N, 3.84. Found: C, 71.02; H, 5.48; N, 3.88.

**5,11,17,23,29,35-Hexa-*tert*-butyl-37,40-dihydroxy-39,42-(succinyldioxy)-38,41-bis[(4-methylbenzyl)oxy]calix[6]arene (11).** A 0.24-g (0.2 mmol) sample of 1,4-bis(*p*-methylbenzyl) ether **6a** was dissolved in 200 mL of $CH_2Cl_2$, treated with 0.2 mL (1.5 mmol) of triethylamine, and stirred until a clear solution was obtained. A solution of succinoyl chloride (0.3 mmol) in 10 mL of $CH_2Cl_2$ was introduced over a 15-min period from an addition funnel. After 15–20 min the solvent was removed, and the product was purified by chromatography on silica gel collecting the fractions eluted with $CH_2Cl_2$–hexane (80:20) which were recrystallized from $CH_2Cl_2$–MeOH to give 138 mg (55%) of 11: mp 269–270 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 8.10 (s, 2), 7.35 (d, 4, $J$ = 8.0 Hz), 7.33 (bs, 2), 7.30 (bs, 2), 7.22 (d, 4, $J$ = 8.0 Hz), 6.98, 6.93, 6.63 and 6.55 (each bs), 5.02 and 4.87 (each d, $J$ = 10.7 Hz), 4.22 (d, 2, $J$ = 15.6 Hz), 4.07 (d, 2, $J$ = 15.7 Hz), 3.93 (d, 2, $J$ = 14.0 Hz), 3.51 (d, 2, $J$ = 15.7 Hz), 3.41 (d, 2, $J$ = 14.0 Hz), 3.21 (d, 2, $J$ = 15.6 Hz), 2.59 (s, 4), 2.39 (s, 6), 1.42, 1.07 and 0.95 (each s, 54); MS (FAB) $(M + H)^+$ 1263. Anal. Calcd for $C_{86}H_{102}O_8$: C, 81.74; H, 8.14. Found: C, 81.94; H, 8.04.

**Acknowledgment.** We are indebted to the National Institutes of Health (GM-23534) and the Robert A. Welch Foundation (P-1163) for generous support of this work.

# Preparation and Cation Complexing Properties of Some Macropolycyclic Ligands

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*Received December 23, 1991*

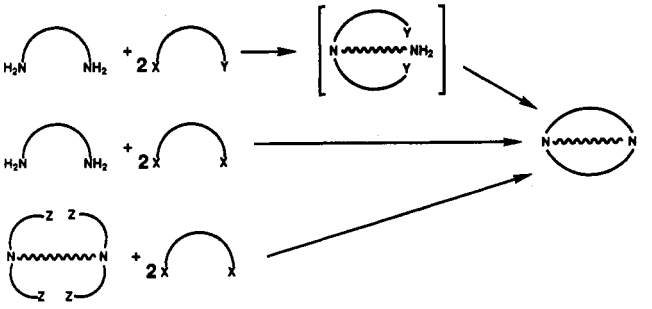
Five new cryptands have been prepared by a 2:1 cyclocondensation of an $\alpha,\omega$-dihalide with an $\alpha,\omega$-diamine. In some cases, other products, such as bis(aza-12-crown-4) ligands and products of a 4:2 cyclocondensation, were isolated also. The structures of the cryptands and bis(aza-crown)s of the same molecular weight were established after careful analysis by $^{13}C$ NMR and X-ray spectroscopy and a few independent syntheses of the bis(aza-crown) ethers. A new TLC test has been developed to distinguish between the cryptands and the bis(aza-crown)s. Log $K$ values for the interaction of two cryptands, each containing two propylene bridges in one arm, with various cations were determined. The results show a much weaker interaction of the cryptands containing two propylene bridges with various cations than that for the corresponding cryptands with only ethylene bridges. The most stable complexes of these new propylene-containing cryptands were those involving $Ba^{2+}$ and $Sr^{2+}$ ions. X-ray analyses of three cryptands, each of which has the $[18]N_2O_4$ macrocycle as part of its structure, show different organizations for the ring heteroatoms.

## Introduction

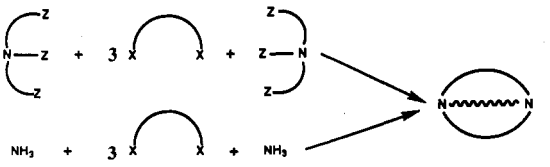
Optimization of synthetic routes to important ligands is critical not only from a financial point of view but also because many synthetic ligands have important chemical applications. The easy access to complicated macrocycles that have hitherto been synthesized in multi steps should be an incentive for a more complete investigation of their physical properties and for finding other chemical and catalytic applications.

The first methods for producing macrocycles were the cyclocondensation of two different difunctionalized linear compounds.[1,2] There is a trend to simplify the total synthesis of macrocycles by using starting materials with only a few atoms, such as ethylene oxide[3] or an aziridine,[4] by cyclopolymerization processes. This idea to react small molecules together in a one-step process has found application in the preparation of the sepulchrates,[5,6] cryptands,[7-15] and bis(aza-crown) ethers.[15]

**Scheme I. General Methods To Form the Cryptands A. By 2:1 Cyclocondensations**



B. By 3:2 Cyclocondensations



Cryptands usually have been prepared by multi-step processes,[16] but recently, one-step methods from three or five molecules have been studied.[17] Indeed, two difunc-

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tional molecules can react in molar ratios of 2:1 or 3:2 to form a cryptand (see Scheme I).[17] There has been considerable success in forming cryptands containing rigid groups, such as benzene, pyridine, bipyridyl, or phenanthroline by the 2:1 cyclocondensation process.[9-11] Small aromatic rings help in the cyclization step since their rigidity favors the formation of cryptands rather than 9- to 12-membered monocyclic rings. These rigid cryptands were formed in yields of 20–60% as the complexed salts and needed a decomplexation step to isolate the free cryptand.

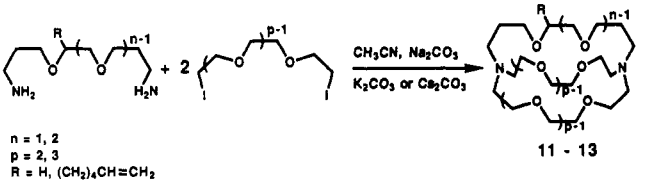
A very attractive synthesis of cryptand 1 (see Figure 1), containing one benzene subcyclic unit, was reported by Pietraszkiewicz and co-workers.[12] They treated one molecule of 1,3-bis(aminomethyl)benzene with two molecules of triethylene glycol ditosylate to give 1 in a 25% yield. In contrast to this easy synthesis of a benzocryptand, an attempt to form cryptand[2.2.2] by a direct 2:1 cyclocondensation of 1,8-diiodo-3,6-dioxadecane and 1,8-diamino-3,6-dioxaoctane was unsuccessful.[18] Kulstad and Malmsten isolated $[18]N_2O_4$ in this reaction. Cyclocondensations of the 3:2 type are less common than 2:1 cyclocondensations, but in a few cases, cryptands in yields of 1–25% have been isolated by the a 3:2 process.[7,8,14] A 2:1 cyclocondensation also has been used to prepare macrobicyclic ligands containing six Schiff-base functions.[19-22] These cyclic hexaSchiff-base materials could be reduced in some cases to the hexaaza macrobicycles containing aromatic or heterocyclic units.[23] Others have reported the synthesis of bis-crown ethers, dipychands, and other macrocycles by 2:1 and 4:2 cyclocondensations.[24-28]

We have published the 2:1 cyclocondensation of $\alpha,\omega$-diiodo compounds and $\alpha,\omega$-diamino compounds to form cryptands **2–6** and bis(aza-12-crown-4)s **8–10** (Figure 1).[15] Preparation of cryptand 7 from triethanolamine and 3-chloro-2-(chloromethyl)-1-propene by a 3:2 cyclization process also has been published.[14] In this paper, we report the preparation of new cryptands **11–16** and bis(aza-12-crown-4)s **17–20** by a 2:1 cyclocondensation, macrotricycles **21–23** by a 4:2 cyclocondensation, and other polycyclic products. The structures of cryptands 1 and **2** were determined by an X-ray crystallographic technique and are compared to the structure of cryptand[2.2.2]. Log $K$, $\Delta H$, and $\Delta S$ values were determined for the interaction in aqueous solution of cryptands **2** and **4** with some alkali metal ions and were compared to interactions with cryptand[2.2.2] and cryptand[3.2.2], respectively. The two propylene bridges in one cryptand arm greatly reduce their interaction with nearly all metal ions studied.

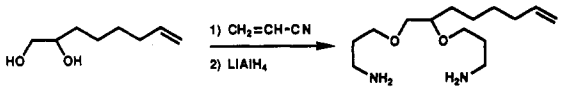
## Results and Discussion

Even though Kulstad and Malmsten reported that only 1,10-diaza-18-crown-6 was formed in the reaction of 2 mol of 1,8-diiodo-3,6-dioxaoctane with 1 mol of 1,8-diamino-3,6-dioxaoctane,[18] we have observed that some cryptand[2.2.2] was formed in this reaction in the presence of $K_2CO_3$, $Cs_2CO_3$, or $MgCO_3$. The MS anayses of the products showed molecular peaks for the macrocycle and molecular peaks for its complex with the metal ion. An attempt to isolate free cryptand[2.2.2] from the reaction mixture (column chromatography followed by decomplexation by acid) was unsuccessful. Since the TLC analysis showed that this reaction formed many products, no further isolation attempts were made. A stepwise cyclocondensation of 1-chloro-8-iodo-3,6-dioxaoctane and 1,8-diamino-3,6-dioxaoctane in the presence of sodium carbonate did give cryptand[2.2.2] (Scheme I, first pathway).[7,29] However, reactions using 1-chloro-8-iodo-3,6-dioxaoctane or other similar compounds containing two different reactive groups are not convenient because these compounds are not available and require additional steps in the synthetic pathway. These results prompted us to study the synthesis of cryptands by a direct 2:1 cyclocondensation from readily available starting materials.

**Scheme II. Preparation of Cryptands 11–13**




**Scheme III. Preparation of 1,10-Diamino-5-(5-hexenyl)-4,7-dioxadecane**




**Scheme IV. Preparation of Sulfur- or Nitrogen-Containing Cryptands**

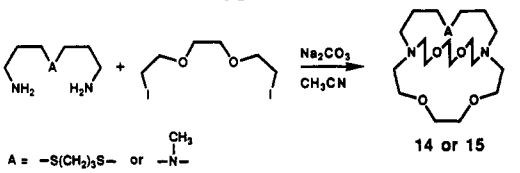



**Table I. 2:1 and 4:2 Cyclocondensation Products**

| cryptand (yield, %) | bis(aza-12-crown-4) (yield, %) | 4:2 condensation product (yield, %) | template cation |
|---|---|---|---|
| **1** (21)[a] | | **21** (2.3) | $Na^+$ |
| | | **22** or **23** (2.2) | |
| **6** (13) | **8** (17) | | $Na^+$ |
| **6** (40) | **8** (17) | | $Cs^+$ |
| **11** (32) | | | $Na^+$ |
| **12** (25) | | (2.1) | $Cs^+$ |
| **12** (33)[b] | | | $Na^+$ |
| **13** (18) | **17** (31) | | $Cs^+$ |
| **13** + **17** (75)[c] | | | |
| **14** (38) | | | $Na^+$ |
| **15** (17) | | | $Na^+$ |
| **16** (18) | **18** (24) | (2.3) | $K^+$ |
| **16** + **18** (50)[c] | | | |
| | **19** (38) | | $K^+$ |

[a] Products of 4:2 cyclocondensations were isolated from the combined reaction products using diiodo and ditosylate starting materials. [b] Other products were not isolated. [c] Not separated.

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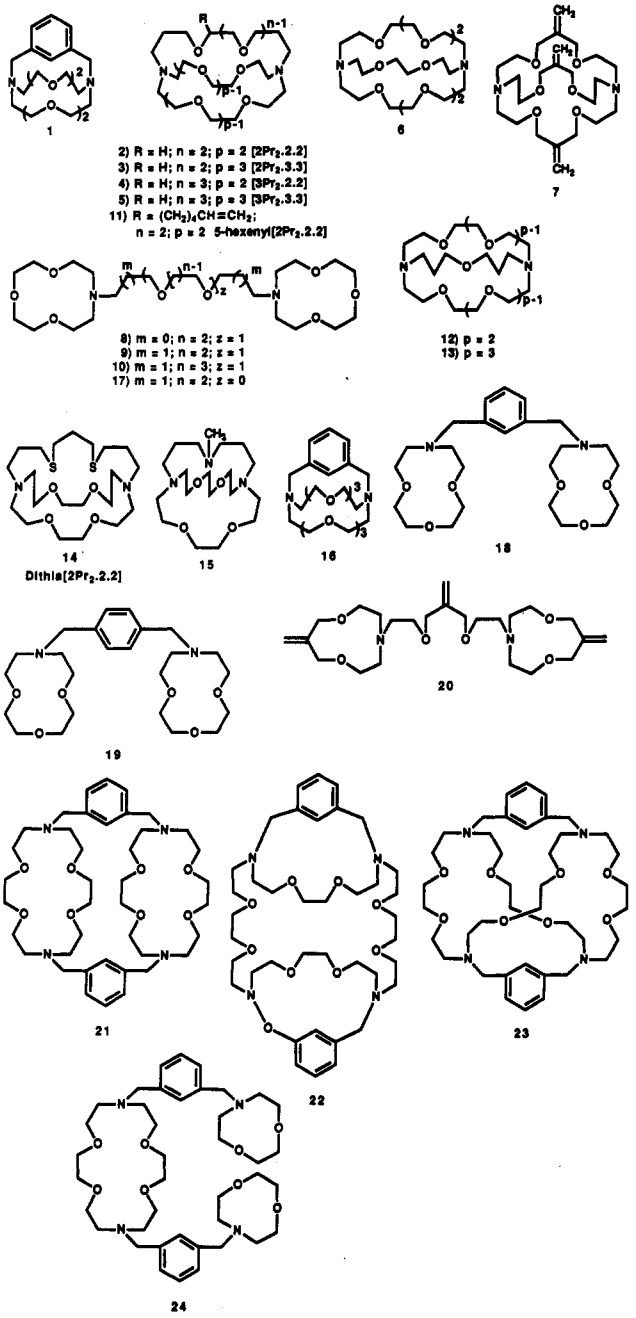
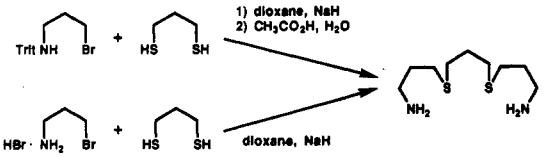


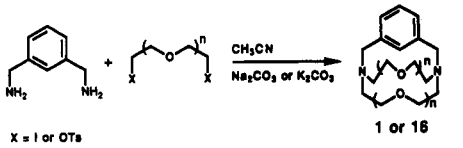

**Figure 1.** New cryptands, bis(aza-crown)s, macrotricycles, and other ligands.

New cryptands **11–13** were prepared from various diamino and diiodo ethers (see Scheme II). Cryptand **11** has a functional group on the side chain which can be used to bond the cryptand onto a solid support, such as silica gel, for continued use in separating cations from water or other solvents.[30-32] 1,10-Diamino-5-(5-hexenyl)-4,7-dioxadecane needed for cryptand **11** was prepared from 7-octene-1,2-diol after cyanoethylation and reduction with lithium aluminum hydride in THF (see Scheme III). Cryptands similar to **11–13** were produced using multistep processes from more expensive starting materials.[33,34]

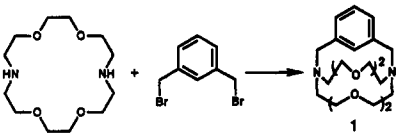
**Scheme V. Preparation of 1,11-Diamino-4,8-dithiaundecane**



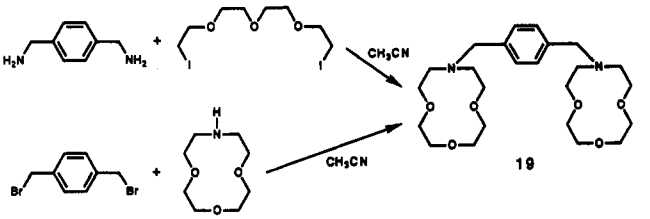

**Scheme VI. Preparation of Cryptands 1 and 16**




**Scheme VII. Preparation of Cryptand 1 from 1,10-Diaza-18-crown-6**



**Scheme VIII. Preparation of Bis(aza-crown) 19**




Bis(aza-12-crown-4) **17** was isolated from the reaction producing cryptand **13**. Indeed, the bis(aza-12-crown-4) ligands are produced as byproducts when a dihalide derivative of tetraethylene glycol is used in these reactions.[15] Table I lists the products and yields for the reactions reported in this work.

Cryptands **14** and **15**, containing sulfur or nitrogen heteroatoms, were synthesized from the appropriate diamine and diiodo polyether in acetonitrile as shown in Scheme IV. 1,11-Diamino-4,8-dithiaundecane needed to prepare **14** was prepared in two different ways (Scheme V). In the first method, the 3-bromo-*N*-tritylpropanamine[35] building block was used. A more direct route from 3-bromopropanamine hydrobromide gave a 70% yield of the dithiadiamine.

Cryptands **1** and **16**, containing one benzene unit, were prepared from the ditosyl ethers of the glycols[12] or from the appropriate diiodo polyethers and diamino ethers, but using different carbonates: sodium for **1** and potassium for **16** (see Scheme VI). The diiodides gave slightly lower yields, but purification of the products was easier than when using the ditosylates.[12] Cryptand **1** also was prepared from 1,10-diaza-18-crown-6 and $\alpha,\alpha'$-dibromo-*m*-xylene as shown in Scheme VII. In our hands, cryptand **1** was obtained by the route shown in Scheme VII in a yield of 68% after purification on alumina. Even with a high yield, this 1:1 synthesis of **1** is not as desirable since the $[18]N_2O_4$ starting reagent is very expensive. It is more cost effective to produce **1** by the 2:1 cyclocondensation (Scheme VI) from inexpensive starting materials.

Bis(aza-12-crown-4) **18** was isolated from the reaction mixture in the preparation of **16**. This compound also was

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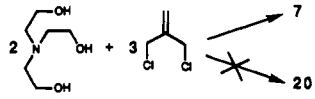
**Scheme IX. Preparation of 7[14]**



prepared from the reaction of $[12]NO_3$ and $\alpha,\alpha'$-dibromo-*m*-xylene.[36] The physical properties and NMR and IR spectra were the same for **18** prepared by the two different methods.

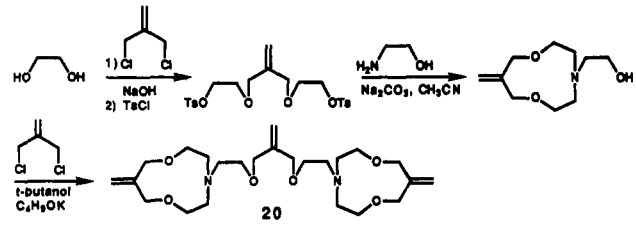
Only bis(aza-12-crown-4) **19** was isolated when $\alpha,\alpha'$-dibromo-*p*-xylene was treated with 1,11-diiodo-3,6,9-trioxaundecane (Scheme VIII). Evidently, the bis(aza-12-crown-4) is easier to prepare than the paracyclophane containing 15 atoms outside the benzene ring. Bis(aza-12-crown-4) **19** was independently synthesized from $[12]NO_3$ and $\alpha,\alpha'$-dibromo-*p*-xylene as shown in Scheme VIII.

The 2:1 cyclocondensation reactions were performed without high dilution conditions using 50–300 mL of $CH_3CN$, 0.01 mol of diamine, and 0.021 mol of the diiodo compound in the presence of excess alkali metal carbonate. No significant change was observed in two cases when a more concentrated solution was reacted (50 mL).

During the synthesis of cryptands **1**, **12**, and **16**, products of a 4:2 cyclocondensation also were isolated. In the preparation of cryptand **1**, two 4:2 cyclocondensation compounds, **21** and **22** or **23**, were isolated. 4:2 Cyclization product **24** probably does not form in this reaction because $[9]NO_2$ macrocycles are difficult to form. Also, complex polymacrocycles liked **24** are probably impossible to prepare in one step. One of the separated compounds is believed to be **21** because of the symmetry of its $^1H$ and $^{13}C$ NMR spectra. Reducing the temperature in 20° increments to −80 °C induced no changes in the $^1H$ NMR spectrum. This indicates that the symmetry of the spectrum is due to the symmetry of the compound and is not a product of motional averaging. Compound **21** was obtained by others using a stepwise synthesis, but its NMR spectrum was not reported.[37,38] The melting point of **21** is similar to that reported. The structure of the second compound has not been solved. The NMR spectrum of this product does not establish its structure because both **22** and **23** exhibit the same degree of symmetry. The $^1H$ and $^{13}C$ NMR spectra are consistent with either structure. Also, the NOESY spectrum did not distinguish between the two structures. The structures of the 4:2 cyclocondensation products isolated along with **16** have not been solved. Additional work needs to be done to establish these structures.

Up to now, cylindrical macropolycycles composed of two diaza-crowns connected by two bridges (like **21**) have been produced by multistep processes and required protection and deprotection procedures on the nitrogen atoms of the diaza-crown building blocks.[39–44] Other methods to prepare these complicated macropolycycles are shorter but require a 2:2 condensation procedure from the diaza-crown ethers.[26,45–49] The cylindrical macropolycycles reported in this work were not previously prepared by the 4:2 cyclocondensation reaction.

**Scheme X. Preparation of Bis(aza-crown) 20**



Cryptand **7** was prepared by a 3:2 cyclization process as shown in Scheme IX.[14] No bis(aza-9-crown-3) (**20**) was found in this reaction as proved by an independent synthesis of **20** (see Scheme X).

The cryptands and bis(aza-12-crown-4)s have the same molecular formulas and cannot be distinguished by their molecular weight or their $^1H$ NMR spectra. The cryptands and bis(aza-12-crown-4)s with propylene bridges can be distinguished from each other by their $^{13}C$ and $^{15}N$ NMR spectra, by a special TLC test, from their X-ray structures, and by independent syntheses. In the $^{13}C$ NMR spectra, the peak attributable to the carbon of the propylene moiety next to the nitrogen is at $\delta = 51.8$ for the cryptands, but at $\delta = 53.9$ for bis(aza-12-crown-4)s.[15] These results are also true for the $^{13}C$ NMR spectra for new cryptand **13** and bisaza-crown **17** where $\delta = 52.02$ and 54.07, respectively. The carbon at the center of the propylene bridge also was shifted by about 1 ppm. There is a shift of about 2 ppm in the $^{15}N$ NMR spectra for the cryptands as compared to that for the bis(aza-12-crown-4)s. This method of distinguishing between the two macrocycles is not very useful since a much greater amount of material is needed for the $^{15}N$ NMR spectra due to the decreased sensivity of this nucleus.

The TLC analyses of the purified cryptands and bis(aza-12-crown-4)s provide an interesting method to distinguish them.[15] The products were first purified on alumina and then placed on a silica gel TLC plate. A methanol/30% aqueous $NH_4OH$ (10/1) solution was used to elute the materials. The TLC spot for all cryptands (those reported herein and many that could be purchased) showed considerable fronting while the spot for all bis(aza-12-crown-4)s exhibited the normal tailing.[15] Similar results were observed using triethylamine instead of the $NH_4OH$ for the two cryptands that were tested. Water, methanol, or a water/methanol mixture did not provide the same results. The unusual TLC spot with fronting also was exhibited by 18-crown-6, dibenzo-14-crown-4, and dibenzo-24-crown-8, but not by phosphorous-containing crowns, the pyridino-crowns, or the aza- or polyaza-crowns. From the above experiments, it is believed that ligands that have superior affinities for the alkali metal ions would exhibit this unusual fronting on silica gel TLC analysis using the methanol–$NH_4OH$ or $-(C_2H_5)_3N$ mixture as eluant. These particular ligands would leach alkali metal

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Table II. Log $K$, $\Delta H$, and $\Delta S$ Values[a] for the Interaction of Cryptands 2, 4, [2.2.2],[b] and [3.2.2][b] with Proton and Some Metal Cations in Aqueous Solution at 25.0 °C, $\mu$ = 0.1 M

| ligand | values | $H^+$(1) | $H^+$(2) | $Cs^+$ | $Rb^+$ | $K^+$ | $Na^+$ | $Ba^{2+}$ | $Sr^{2+}$ | $Ca^{2+}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 2 | log $K$ | 9.65 (2) | 7.40 (2) | <1.0 | <1.0 | 1.2 (3) | 1.3 (2) | 4.40 (2) | 2.0 (1) | 1.7 (2) |
| | $\Delta H$ | -44.2 (9) | -17.3 (7) | | | | | -25.7 (8) | c | |
| | $\Delta S$ | 36.4 | 83.7 | | | | | -1.99 | c | |
| [2.2.2][b] | log $K$ | 9.71 | 7.31 | 1.44 | 4.06 | 5.58 | 4.11 | 9.7 | 8.26 | 4.57 |
| | $\Delta H$ | -45.2 | -18.8 | -21.7 | -49.4 | -46.0 | -31.0 | -59.8 | -44.4 | -0.8 |
| | $\Delta S$ | 34.3 | 76.6 | -45.2 | -87.4 | -48.1 | -25.1 | -15.5 | 9.2 | 84.5 |
| 4 | log $K$ | 9.41 (4) | 7.29 (4) | NR | 1.1 (5) | 1.3 (3) | | 3.13 (8) | 3.62 (7) | |
| | $\Delta H$ | -45.4 (9) | -20.8 (7) | | | | | -30.1 (7) | -38.6 (8) | |
| | $\Delta S$ | 27.9 | 69.8 | | | | | -41.0 | -60.2 | |
| [3.2.2][b] | log $K$ | 8.50 | 7.33 | 1.8 | 2.05 | 2.2 | 1.65 | 6.0 | 3.4 | ≈2.0 |
| | $\Delta H$ | c | c | -23 | -17.6 | -12.6 | c | -25.9 | -13.8 | 0.67 |
| | $\Delta S$ | c | c | -41 | -19.7 | 0 | c | 28.0 | 18.4 | 40.2 |

[a] log $K$ values were determined potentiometrically. The $\Delta H$ values were determined calorimetrically. $\Delta S$ values were calculated according to $-2.303\,RT \log K = \Delta H - T\Delta S$. The uncertainties of the log $K$ and $\Delta H$ values are indicated in parentheses. [b] Values for the interactions of [2.2.2] and [3.2.2] are from ref 51. [c] The heats of reaction were too small to allow accurate measurements.

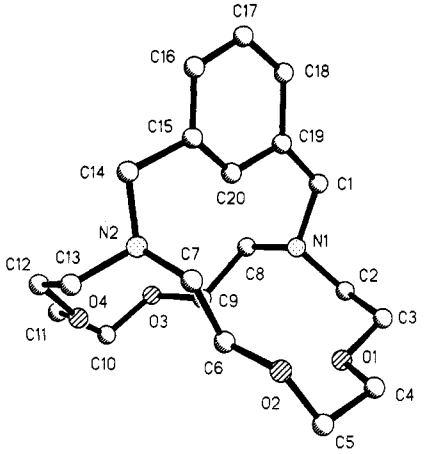


Figure 2. Computer drawing of the X-ray results showing conformations of 1 with hydrogen atoms omitted for clarity.

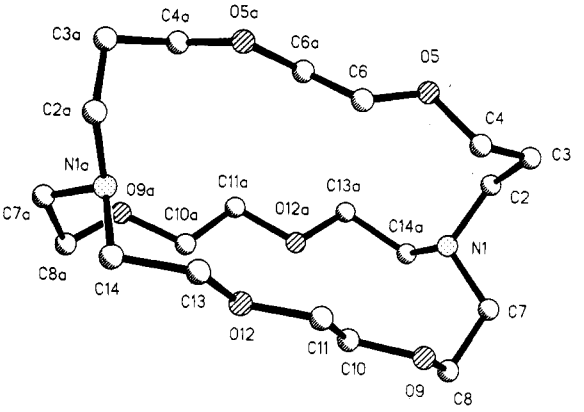


Figure 3. Computer drawing of the X-ray results showing conformation of 2 with hydrogen atoms and disordered C6′ omitted for clarity.

ions from the silica gel, and the complex would move faster causing the fronting. Indeed, a sodium–cryptand[2.2.2] complex moved with the solvent front under these TLC analysis conditions.

X-ray studies of 1 and 2 established that these compounds are cryptands and not bis(aza-12-crown-4)s. Computer drawings, of 1 and 2 are shown in Figures 2 and 3, respectively. These figures show the conformations and atom labels of the molecules. While both compounds can be regarded as tricyclic compounds, they can also be considered as derivations of 1,10-diaza-18-crown-6 ([18]-$N_2O_4$) with an alkylene–ether chain linking the two nitrogens (see Figures 2 and 3). The length and rigidity of the linking chain greatly affects the conformation of the diaza-18-crown-6 ring. In 1, the bridge consists of five atoms with its flexibility limited by the presence of a rigid benzene group which shares three atoms with the bridge. The result is an elliptical 18-crown-6 ring with the short axis between the two nitrogen atoms (see Figure 2). The interatomic distance between the two nitrogens is 4.67 Å. In 2, a more flexible bridge of 10 atoms joins the nitrogens. The 18-atom ring is also elliptical but with the long axis between the nitrogen atoms. The N–N interatomic distance is 7.08 Å, which is approximately 0.2 Å greater than the 6.87 Å for cryptand[2.2.2].[50] [2.2.2] can be considered a derivative of [18]$N_2O_4$ with an eight-atom bridge joining the nitrogen atoms. The geometry of the [18]$N_2O_4$ portion of 2 resembles that for the similar atoms found in [2.2.2]. A comparison of the structures of 1 and 2 with that of [2.2.2] is found in the supplementary material. The effect of conformational differences of the ether rings of 1 and 2 has not been studied since solid-state complexes of these ligands have not been prepared.

Because of increased cavity sizes for 2 and 4, compared to those of cryptands[2.2.2] and [3.2.2], respectively, it was expected that 2 and 4 should form more stable complexes with larger cations such as $Cs^+$.[51] However, the log $K$ values listed in Table II show that 2 and 4 have no significant interaction with $Cs^+$ or the other alkali metal ions and have only moderate interactions with $Ba^{2+}$ and $Sr^{2+}$ in aqueous solution. For comparison, the thermodynamic parameters for the interaction of cryptands[2.2.2] and [3.2.2] with several cations also are given in Table II. It is apparent from the data in Table II that the new cryptands form much weaker complexes with all cations studied than do [2.2.2] and [3.2.2] except for 4 which formed a stronger complex with $Sr^{2+}$ than does [3.2.2] (Table II). A likely reason for the decreased interactions of 2 and 4 is that the incorporation of two more methylene units into the regular [2.2.2] and [3.2.2] molecules increases the flexibility of the resulting ligands. As the flexibility of the ligand increases, the dissociation rate of the complex also increases. The most striking feature that makes [2.2.2] and [3.2.2] interact with cations so strongly is the high rigidity of the ligand and the remarkably slow dissociation

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rate of the complexes.[52] The loss of this rigidity should make the ligand less effective in forming strong complexes with cations. Selectivity of certain cations by the cryptands is partly based on the match between the cation radius and rigid ligand cavity size. Cryptands 2 and 4 with much reduced rigidities should have decreased size selectively for the cations. It is interesting to note that both [2.2.2] and [3.2.2] exhibit selectivity for $Ba^{2+}$ over $Sr^{2+}$, while ligand 4 shows the reverse selectivity for $Sr^{2+}$ over $Ba^{2+}$ (Table II). It is possible that the six-membered chelating ring of 4 favors the smaller cations.[53] The introduction of two additional methylene units into [2.2.2] and [3.2.2] to form 2 and 4, respectively, makes two of the N–$M^+$–O chelating rings six-membered. In case of the 4 complexes, both $Ba^{2+}$ and $Sr^{2+}$ are expected to be much smaller than the cavity; hence, the effect of chelating ring size becomes more important. In the case of complexes with 2, the size of $Ba^{2+}$ may not be much smaller than the ligand cavity; hence, size selectivity may still be an important effect.

## Experimental Section

Proton and carbon NMR spectra were obtained at 200 MHz in $CDCl_3$. Nitrogen NMR spectra were obtained at 500 MHz. All variable-temperature spectra were obtained at 500 MHz. Molecular weights were determined by electron impact HRMS. Starting compounds were used as received from American Tokyo-Kassei, Aldrich, Fluka, and Alfa Chemical Companies. 1,11-Diiodo-3,6,9-trioxaundecane was prepared from the corresponding dichloride. 5-Methylene-3,7-dioxa-1,9-nonanediol and its ditosylate derivative were prepared as reported.[54,55] Silica gel 60 F 254 and aluminum oxide 60 F 254 (neutral, Type E) plates (Merck) were used for TLC. Kieselgel 60 (230–400 mesh) (Merck) and aluminium oxide (activated, neutral, Brockmann 1–150 mesh) (Aldrich) were used for column chromatography. Compound detection on the TLC plates was obtained by iodine vapor. Spectral grade or high-pressure liquid chromatography grade solvents were used throughout.

**1,11-Diamino-4,8-dithiaundecane (Method A)** (Scheme V). 1,3-Propanedithol (0.54 g, 5 mmol) was added to 20 mL of dioxane containing 0.25 g (10 mmol) of NaH, and the mixture was stirred under $N_2$ at 60 °C for 15 min. 3-Bromo-*N*-tritylpropanamine[35] (4.0 g, 10 mmol) was added, and the mixture was heated at 80 °C for 10 h and refluxed for 2 h. The solution was cooled, filtered, and concentrated. The residue was chromatographed on silica gel with toluene/$C_2H_5OH$ (100/1) as eluant to give 2.7 g (75%) of 1,11-ditrityl-1,11-diamino-4,8-dithiaundecane: $^1H$ NMR $\delta$ 1.50 (s, 2 H), 1.80 (m, 6 H), 2.20 (t, $J$ = 6.3 Hz, 4 H), 2.60 (m, 8 H), 7.20–7.50 (two m, 30 H).

This ditrityl compound was added to a mixture of 27 mL of $CH_3CO_2H$ and 3 mL of $H_2O$, and the mixture was stirred under Ar at 90 °C overnight. The mixture was evaporated, and 60 mL of $H_2O$ was added. The mixture was filtered, and the filtrate was evaporated. During the evaporation, toluene was added a few times to help remove the solvents. The residue was separated on a short silica gel column using $CH_3OH/NH_4OH$ (50/1–5/1) as eluants to give 0.5 g (64%) of the title compound: $^1H$ NMR $\delta$ 1.35 (s, 4 H), 1.80 (m, 6 H), 2.6 (m, 8 H), 2.8 (t, $J$ = 7.8 Hz, 4 H). Anal. Calcd for $C_9H_{22}N_2S_2$: C, 48.60; H, 9.97. Found: C, 48.48; H, 10.00.

**1,11-Diamino-4,8-dithiaundecane (Method B)** (Scheme V). To 1.08 g (10 mmol) of 1,3-propanedithiol in a mixture of 20 mL of dioxane and 20 mL of THF was added 1 g (40 mmol) of NaH under $N_2$ and the mixture was stirred at 50–60 °C for 15 min. 3-Bromopropanamine hydrobromide (4.5 g, 20.5 mmol) was slowly added in portions to the mixture at −50 °C, and the mixture was stirred at −50 °C for 1 h. The temperature was then increased slowly to rt. After being stirred at rt overnight, the mixture was filtered. The solid was washed with $CH_2Cl_2$, and the filtrate was evaporated. The residue was distilled under reduced pressure to give the diamine (75%): bp 137–139 °C (0.018 mmHg). The spectral properties of this material were the same as those reported above.

**4-(2-Hydroxyethyl)-9-methylene-1,7-dioxa-4-azacyclodecane** (Scheme X). A stirred solution of 4.84 g (10 mmol) of 5-methylene-3,7-dioxanonane-1,9-diol ditosylate;[54,55] and ethanolamine (0.61 g, 10 mmol) in 300 mL of $CH_3CN$ containing 10.6 g (100 mmol) of $Na_2CO_3$ was heated at reflux temperature under $N_2$ for 24 h. The mixture was cooled, filtered, and concentrated. The residue was stirred with 120 mL of $CH_2Cl_2$ and filtered to removal residual salts. The solvent was evaporated from the filtrate. The residue was purified by column chromatography using toluene/$C_2H_5OH$ (50/1) and (25/1) as eluants to give the desired product (29%): $^1H$ NMR $\delta$ 2.75 (t, $J$ = 5.3 Hz, 2 H), 2.85 (t, $J$ = 5.5 Hz, 4 H), 3.55 (t, $J$ = 6 Hz, 2 H), 3.65 (t, $J$ = 5.5 Hz, 4 H), 4.15 (s, 4 H), 5.05 (s, 2 H); IR 3530 $cm^{-1}$; MS $m/e$ 201 and 202 (CI). This material was used in the next step without further purification.

**Bis(aza-10-crown-3) 20** (Scheme X). To 50 mL of *tert*-butyl alcohol under $N_2$ was added 0.6 g of KO-*t*-$C_4H_9$ and 0.43 g of the above compound. 3-Chloro-2-(chloromethyl)-1-propene (0.125 g, 1 mmol) in 10 mL of dioxane was added slowly into the mixture of 50 °C, and the mixture was stirred overnight at 70 °C. After being cooled, the mixture was filtered and concentrated. Water (15 mL) was added to the residue, and the aqueous solution was extracted twice with 100-mL portions of $CH_2Cl_2$. The organic layer was dried ($MgSO_4$). After concentration, the residue was purified on alumina (ethyl acetate) to give **20** (35%) as an oil: $^1H$ NMR $\delta$ 2.8 (m, 12 H), 3.48 (t, $J$ = 6.3 Hz, 4 H), 3.6 (t, $J$ = 5 Hz, 8 H), 3.92 (s, 4 H), 4.15 (s, 8 H), 4.97 (s, 4 H), 5.12 (s, 2 H). $^{13}C$ NMR $\delta$ 55.17, 56.56, 69.56, 71.23, 72.10, 72.26, 113.77, 114.02, 143.33, 146.46; MS $m/e$ 454, 455 (CI). Anal. Calcd for $C_{24}H_{42}N_2O_6$: C, 63.41; H, 9.31. Found: C, 63.31; H, 9.29.

**1-(5-Hexenyl)-1,2-bis(3-cyanoethoxy)ethane** (Scheme III). A mixture of 14.42 g (0.1 mol) of 7-octene-1,2-diol and 0.30 g of 40% aqueous KOH was stirred under reflux temperature. The mixture was cooled, and $CH_3CN$ (10.6 g, 0.2 mmol) was added at a rate such that the temperature did not exceed 35 °C. After the $CH_3CN$ was added, the mixture was stirred for 1 h and then was made acidic with 6 N HCl. The solution was extracted with 200 mL of $CHCl_3$. The organic layer was washed twice with 200-mL portions of $H_2O$, dried ($MgSO_4$), and concentrated. The residue was distilled under vacuum to give 20.1 g (80%) of the dinitrile: bp 165–170 °C (0.014 mm); $^1H$ NMR $\delta$ 1.44 (m, 6 H), 2.07 (m, 2 H), 2.60 (t, $J$ = 7.1 Hz, 2 H), 2.63 (t, $J$ = 7.1 Hz, 2 H), 3.42–3.97 (m, 7 H), 4.98 (m, 2 H), 5.81 (m, 1 H). This material was used in the next step without further purification.

**1,10-Diamino-5-(5-hexenyl)-4,7-dioxadecane** (Scheme III). To a cooled (ice-bath) mixture of 3.8 g (0.10 mol) of $LiAlH_4$ and 200 mL of anhyd ethyl ether was slowly added 6.25 g (0.025 mol) of the above dicyano compound in 20 mL of anhyd ethyl ether. The reaction mixture was stirred under reflux for 10 h. Water (4 mL) was added to the vigorously stirred mixture at 0 °C. The ether solution was decanted from the white, granular inorganic residue. This residue was washed twice with ether, and the ether portions were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on silica gel ($CH_3OH/NH_4OH$ = 10/1) to give 1.78 g (27%) of the desired product: IR 3361, 3297, 3047, 2930, 2859, 1640, 1590, 1461, 1115 $cm^{-1}$; $^1H$ NMR $\delta$ 1.40 (m, 6 H), 1.70 (m, 4 H), 1.79 (s, $NH_2$, 4 H), 2.03 (m, 2 H), 2.79 (t, 4 H, $J$ = 7.1 Hz), 3.28–3.81 (m, 7 H), 4.99 (m, 2 H), 5.79 (m, 1 H); MS $m/e$ 259 (M + 1). This material was used to prepare 11 without further purification.

**General Procedure for the Preparation and Separation of Cryptands and Bis(aza-12-crown-4)s.** The diiodo compound (11 mmol) was added to a mixture of 5 mmol of the appropriate diamine and 12 g of anhyd $M_2CO_3$ in 200 mL of $CH_3CN$. The stirred mixture was refluxed for 24–36 h, cooled, filtered, and evaporated. Then 50–80 mL of $CH_2Cl_2$ was added, and the mixture was stirred for a few min. The mixture was filtered and evaporated, and the residue was passed through an alumina

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column (THF followed by THF/ethanol) and was chromatographed on silica gel ($CH_3OH$/30% $NH_4OH$ = 20/1, 10/1, 5/1, and 2/1). This elution process separated the bis(aza-12-crown-4) from the cryptand ($R_f$ values for bis(aza-12-crown-4)s and cryptands differ by about 0.1–0.2 on the silica gel TLC). Analytically pure samples were obtained by mixing the products with $CH_2Cl_2$, filtering the mixtures through a glass fiber filter, and evaporating the $CH_2Cl_2$. The products and yields are listed in Table I. $^1H$, $^{13}C$, and $^{15}N$ NMR spectral data and elemental analyses for all products are as follows.

**Cryptand 12**: $^1H$ NMR $\delta$ 1.7 (m, 4 H), 2.5 (t, $J$ = 6.3 Hz, 4 H), 2.60 (m, 8 H), 3.65 (m, 20 H); $^{13}C$ NMR $\delta$ 24.2, 46.0, 47.6, 69.4, 70.0, 70.5; MS $m/e$ 360. Anal. Calcd for $C_{18}H_{36}N_2O_5$: C, 59.97; H, 10.06. Found: C, 59.81; H, 10.27.

**4:2 cyclocondensation product from the reaction to prepare 12**: $^1H$ NMR $\delta$ 1.7 (m, 8 H), 2.7 (m, 24 H), 3.6 (m, 40 H); MS $m/e$ 720. Anal. Calcd for $C_{36}H_{72}H_4O_{10}$: C, 59.97; H, 10.06. Found: C, 59.81; H, 10.09.

**Cryptand 13**: $^1H$ NMR $\delta$ 1.75 (m, 4 H), 2.65 (m, 12 H), 3.6 (m, 12 H), 3.7 (s, 16 H); $^{13}C$ NMR $\delta$ 28.13, 52.02, 55.44, 69.32, 69.74, 71.35, 71.40; MS $m/e$ 449. Anal. Calcd for $C_{22}H_{44}N_2O_7$: C, 58.90; H, 9.89. Found: C, 58.87; H, 10.07.

**Bis(aza-12-crown-4) 17**: $^1H$ NMR $\delta$ 1.70 (m, 4 H), 2.55 (t, $J$ = 8.9 Hz, 4 H), 2.70 (t, $J$ = 5.2 Hz, 4 H), 3.4 (t, $J$ = 7.8 Hz, 4 H), 3.65 (m, 24 H); $^{13}C$ NMR $\delta$ 27.54, 54.07, 55.23, 69.25, 70.54, 71.34; MS $m/e$ 449. Anal. Calcd for $C_{22}H_{44}N_2O_7$: C, 58.90; H, 9.89. Found: C, 58.95; H, 9.98.

**Cryptand 14**: $^1H$ NMR $\delta$ 1.75 (m, 4 H), 1.9 (m, 2 H), 2.6 (m, 20 H), 3.6 (m, 8 H), 3.7 (s, 8 H); $^{13}C$ NMR $\delta$ 28.1, 29.7, 31.1, 54.2, 55.8, 70.1, 71.1; MS $m/e$ 450. Anal. Calcd for $C_{22}H_{42}N_2S_2O_4$: C, 55.97; H, 9.39. Found: C, 55.93; H, 9.13.

**Cryptand 15**: $^1H$ NMR $\delta$ 1.60 (m, 4 H), 2.25 (s, 3 H), 2.40 (t, $J$ = 6.8 Hz, 4 H), 2.60 (m, 12 H), 3.60 (m, 16 H); $^{13}C$ NMR $\delta$ 25.23, 42.17, 53.50, 54.27, 56.10, 70.08, 71.21; MS $m/e$ 373. Anal. Calcd for $C_{19}H_{39}N_3O_4$: C, 61.10; H, 10.52. Found: C, 60.98; H, 10.34.

**Cryptand 16**: $^1H$ NMR $\delta$ 2.65 (t, $J$ = 6.3 Hz, 8 H), 3.60 (m, 28 H), 7.1 (m, 3 H), 7.9 (s, 1 H); $^{13}C$ NMR $\delta$ 55.24, 60.60, 70.44, 70.89, 71.20, 127.52, 127.72, 129.61, 141.14; MS $m/e$ 452. Anal. Calcd for $C_{24}H_{40}N_2O_6$: C, 63.69; H, 8.90. Found: C, 63.48; H, 9.02.

**Bis(aza-12-crown-4) 18**: $^1H$ NMR $\delta$ 2.7 (t, $J$ = 5 Hz, 8 H), 3.65 (m, 28 H), 7.25 (s, 3 H), 7.30 (s, 1 H); $^{13}C$ NMR $\delta$ 55.02, 61.29, 70.64, 70.83, 71.68, 128.13, 128.51, 130.13, 139.77; MS $m/e$ 452, 453 (CI).

**4:2 cyclocondensation product from the reaction to prepare 16** (similar to 21–23 but with more ethyleneoxy units): $^1H$ NMR $\delta$ 2.70 (m, 16 H), 3.65 (m, 56 H), 7.20 (s, 6 H), 7.24 (s, 2 H); $^{13}C$ NMR $\delta$ 53.96, 55.04, 60.15, 61.29, 70.34, 70.63, 70.84, 70.91, 71.18, 71.70, 128.05, 128.53, 129.99, 139.74. Anal. Calcd for $C_{48}H_{80}N_4O_{12}$: C, 63.69; H, 8.90. Found: C, 63.49; H, 8.78.

**Cryptand 11**: $^1H$ NMR $\delta$ 1.43 (m, 6 H), 1.71 (m, 4 H), 2.05 (m, 2 H), 2.60 (m, 12 H), 3.50 (m, 27 H), 4.98 (m, 2 H), 5.8 (m, H); MS $m/e$ 486, 487 (CI). Anal. Calcd for $C_{26}H_{50}N_2O_6$: C, 64.16; H, 10.36. Found: C, 63.93; H, 10.14.

**Cryptand 1**: mp 101 °C (lit.[12] mp 103 °C; lit.[56] mp 100–101 °C); $^1H$ NMR $\delta$ 2.7 (m, 8 H), 3.6 (m, 20 H), 6.9–7.15 (m, 3 H), 8.4 (s, 1 H); $^{13}C$ NMR $\delta$ 56.12, 59.64, 69.67, 70.60, 125.62, 127.24, 129.88, 142.07.

**4:2 cyclocondensation product 21**: mp 114–115 °C (lit.[38] mp 111–113 °C; lit.[37] mp 116 °C); $^1H$ NMR $\delta$ 2.8 (t, $J$ = 6.3 Hz, 16 H), 3.7 (m, 40 H), 7.15 (s, 6 H), 7.5 (s, 2 H); $^{13}C$ NMR $\delta$ 54.56, 60.36, 70.49, 71.14, 127.73, 128.42, 129.63, 140.38; MS $m/e$ 728, 729 (CI). Anal. Calcd for $C_{40}H_{64}N_4O_8$: C, 65.90; H, 8.84. Found: C, 66.17; H, 8.74.

**4:2 cyclocondensation product 22 or 23**: $^1H$ NMR $\delta$ 2.65 (t, 8 H), 2.8 (t, $J$ = 5.5 Hz, 8 H), 3.65 (m, 40 H), 7.1 (m, 6 H), 7.85 (s, 2 H); $^{13}C$ NMR $\delta$ 55.17, 55.68, 60.06, 69.47, 70.50, 70.68, 70.92, 127.15, 127.65, 130.05, 140.95; MS $m/e$ 728, 729 (CI). Anal. Calcd for $C_{40}H_{64}N_4O_8$: C, 65.90; H, 8.84. Found: C, 65.76; H, 8.62.

**Bis(aza-12-crown-4) 19**: $^1H$ NMR $\delta$ 2.70 (t, $J$ = 5.2 Hz, 8 H), 3.65 (m, 28 H), 7.28 (s, 4 H); $^{13}C$ NMR $\delta$ 55.05, 61.05, 70.66, 70.84, 71.66, 129.31, 138.52; MS $m/e$ 452. Anal. Calcd for $C_{24}H_{40}N_2O_6$: C, 63.69; H, 8.90. Found: C, 63.51; H, 8.82.

**Cryptand 2**:[15] $^{15}N$ NMR $\delta$ 348.526.

**Cryptand 6**:[15] $^{15}N$ NMR $\delta$ 353.585.

**Bis(aza-12-crown-4) 8**:[15] $^{15}N$ NMR $\delta$ 351.525.

**Preparation of Cryptand 1 from [18]$N_2O_4$** (Scheme VII). [18]$N_2O_4$ (0.65 g, 2.48 mmol) was stirred with 0.68 g (2.57 mol) of $\alpha,\alpha'$-dibromo-$m$-xylene in 15 mL of $CH_3CN$ containing 15 g of $Na_2CO_3$ at rt and then under reflux overnight. After being cooled, the reaction mixture was filtered and concentrated. $CH_2Cl_2$ (50 mL) was added, and the mixture was stirred and filtered. The filtrate was concentrated and the residue chromatographed on alumna using THF/$CH_2Cl_2$ (1:1) to obtain 75% of 1. The physical and spectral properties were the same as reported.[12]

**Preparation of Compounds 18 and 19 from [12]$NO_3$.** [12]$NO_3$ (250 mg, 1.42 mmol) was placed in 30 mL of $CH_3CN$ containing 3 g of anhyd $Na_2CO_3$. Then, 188 mg (0.712 mmol) of $\alpha,\alpha'$-dibromo-$m$-xylene or $\alpha,\alpha'$-dibromo-$p$-xylene was added, and the mixture was stirred and refluxed overnight. When cooled, the mixture was filtered and 25 mL of $CH_2Cl_2$ was added. The mixture was filtered and concentrated, and the residue was purified on alumina using THF/$CH_2Cl_2$ (1:4) and (1:1) as eluants to give 18 (65%) and 19 (56%). The physical and spectral properties were the same as above.

**Potentiometric Measurements.** Protonation and metal ion binding constants for ligands 2 and 4 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 ± 0.1 °C) under a $CO_2$ free nitrogen atmosphere. During each tiration run, the emf values of the glass electrode which are linearly related to pH values under constant ionic strength, were recorded as a function of amount titrant added.

Standard electrode potential, $E^{0\prime}$ (300.2 mV), and the ion product of water at 0.1 M ionic strength, $pK'_w$ (13.70), were determined by titrating a $HNO_3$ solution to a standardized $Me_4NOH$ solution. The log $K$ values (Table II) for ligand protonation and metal ion–ligand interaction were computed from data obtained by titrating acidified ligand solutions with $Me_4NOH$ in the absence and presence, respectively, of the metal ion.

The ionic strength was maintained at 0.1 M with $Me_4NNO_3$ for all the titrations. The filling solution of the electrode was 0.8 M $Me_4NNO_3$. Program SUPERQUAD[52] was used for all the calculations.

**Calorimetric Measurements.** Enthalpies of protonation and metal ion binding for ligand 2 and 4 were determined by a titration calorimetric technique which has been described earlier.[53] Corresponding entropy values were calculated according to the relation: $2.303RT \log K = \Delta H - T\Delta S$. The ionic strength of 0.1 M was also maintained with $Me_4NNO_3$ for all the calorimetric titrations. Program REACTIONS[58] was used for the calculation of the calorimetric data.

**Acknowledgment.** This work was supported by the U.S. Department of Energy, Chemical Sciences Division, Office of Basic Energy Sciences, Contract No. DE-FG02-86 Er 13463.

**Registry No.** 1, 61696-66-0; 2, 117875-33-9; 4, 119017-40-2; 6, 31249-78-2; 8, 140605-14-7; 11, 140605-15-8; 12, 119017-39-9; 13, 140605-16-9; 14, 140605-17-0; 15, 140605-18-1; 16, 140605-19-2; 17, 140605-20-5; 18, 140605-21-6; 19, 140605-22-7; 20, 140605-23-8; 21, 140605-24-9; 22, 140605-25-0; 23, 140605-26-1; $H^+$, 12408-02-5; $Cs^+$, 18459-37-5; $Rb^+$, 22537-38-8; $K^+$, 24203-36-9; $Na^+$, 17341-25-2; $Ba^{2+}$, 22541-12-4; $Sr^{2+}$, 22537-39-9; $Ca^{2+}$, 14127-61-8; $ICH_2(CH_2OCH_2)_2CH_2O(CH_2)_2I$, 36839-56-2; $I(CH_2)_2O(CH_2)_2O(CH_2)_2I$, 36839-55-1; $NO_3$, 41775-76-2; $BrCH_2C_6H_4$-$m$-$CH_2Br$, 626-15-3; $N_2O_4$, 23978-55-4; $HS(CH_2)_3SH$, 109-80-8; $TritNH(CH_2)_3Br$, 88811-16-9; $TritNH(CH_2)_3S(CH_2)_3S(CH_2)_3NHTrit$, 133146-46-0; $H_2N(CH_2)_3S(CH_2)_3S(CH_2)_3NH_2$, 65755-73-9; $H_2N(CH_2)_3Br$·HBr, 5003-71-4; $TsO(CH_2)_2OCH_2C(=CH_2)CH_2O(CH_2)_2OTs$, 137378-08-6; $H_2N(CH_2)_2OH$, 141-43-5; $(ClCH_2)_2C=CH_2$, 1871-57-4; $HOCH_2CH(OH)(CH_2)_4CH=CH_2$, 85866-02-0; $H_2C=CHCN$, 107-13-1; $NC(CH_2)_2OCH_2CH(O(CH_2)_2CN)(CH_2)_4CH=CH_2$, 140605-28-3; $H_2N(CH_2)_3OCH_2CH(O(CH_2)_3NH_2)(CH_2)_4CH=CH_2$, 140605-29-4; $H_2N(CH_2)_3O(CH_2)_2O(CH_2)_3NH_2$, 2997-01-5; $H_2N$-

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$(CH_2)_3OCH_2(CH_2OCH_2)_2(CH_2)_2NH_2$, 4246-51-9; $H_2N(CH_2)_3N(Me)(CH_2)_3NH_2$, 105-83-9; $H_2NCH_2C_6H_4$-*p*-$CH_2NH_2$, 539-48-0; $BrCH_2C_6H_4$-*p*-$CH_2NH_2$, 623-24-5; 4-(2-hydroxyethyl)-9-methylene-1,7-dioxa-4-azacyclodecane, 140605-27-2.

**Supplementary Material Available:** $^1H$ NMR spectra for *N,N'*-ditrityl-4,8-dithia-1,11-undecanediamine, 1-(5-hexenyl)-1,2-bis(3-cyanoethoxy)ethane, 1,10-diamino-5-(5-hexenyl)-4,7-dioxadecane, 4-(2-hydroxyethyl)-9-methylene-1,7-dioxa-4-azacyclodecane, and 18, $^{13}C$ NMR spectrum for 18, experimental details for the X-ray data, a comparison of the conformations of the 18-membered rings of 1, 2, and [2.2.2], and 10 tables of X-ray data for 1 and 2 (22 pages). Ordering information is given on any current masthead page.

# Synthesis of Hydrindan Derivatives Related to Vitamin D[1]

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*Received December 12, 1991*

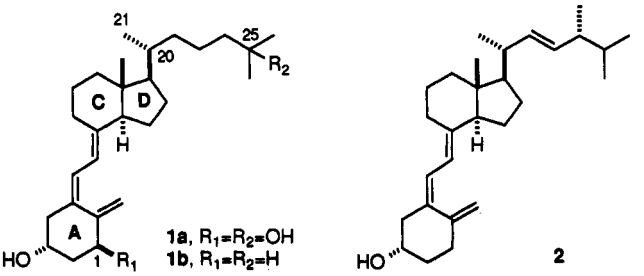
Two independent routes to the CD fragment of vitamin D metabolites and analogues are described. The *trans*-hydrindanol **4** was synthesized from enedione **5**. The key step in this synthesis was the hydroxyl-directed hydrogenation of hydrindenols of type **15** in the presence of Wilkinson's catalyst. The *trans*-hydrindanone **6** was efficiently prepared by degradation of the Lythgoe–Inhoffen diol (**3**). Both **4** and **6** are suitable precursors for the preparation of new potentially useful analogues of 1α,25-dihydroxyvitamin $D_3$ that are funtionalized at $C_{20}$, $C_{21}$, or ring D.

## Introduction

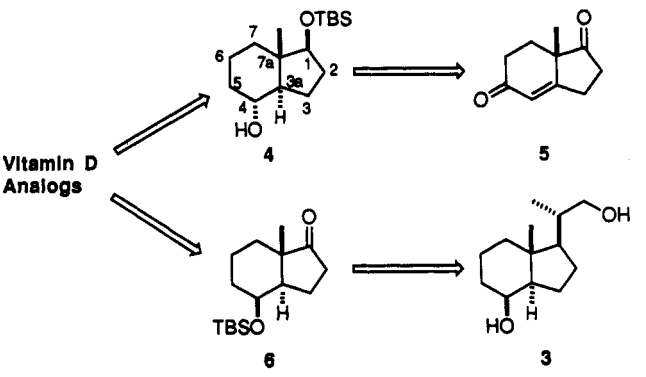
1α,25-Dihydroxyvitamin $D_3$ [**1a**, 1α,25-$(OH)_2$-$D_3$, calcitriol] (Chart I), the hormonally active form of vitamin $D_3$ (**1b**), in addition to controlling intestinal calcium absorption and bone calcium mobilization,[2] is also involved in cell differentiation and proliferation processes.[3] The fact that this hormone cannot be used for the treatment of certain cancers due to its potent calcemic effects[4] has led to interest in the synthesis of structurally modified analogues of 1α,25-$(OH)_2$-$D_3$ with potent effects on cell differentiation and proliferation without causing hypercalcemia.[5] To date, a number of side-chain-modified analogues of 1α,25-$(OH)_2$-$D_3$ have been subjected to preliminary clinical studies with promising results.[6]

Among the various routes now available for the synthesis of vitamin D metabolites and analogues, those based on the convergent coupling of the upper fragment (bicycle CD and side chain) to the bottom fragment (ring A) are particularly attractive.[7] In these syntheses the CD and side-chain fragments are usually prepared from the Lythgoe–Inhoffen diol (**3**), which is obtained by degradation

Chart I




Scheme I




(1) A short account of this work was partially been presented at the 7th workshop on vitamin D: *Vitamin D. Molecular, Cellular and Clinical Endocrinology*; Norman, A. W., Schaefer, K., Grigoleit, H. G., Herrath, D. V., Eds.; Walter de Gruyter: Berlin, New York, 1988; p 34. This work was taken in part from the PhD thesis of B. Fernandez.

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