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Synthesis and Characterization of Two Nitrogen-Donor Cryptands

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Introduction

The ability to design ligands such as crown ethers[1,2] and cryptands[3,4] which can target one desired ion among several provides a means of selectively binding and isolating that ion from its surrounding environment.[5-7] Lehn's [2.2.2] cryptand 1[8] (marketed as Kryptofix 222) has applications as a phase-transfer catalyst[9,10] and as a cation chelator.[11] The analogous all-nitrogen donor cryptands have only more recently been investigated and offer possibilities for enhanced binding of soft, environmentally relevant cations[11-17] and of anions such as fluoride[12] at low pH. Nelson[18] and Bharadwaj[19] have reported the preparation of metal complexes of 2 and 3[20] by template procedures. An earlier report by Lehn describes the only published synthesis of free ligand 3.[12] Herein we report nontemplate syntheses and full characterization including crystal structures of the metal-free macrobicycles 2 and 3.

Results and Discussion

The key step in the synthesis of these cryptands is the condensation of tris(2-aminoethyl)amine (tren) with glyoxal in the absence of a template ion. After substantial variation of reaction conditions and workup procedures, we have optimized the yield of this step to >50%. The essential element of this reaction appears to be the slow addition of glyoxal to tren at reduced temperatures (0 °C). Higher temperatures and faster addition rates lead to variable yields ranging from 10–30%. The reduction of the resulting imine proceeds in nearly quantitative yield using either LAH/THF or NaBH$_4$/MeOH.

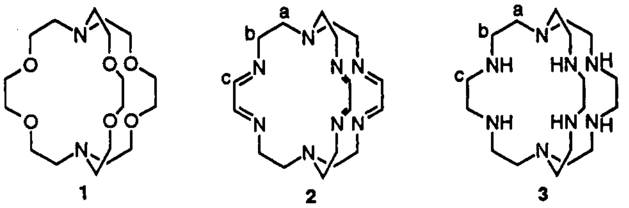

Figure 1. Structures of [2.2.2] cryptand 1 and octaaza analogs 2 and 3.

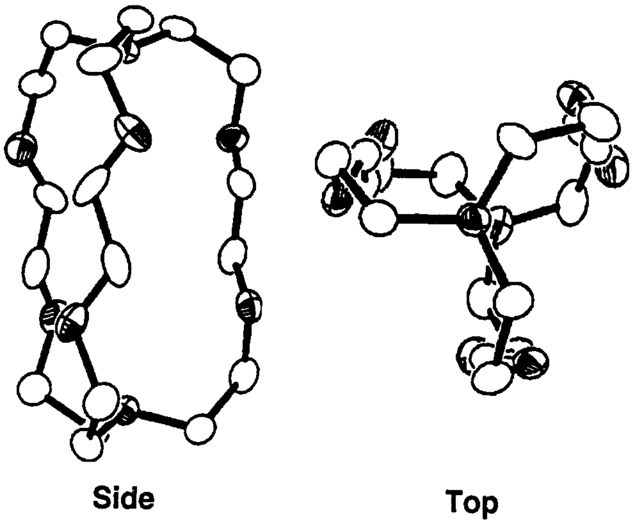

Figure 2. ORTEP side and top views of 2.

While Lehn's synthesis of 3 affords useful macrocyclic intermediates, the procedure described herein provides a 6-fold increase in the overall yield of free ligand 3. In addition, this procedure furnishes the Schiff's base macrobicyclic intermediate 2 which is previously unreported in its metal-free form. Nelson has reported the template synthesis and transmetalation of 2; however, yields are not reported and no procedure for demetalation is described.[18] Bharadwaj reports the synthesis of *metal complexes* of both 2 and 3 using Cs$^+$ and Rb$^+$ as template ions in yields similar to those reported here, but again, no procedure for demetalation is provided.[19] Given that the 3 + 2 condensation proceeds in similar yields in both the absence and presence of a metal ion, the role of the metal as a template in this reaction may be questionable. Indeed, nontemplate 3 + 2 condensations of tren with dialdehydes are not unprecedented.[17,21,22]

The crystal structure of 2 is illustrated in Figure 2 (See Table I).[23] The molecule exhibits pseudo D_3 symmetry. The two tertiary amines are 6.84 Å apart and have their lone pairs directed toward the center of the cavity. The conformation of the α-diimine linkages is *s*-trans, and the imine lone pairs are directed tangent to the ellipsoid-

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(20) 2 = 1,4,7,10,13,16,21,24-octaazabicyclo[8.8.8]hexacosa-4,6,13,15,21,23-hexaene, 3 = 1,4,7,10,13,16,21,24-octaazabicyclo[8.8.8]hexacosane.

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Table I. Data Collection and Refinement Parameters for 2 and 3

compound	2	3
chemical formula	$C_{18}H_{30}N_8$	$C_{18}H_{42}N_8(H_2O)_{18}$
formula weight	358.49	694.87
lattice parameters		
a (Å)	7.620(1)	10.969(2)
b (Å)	12.462(2)	-
c (Å)	22.063(5)	26.872(5)
unit cell volume (Å^3)	2095.2(7)	2800.0(9)
space group	$P2_12_12_1$ (no. 19)	$R32$ (no. 155)
Z value	4	3
D_{calcd} (g/cm^3)	1.137	1.236
μ(Mo K-α) (cm^{-1})	0.68	1.1
radiation Mo K-α (λ, Å) (graphite-monochromated)	0.71073	0.71069
temperature (K)	298	203
residuals: R; R_w	0.0779; 0.0850	0.0573; 0.0698

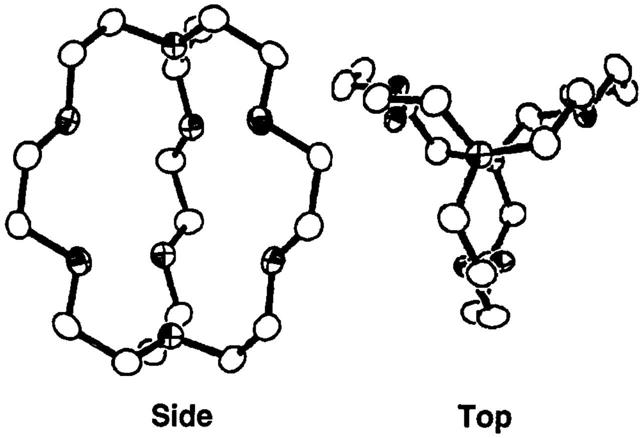
Side
Top

Figure 3. ORTEP side and top views of 3.

shaped cavity. The bond distances and angles are similar to those found in other α-diimines.[24]

Figure 3 illustrates the crystal structure of 3 (see Table I).[25] The cryptand exhibits crystallographic D_3 symmetry. The two tertiary amines along the three-fold axis are 6.37 Å apart and have their lone pairs directed toward the center of the cavity. The hydrogens of the secondary amines are also directed toward the center of the cavity, and the lone pairs participate in an extented network of hydrogen bonds with water molecules in the lattice.

Two crystal structures of the uncomplexed form of 1 were found in the Cambridge Crystallographic Data Centre (Version 4.5),[26,27] and each of them illustrates similarities to the structure of 2 and 3 determined here. The similarities and differences can best be described by discussing the average dihedral angles about the non-bridgehead heteroatoms and the average distances of the heteroatoms to the centroid (Table II).

These structures fall into two classes: those which have dihedral angles of approximately 180°, **1b** and **2** (anti), and those which have dihedral angles of approximately 60°, **1a** and **3** (gauche). The cavities of **1b** and **2** (anti) are elongated by approximately 1 Å along the axis defined by the bridgehead nitrogens relative to **1a** and **3** (gauche). Also, the centroid-to-NBH distances are somewhat longer in the anti conformation. Comparison of the conformationally similar cryptands **1a** and **3** illustrates that the octaaza cryptand **3** cavity is significantly larger than that of the oxygen analog **1a**. In contrast, the cavity dimensions of **1b** and **2** are very similar. It is noteworthy that the ratio of the average NBH-centroid to BH-centroid distances for all four cryptands is relatively constant ranging from 0.86 for **2** to 0.89 for **3**, indicating that they have similarly shaped cavities. Furthermore, a qualitative comparison of the conformation of **3** found here to that of the fluoride cryptate complex of Lehn[12] indicates a high degree of preorganization for fluoride binding.

Experimental Section

General. All solvents and reagents were reagent grade and used without further purification, except as noted below. THF was distilled over sodium/benzophenone ketyl. Melting points were determined on a capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 200-, 250-, or 300-MHz instrument. Chemical shifts are reported relative to TMS in $CDCl_3$ and to TSP (3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid, sodium salt) in D_2O. Elemental analyses were performed in our laboratory using a CHN elemental analyzer.

1,4,7,10,13,16,21,24-Octaazabicyclo[8.8.8]hexacosa-4,6,13,-15,21,23-hexaene (2). Tren (8.20 g, 56.1 mmol) and 500 mL of 2-propanol were added to a 2-neck 1-L round-bottom flask equipped with a stir bar and an addition funnel containing a solution of glyoxal (13.6 g of a 40 wt % aqueous solution, 93.7 mmol) diluted to 200 mL with 2-propanol. The tren solution was cooled in an ice bath, and the glyoxal solution was added dropwise (1 drop/2–3 s) allowing for complete dispersion of each drop between additions. After 3 h approximately one-half of the glyoxal solution had been added, and the rate of addition was increased to 1 drop/s. After all of the glyoxal was added (5 h total), the clear yellow solution was allowed to stir at room temperature for 1 h. The solvent was then removed under vacuum yielding an orange solid which was mixed with 200 mL of $CHCl_3$ and stirred at rt for 2 h. A pale orange solid was removed by filtration and 3 g of Celite was added to the filtrate. The $CHCl_3$ was removed under vacuum and the resulting solid material transferred into a cellulose Soxhlet thimble. Crude cryptand **2** was extracted using a mixture of 400 mL of hexane and 100 mL of heptane over a period of 60 h, and the resulting cloudy extract was clarified by vacuum filtration. The solvent was removed under reduced pressure to give 5.23 g of **2** (52% yield): mp 125–140 °C dec; IR (mull) 1630 (C=N), 2795 cm^{-1} (=CH); ^{1}H NMR ($CDCl_3$) δ 7.70 (s, 6 H$_c$), 3.52 (t, 12 H$_b$), 2.71 (t, 12 H$_a$); ^{13}C NMR ($CDCl_3$) δ 163.6, 59.5, 52.9. Anal. Calcd for $C_{18}H_{30}N_8$: C, 60.31; H, 8.44; N, 31.26. Found: C, 60.46; H, 8.70; N, 31.49.

1,4,7,10,13,16,21,24-Octaazabicyclo[8.8.8]hexacosane (3). Method a. Cryptand **2** (5.08 g, 14.2 mmol) was dissolved in 200

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(23) The cryptand 2 crystallized from hexane in the orthorhombic space group $P2_12_12_1$ with unit cell parameters given in Table I. The Laue symmetry was determined by precession photographs and the space group was confirmed by successful refinement. Data were collected while two intensity standards were monitored every 2 h of X-ray exposure time. The orientation of the same two reflections was monitored after every 200th scan. The data was corrected for Lorentz and polarization effects. Hydrogen atoms were observed in the difference Fourier map. The atomic coordinates for 2 have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

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(25) The cryptand 3 crystallized from water in the hexagonal space group $R32$ with unit cell parameters given in Table I. The Laue symmetry was determined by rotation photographs and the space group was confirmed by successful refinement. Data were collected while two intensity standards were monitored every 2 h of X-ray exposure time. The orientation of the same two reflections was monitored after every 200th scan. The data was corrected for Lorentz and polarization effects. Hydrogen atoms were observed in the difference Fourier map. The atomic coordinates for 3 have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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Table II. Average Centroid–Heteroatom Distances for [2.2.2] Cryptands[a,b]

	1a[c] (gauche) 	3 (gauche) 	1b[d] (anti) 	2 (anti) 
average dihedral angle (deg)	70.12 (2.87)	65.18	177.52 (1.83)	169.87 (2.28)
BN[e]–centroid distance (Å)	2.995 (0.013)	3.181 (0)	3.436 (0.072)	3.419 (0.011)
NBH[f]–centroid distance (Å)	2.648 (0.121)	2.817 (0)	2.973 (0.509)	2.929 (0.112)

[a] The centroid is defined as the center of gravity of the eight heteroatoms. [b] Numbers in parentheses are the standard deviations of the mean of two distances for the bridgehead nitrogens and six distances and three dihedral angles for the six nonbridgehead heteroatoms. [c] Reference 28. [d] Reference 29. [e] Bridgehead nitrogen. [f] Nonbridgehead heteroatom.

mL of dry THF in a 500-mL flask and the solution was cooled to −78 °C under a nitrogen atmosphere. LAH (43 mL of 1 M LAH in THF, 43.0 mmol) was added slowly via syringe. The solution was allowed to warm to room temperature and was then refluxed for 1.5 h during which time it became cloudy. The reaction mixture was then cooled to −78 °C and 10 mL of water was added dropwise. The resulting mixture was vacuum filtered through Celite, and the filtrate (designated A) was set aside. The filter pad was extracted with 300 mL of boiling THF (3×). After filtration the extracts were combined, and the solvent was removed under reduced pressure. Recrystallization of the resulting solid from THF yielded 3.78 g (10.2 mmol) of **3** as a white solid. The filter pad was further extracted (3×) with 400 mL of a 1:1 mixture of refluxing ethanol/THF. These extracts were combined with the original THF filtrate A. Removal of the solvent under reduced pressure gave a yellow solid which was recrystallized from water to yield 0.90 g of **3**·4H_2O (2.04 mmol, determined by titration after drying under ambient conditions[30]). The total yield of purified **3** was 86%: mp 105 °C; IR (mull) 3250 cm^{-1} (NH); ^{1}H NMR (D_2O, pD = 11.8) δ 2.76 (s, 12 H_c), 2.66 (m, 12 H_b), 2.49 (m, 12 H_a); ^{13}C NMR (D_2O, pD = 11.8) δ 55.2, 51.5, 49.1. Anal. Calcd for $C_{18}H_{40}N_{8}1.3H_{2}O$: C, 54.94; H, 11.41; N, 28.47. Found: C, 55.05; H, 11.38; N, 28.33.

Method b. To a flask was added 0.50 g (1.4 mmol) of **2** and 1.0 g (26 mmol) of $NaBH_4$ in 120 mL of MeOH. The cloudy reaction solution was stirred under argon at 25 °C for 4 h. Removal of the reaction solvent under reduced pressure gave a white solid which was recrystallized from a minimum volume of water to give a white powder. Further product was obtained from the mother liquors by evaporating half the solvent and cooling in a ice–salt bath. The combined products were sublimed at 10^{-3} torr and 105 °C. The overall reaction yield was 85%.

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(30) The hydration number of **3** varies according to the sample treatment. Samples can be dried under vacuum at 50 °C overnight, but the resulting powder is hygroscopic.