 0 °C, and the mixture was stirred for an additional 30 min. The mixture was then heated to 60 °C. Saturated NaOH was added slowly at 0 °C to neutralize the mixture to a pH of 13 or 14. The THF layer was separated; the H_2O layer was extracted with the THF and CH_2Cl_2. The combined organic solution was dried ($MgSO_4$) and evaporated to give a pale yellow oil. The oil was chromatographed on neutral alumina using CH_3CN/C_2H_5OH, 15/1, 8/1, and 3/1, as eluents to give 1.75 g (80%) of 14 as a pale yellow oil: ^1H NMR δ 1.85–2.02 (m, 2 H), 2.40–2.50 (s, 2 H, disappeared in D_2O), 2.53–2.78 (m, 12 H), 3.46–3.78 (m, 20 H); IR 3380, 1355, 1100 cm^{-1}; MS m/e 376 (M^+). Anal. Calcd for $C_{18}H_{36}N_2O_6$: C, 57.42; H, 9.63. Found: C, 57.65; H, 9.52.

10,25-Ditosyl-4,7,13,16,22,28-hexaoxa-1,10,19,25-tetraazabicyclo[17.11.2]dotriacontane (16) (Scheme III). A mixture of **12** (3 g, 6.5 mmol), 300 mL of THF and 2.4 g of KO-*t*-C_4H_9 (or 1.2 g of NaH) was stirred for 3 h under reflux. A solution of 4.26 g (6.5 mmol) of **33** in 200 mL of THF was added, and the resulting mixture was stirred under reflux for 3 days (or 2 days when NaH was used as the base). The cooled mixture was filtered, and the solid was washed with THF. After evaporation of the filtrate, the residue was purified by chromatography on neutral alumina using toluene/ethanol, 100/1 and 80/1, as eluents. Evaporation of the solvent gave 4.2 g (80%) of **16** as a pale yellow oil: ^1H NMR δ 2.49 (s, 6 H), 2.62–2.73 (m, 12 H), 3.28–3.40 (m, 8 H), 3.43–3.67 (m, 24 H), 7.26 (d, 4 H, J = 7.8 Hz), 7.60–7.71 (m, 4 H); IR 1590, 1460, 1340, 1110 cm^{-1}; MS m/e 770 (M^+). Anal. Calcd for $C_{36}H_{58}N_4S_2O_{10}$: C, 56.08; H, 7.58. Found: C, 55.91; H, 7.35.

8,21-Ditosyl-4,12,18,24-tetraoxa-1,8,15,21-tetraazabicyclo[13.11.2]octacosane (17) (Scheme III). Diprotected macrobicycle **17** was synthesized as above for **16** from 4.14 g (9 mmol) of **12**, 1.6 g of NaH, 5.36 g (9 mmol) of **36**, and 550 mL of THF and refluxing for 48 h. Purification by chromatography on neutral alumina using toluene/ethanol, 100/1, as eluent gave 4.9 g (77%) of **17** as a pale yellow oil: ^1H NMR δ 1.72–1.94 (m, 4 H), 2.43 (s, 6 H), 2.63–2.78 (m, 12 H), 3.11–3.24 (m, 4 H), 3.32–3.68 (m, 20 H), 7.30 (d, 4 H, J = 7.8 Hz), 7.63–7.74 (m, 4 H); IR 1590, 1455, 1340, 1110 cm^{-1}; MS m/e 710 (M^+). Anal. Calcd for $C_{34}H_{54}N_4S_2O_8$: C, 57.44; H, 7.65. Found: C, 57.24; H, 7.69.

4,7,13,16,22,28-Hexaoxa-1,10,19,25-tetraazabicyclo[17.11.2]dotriacontane (18) (Scheme III). A solution of **16** (3.7 g, 4.78 mmol) in 50 mL of dry THF was slowly added to a stirred suspension of 3 g of $LiAlH_4$ in 100 mL of dry THF at rt. The resulting mixture was stirred under reflux for 4 days. A mixture of ethyl acetate and water was carefully added with stirring at 0 °C to decompose the excess of $LiAlH_4$. A precipitate was filtered and washed thoroughly with ethyl acetate and $CHCl_3$. The combined filtrates were dried ($MgSO_4$) and evaporated. The colorless residue was chromatographed on silica gel using CH_3OH/30% aqueous NH_4OH, 20/1 and 10/1, as eluents. Evaporation of the solvent gave 1.15 g (52%) of **18** as a colorless oil: ^1H NMR δ 2.66–2.92 (m, 22 H, 20 H in D_2O), 3.47–3.66 (m, 24 H); IR 3331, 1453, 1352, 1108 cm^{-1}; MS m/e 462 (M^+). Anal. Calcd for $C_{22}H_{46}N_4O_6$: C, 57.11; H, 10.02. Found: C, 57.08; H, 9.91.

4,12,18,24-Tetraoxa-1,8,15,21-tetraazabicyclo[13.11.2]octacosane (19) (Scheme III). Macrobicycle **19** was synthesized as above for **18** from 1.3 g (1.8 mmol) of **17**, 1.2 g of $LiAlH_4$ and 70 mL of THF. Purification by chromatography on silica gel using CH_3OH/30% aqueous NH_4OH, 15/1, 10/1, and 5/1, as eluents gave 0.28 g (39%) of **19** as a colorless oil: ^1H NMR δ 1.67–1.83 (m, 4 H), 2.57–2.90 (m, 22 H, 20 H in D_2O), 3.42–3.65 (m, 16 H); IR 3332, 1465, 1352, 1120 cm^{-1}; MS m/e 402 (M^+). Anal. Calcd for $C_{20}H_{42}N_4O_4$: C, 59.67; H, 10.51. Found: C, 59.48; H, 10.35.

4,8,11,14,18,26,29-Heptaoxa-1,21-diazatricyclo[19.4^{1,16}.4^{6,21}.2]hentriacontane (1) (Scheme II). A mixture of **14** (0.22 g, 0.58 mmol), 50 mL of THF, and 0.25 g of NaO-*t*-C_4H_9

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was stirred for 2 h under reflux. A solution of 0.24 g (0.57 mmol) of **25** in 50 mL of THF was added. The resulting mixture was stirred under reflux for 48 h, cooled, and filtered, and the solid was washed with $CHCl_3$. The solvent was evaporated to give a yellow oil. The oil was purified by chromatography on neutral alumina using CH_3CN/C_2H_5OH, 25/1 and 20/1, as eluents to give 0.08 g (30%) of **1** as a pale yellow oil: ^1H NMR δ 1.80–2.10 (m, 2 H), 2.58–2.82 (m, 12 H), 3.40–3.72 (m, 28 H); IR 1450, 1355, 1115 cm^{-1}; MS *m/e* 446 (M^+). Anal. Calcd for $C_{22}H_{42}N_2O_7$: C, 59.17; H, 9.48. Found: C, 59.37; H, 9.27.

4,8,11,14,17,21,29,32-Octaoxa-1,24-diazatricyclo-[22.4^{1,19}.4^{6,24}.2]tetratriacontane (2) (Scheme II). Macrotricyclic polyether **2** was synthesized as above for **1** from 0.3 g (0.79 mmol) of **14**, 0.3 g of NaO-*t*-C_4H_9, and 0.36 g (0.78 mmol) of **26** in 100 mL of THF by stirring the reaction mixture under reflux for 3 days. Purification by chromatography on neutral alumina using CH_3CN/C_2H_5OH, 30/1 and 20/1, as eluents gave 0.08 g (20%) of **2** as a pale yellow oil: ^1H NMR δ 1.88–2.05 (m, 2 H), 2.40–2.80 (m, 12 H), 3.35–3.72 (m, 32 H); IR 1455, 1350, 1100 cm^{-1}; MS *m/e* 490 (M^+). Anal. Calcd for $C_{24}H_{46}N_2O_8$: C, 58.75; H, 9.45. Found: C, 58.65; H, 9.61.

6,16-Bis[(allyloxy)methyl]-4,8,14,18-tetraoxa-1,11-diazabicyclo[9.9.2]docosane (15) (Scheme II). Bis[(allyloxy)methyl] macrobicyclic polyether **15** was unexpectedly obtained using the procedure for **1** above from 0.4 g (1.06 mmol) of **14**, 0.5 g of NaO-*t*-C_4H_9, and 0.4 g (1.04 mmol) of ditosylate **28** in 200 mL of THF. Purification by chromatography on silica gel using methanol/30% aqueous NH_4OH, 25/1, as eluent gave 0.05 g (23%) of **15** as a pale yellow oil: ^1H NMR δ 1.98–2.18 (m, 2 H), 2.52–2.65 (m, 8 H), 2.73 (s, 4 H), 3.35 (d, 4 H, J = 7.8 Hz), 3.42–3.67 (m, 16 H), 3.92 (d, 4 H, J = 5.2 Hz), 5.09–5.29 (m, 4 H), 5.75–5.98 (m, 2 H); IR 3020, 1470, 1350, 1110 cm^{-1}; MS *m/e* 456 (M^+). Anal. Calcd for $C_{24}H_{44}N_2O_6$: C, 63.11; H, 9.71. Found: C, 63.09; H, 9.70. Macrobicyclic polyether **15** obtained from **14** and allyl bromide exhibited the same spectral properties.

15-Methylene-4,7,13,17,23,31,36,39-octaoxa-1,10,20,26-tetraazatricyclo[24.5^{1,20}.8^{10,26}.2]hentetracontane (3) (Scheme IV). A mixture of **18** (0.54 g, 1.15 mmol), 0.56 g (1.15 mmol) of ditosylate **23**, 550 mL of CH_3CN, and 35 g of anhyd Na_2CO_3 was stirred under reflux for 4 days. The cooled reaction mixture was filtered, and the solid was washed with $CHCl_3$. The combined organic solution was evaporated, and a minimum amount of $CHCl_3$ was added to the residue to dissolve the product. After mixing, the suspended solid was filtered and washed with $CHCl_3$. After evaporation of the solvent, the yellow oil residue was purified by chromatography on silica gel using CH_3OH/30% aqueous NH_4OH, 28/1 and 20/1, as eluents. Evaporation of the solvent gave 0.2 g (29%) of **3** as a pale yellow oil: ^1H NMR δ 2.63–2.90 (m, 24 H), 3.46–3.76 (m, 28 H), 3.99 (s, 2 H), 4.04 (s, 2 H), 5.20 (s, 2 H); IR 1460, 1350, 1120 cm^{-1}; MS *m/e* 602.8 (M^+). Anal. Calcd for $C_{30}H_{58}N_4O_8$: C, 59.77; H, 9.69. Found: C, 60.00; H, 9.89.

4,7,13,16,22,30,35,38-Octaoxa-1,10,19,25-tetraazatricyclo-[23.5^{1,19}.8^{10,25}.2]tetracontane (4) (Scheme IV). Macrotricycle **4** was synthesized as above for **3** from 0.2 g (0.42 mmol) of **18**, 0.19 g (0.41 mmol) of ditosylate **26**, 220 mL of CH_3CN, and 15 g of anhyd Na_2CO_3. Purification by chromatography on sillica gel using CH_3OH/30% aqueous NH_4OH, 30/1, as eluent gave 0.07 g (29%) of **4** as a pale yellow oil: ^1H NMR δ 2.54–2.82 (m, 24 H), 3.39–3.69 (m, 32 H); IR 1470, 1350, 1115 cm^{-1}; MS *m/e* 576 (M^+). Anal. Calcd for $C_{28}H_{56}N_4O_8$: C, 58.31; H, 9.78. Found: C, 58.58; H, 9.69.

13-Methylene-4,11,15,21,29,35-hexaoxa-1,8,18,24-tetraazatricyclo[22.5^{1,18}.6^{8,24}.2]heptatriacontane (5) (Scheme V). Macrotricycle **5** was synthesized as above for **3** from 0.2 g (0.50 mmol) of **19**, 0.24 g (0.50 mmol) of ditosylate **23**, 250 mL of CH_3CN, and 15 g of anhyd Na_2CO_3. Purification by chromatography on silica gel using CH_3OH/30% aqueous NH_4OH, 30/1, 25/1, and 20/1, as eluents gave 0.07 g (27%) of **5** as a pale yellow oil: ^1H NMR δ 1.62–1.77 (m, 4 H), 2.50–2.89 (m, 24 H), 3.40–3.74 (m, 20 H), 4.00 (s, 2 H), 4.07 (s, 2 H), 5.21 (s, 2 H); ^{13}C NMR δ 28.08, 51.07, 53.84, 54.21, 54.95, 55.16, 55.80, 56.85, 69.19, 69.38, 70.53, 71.86, 73.16, 112.97, 143.76; MS *m/e* 542 (M^+). Anal. Calcd for $C_{28}H_{54}N_4O_6$: C, 61.96; H, 10.02. Found: 61.75; H, 9.89.

4,11,14,20,28,34-Hexaoxa-1,8,17,23-tetraazatricyclo-[21.5^{1,17}.6^{8,23}.2]hexatriacontane (6) (Scheme V). Macrotricycle **6** was synthesized as above for **3** from 0.25 g (0.62 mmol) of **19**, 0.28 g (0.61 mmol) of ditosylate **26**, 250 mL of CH_3CN, and 15 g of anhyd Na_2CO_3. Purification by chromatography on silica gel using CH_3OH/30% aqueous NH_4OH, 30/1, as eluent gave 0.13 g (41%) of **6** as a pale yellow oil: ^1H NMR δ 1.54–1.78 (m, 4 H), 2.32–2.78 (m, 24 H), 3.34–3.68 (m, 24 H); ^{13}C NMR δ 27.89, 50.98, 54.35, 55.12, 55.42, 55.71, 55.98, 69.24, 69.37, 69.77, 70.07, 70.38, 70.58, 70.82, 70.99; IR 1450, 1350, 1115 cm^{-1}; MS *m/e* 516 (M^+). Anal. Calcd for $C_{26}H_{52}N_4O_6$: C, 60.43; H, 10.14. Found: C, 60.17; H, 10.37.

11,15-Dioxo-4,7,13,19,27,32,35-heptaoxa-1,10,16,22-tetraazatricyclo[20.5^{1,16}.8^{10,22}.2]heptatriacontane (7) (Scheme IV). To 350 mL of stirred dry benzene were added simultaneously by means of syringe pumps at rt over a period of 6–7 h, a mixture of 1.1 g (2.37 mmol) of **18** and 1.6 g of proton sponge, 1,8-bis-(dimethylamino)naphthalene, in 55 mL of benzene, and a solution of 0.49 g (2.34 mmol) of **37** in 55 mL of benzene. The resulting mixture was stirred at rt for an additional 10 h. The solvent was evaporated. The residue was purified by chromatography on silica gel using CH_3OH/30% aqueous NH_4OH, 30/1 and 20/1, as eluents. Evaporation of the solvent gave 0.69 g (53%) of **7** as a pale yellow oil: ^1H NMR δ 2.50–2.97 (m, 20 H), 3.45–3.82 (m, 24 H), 4.04–4.47 (m, 4 H); IR 1650, 1460, 1356, 1117 cm^{-1}; MS *m/e* 560 (M^+); the structure was further confirmed by its reduction product **9**.

9,13-Dioxo-4,11,17,25,31-pentaoxa-1,8,14,20-tetraazatricyclo[18.5^{1,14}.6^{8,20}.2]tritriacontane (8) (Scheme V). Macrotricyclic diamide **8** was synthesized as above for **7** from 420 mL of dry benzene, 1.1 g (2.7 mmol) of **19**, and 1.7 g of the proton sponge, and 0.47 g (2.7 mmol) of **37** each in 52 mL of dry benzene. Purification by chromatography on silica gel using CH_3OH/30% aqueous NH_4OH, 40/1 and 30/1, as eluents gave 0.7 g (51%) of **8** as a pale yellow oil: ^1H NMR δ 1.60–2.05 (m, 4 H), 2.32–2.98 (m, 20 H), 3.34–3.82 (m, 16 H), 3.90–4.40 (m, 4 H); IR 1651, 1454, 1359, 1096 cm^{-1}; MS *m/e* 500 (M^+). The structure was further confirmed by its reduction product **10**.

4,7,13,19,27,32,35-Heptaoxa-1,10,16,22-tetraazatricyclo-[20.5^{1,16}.8^{10,22}.2]heptatriacontane (9) (Scheme IV). A 1 M solution of BH_3–THF (80 mL) was added to a stirred solution of **7** (0.63 g, 1.1 mmol) in 20 mL of THF. The resulting mixture was gradually heated to reflux and stirred under reflux for 24 h. Water (5 mL) was carefully added dropwise to the mixture at 0 °C to decompose the excess borane. The solvent was evaporated, and the residue was mixed with 70 mL of 37% aqueous HCl and 60 mL of water. The resulting mixture was stirred at rt for 18 h and then at 90 °C for 15 min. The mixture was cooled, and most of the water was evaporated. Aqueous NH_4OH (30%) was added to the cooled residue to attain a pH of 12.5. This solution was extracted four times with CH_2Cl_2. NaCl was added to saturate the aqueous layer before the third extraction. The combined CH_2Cl_2 layers were dried ($MgSO_4$) and evaporated. The residue was purified by chromatography on silica gel using CH_3OH/30% aqueous NH_4OH, 25/1 and 10/1, as eluents to give 0.34 g (59%) of **9** as a pale yellow oil: ^1H NMR δ 2.54–2.67 (m, 4 H), 2.69–2.87 (m, 20 H), 3.47–3.74 (m, 28 H); ^{13}C NMR δ 53.19, 54.82, 55.12, 55.46, 55.83, 55.97, 56.94, 69.16, 69.90, 70.14, 70.52, 70.62, 71.12; IR 3450, 1470, 1355, 1120 cm^{-1}; MS *m/e* 532 (M^+ – 18). Anal. Calcd for $C_{26}H_{52}N_4O_7 \cdot H_2O$: C, 56.70; H, 9.87. Found: C, 56.80; H, 9.79.

4,11,17,25,31-Pentaoxa-1,8,14,20-tetraazatricyclo-[18.5^{1,14}.6^{8,20}.2]tritriacontane (10) (Scheme V). Macrotricycle **10** was synthesized as above for **9** from 0.4 g (0.8 mmol) of **8** in 20 mL of THF and 60 mL of 1 M BH_3–THF solution. Purification by chromatography on silica gel using CH_3OH/30% aqueous NH_4OH, 20/1 and 10/1, as eluents gave 0.2 g (53%) of **10** as a pale yellow oil: ^1H NMR δ 1.62–1.77 (m, 4 H), 2.47–2.80 (m, 24 H), 3.42–3.72 (m, 20 H); ^{13}C NMR δ 28.54, 51.58, 54.26, 55.49, 55.60, 56.15, 56.64, 56.77, 69.66, 69.78, 70.68, 71.08; IR 1462, 1359, 1117 cm^{-1}; MS *m/e* 472 (M^+). Anal. Calcd for $C_{24}H_{48}N_4O_5$: C, 60.98; H, 10.23. Found: C, 61.12; H, 10.12.

Formation of Unexpected Elimination Product 35 (Scheme III). **35** was obtained as above for the preparation of **16** from 1 g (2.1 mmol) of **12**, 0.7 g (7.3 mmol) of KO-*t*-C_4H_9, 1.19 g (2.1 mmol) of **34**, and 250 mL of CH_3CN by refluxing for 2 days. Purification by chromatography on neutral alumina using toluene/ethanol, 40/1 and 30/1, as eluents gave 0.13 g (28%) of **35** as a colorless oil: ^1H NMR 2.40 (s, 3 H), 4.72–4.97 (q, 4 H),

6.30–6.46 (q, 2 H), 7.28 (d, 2 H, J = 7.8 Hz); 7.64 (d, 2 H, J = 7.8 Hz): IR 1630, 1590, 1360, 1180, 960 cm^{-1}; MS m/e 223 (M^+).

X-ray Crystallographic Analysis of the 13-$NaClO_4$ Complex. Experimental details are in the supplementary material.

log β Determinations. Binding constants for the interaction of ligands **3**, **4**, **6**, **9**, and **10** with protons and selected metal cations were determined potentiometrically using an Orion-Ross double junction semimicro combination glass electrode. The semimicro potentiometric titrations were carried out in a sealed, thermostated vessel (5 mL, 25.0 ● 0.1 °C) under a CO_2-free N_2 atmosphere. During each titration experiment, the emf values of the glass electrode, which are linearly related to p[H] under constant ionic strength, were recorded as a function of the amount of titrant added.

Standard electrode potential, ϵ^0 (462.0 mV), and the ion products of water, pK'_w (13.76), at 0.1 M ionic strength were determined by titrating a standardized $(CH_3)_4NOH$ solution into a HNO_3 solution.

The proton binding constants for the ligands were computed from data obtained by titrating acidified ligand solutions with the $(CH_3)_4NOH$ solution. Binding constants for the ligands with metal ions were calculated from data obtained from titrating acidified ligand solution in the presence of the guest ions.

The ionic strength of the solutions was maintained at 0.1 M with $(CH_3)_4NNO_3$. The electrode filling solution was a saturated $(CH_3)_4NNO_3$ solution. Program SUPERQUAD[36] was used for all the calculations.

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Supplementary Material Available: Experimental details for the X-ray structural study, tables of X-ray structural data, and ^1H NMR spectra for compounds **7**, **8**, **22**, **23**, and **35** (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Assessment of the Active-Site Requirements of 5-Aminolaevulinic Acid Dehydratase: Evaluation of Substrate and Product Analogues as Competitive Inhibitors

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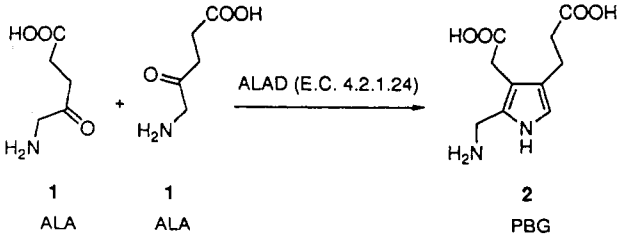
The enzyme 5-aminolaevulinic acid dehydratase (ALAD) is responsible for the synthesis of porphobilinogen (PBG) from two molecules of 5-aminolaevulinic acid (ALA). Porphobilinogen is an important committed intermediate in the biosynthesis of tetrapyrroles. The inhibition of ALAD from the purple bacterium *Rhodopseudomonas sphaeroides* was tested with various substrate and product analogues. Excellent inhibition was observed with the nitro analogue **5** (K_i = 0.018 mM) of laevulinic acid (**10**) (K_i = 1 mM), *rac*-2-hydroxy- (**7**) (K_i = 0.43 mM), *rac*-3-hydroxy- (**8**) (K_i = 1.2 mM), 5-hydroxy- (**11**) (K_i = 0.25 mM), and 5-nitrilolaevulinic acid (**12**) (K_i = 0.060 mM). The sulfonic acid **3** and the phosphonic acid analogue **4** did not inhibit the enzyme. The product analogues **15–18** only showed a moderate inhibition (K_i = 10–15 mM) whereas the pyrazole **19**, a close analogue of porphobilinogen, did not inhibit the enzyme at all (K_i = 32 mM). Comparison of the K_i values for the substrate analogues indicated the ALAD active site to be sensitive to the hybridization and charge at position 1, to be insensitive to polar and neutral substituents at position 5 unless they are negatively charged (**14**) or too bulky (**13**), and to require flexibility of the carbon chain of the substrate, since stiff molecules like β-acetylacrylic acid **6** showed no affinity. The product analogues **15–19** indicated that the active site of ALAD was not inhibited by its direct product PBG.

Introduction

5-Aminolaevulinic acid dehydratase[1,2] (ALAD, porphobilinogen synthetase, EC 4.2.1.24) catalyzes the condensation of two molecules of 5-aminolaevulinic acid (ALA) to produce porphobilinogen (PBG) which is a committed intermediate in the biosynthesis of tetrapyrrolic natural products like porphyrins, chlorophylls, and corrins[3] (Scheme I). 5-Aminolaevulinic acid dehydratase has been purified to homogeneity from a wide variety of sources, including bovine liver,[4] photosynthetic bacteria,[5,6] and human erythrocytes.[7] The dehydratases from all sources studied so far require the presence of an exogenous thiol such as 2-mercaptoethanol or dithioerythritol and of a metal ion (K^+, Mg^{2+}, Zn^{2+})[4,6,8] to maintain the catalytic

Scheme I. Enzymic Formation of Porphobilinogen from Two Molecules of 5-Aminolaevulinic Acid



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