New Cryptaspherands and Their Complexation Properties with the Alkali Metal Ions

Krzysztof E. Krakowiak,† Jerald S. Bradshaw,*,‡ Chengyue Zhu,‡ Jon K. Hathaway,‡ N. Kent Dalley,‡ and Reed M. Izatt‡

IBC Advanced Technologies, Inc., P.O. Box 656, Provo, Utah 84606, and Department of Chemistry, Brigham Young University, Provo, Utah 84602-4672

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New cryptaspherands **5–7** were prepared in 50–63% yields by treating 1 mol of the appropriate dioxa- or oxaalkanediamine with 2 mols of 2,6-bis[3-(bromomethyl)-2-methoxy-5-methylphenyl]-4-methylanisole in acetonitrile using Na_2CO_3 as the base. The affinities of these ligands for the alkali metal ions in a $CHCl_3$–DMSO mixture were determined by a titration calorimetric procedure. The resulting log K, ΔH, and $T\Delta S$ values are compared to those for the interaction of two cryptahemispherands (**3** and **4**) prepared by the reported procedures. The more rigid cryptaspherands **5-7** were more selective for Cs^+ over K^+ or Na^+ than the cryptahemispherands. The structure of new nitro-substituted cryptahemispherand **3** was determined by X-ray diffraction methods.

Introduction

The alkali metals are complexed most strongly with rigid macrocycles such as the spherands,[1] cryptahemispherands,[2] calixspherands,[3] torands,[4] and cryptands[5] (see Figure 1). An extensive review of the complexing properties of all types of macrocycles including the rigid systems shown in Figure 1 has been published.[6] Most of the applications of macrocyclic ligands concern the removal of metal ions from aqueous solutions. These applications require high metal ion–ligand stability constants and metal ion selectivities. This is particularly true when using ligands bonded to solid supports[7] and in clinical chemistry for the determination of lithium, sodium, and potassium ions.[8] One major problem in studying the interaction of these rigid systems with various guest species is that the macropolycycles are insoluble in water, and stability constants must be determined in nonaqueous solvents such as $CHCl_3$ saturated with water.

Table 1 shows the stability constants for the interaction of various rigid ligands with some of the alkali metal ions in water-saturated $CHCl_3$. All of these rigid ligands form strong complexes with the alkali metal ions studied. Some are selective for certain metal ions such as the spherand which is selective for Li^+ with a log K greater than 16.9[1c] (see Table 1). The log K values for the interaction of cryptand 222 for Na^+ and K^+ in water are 3.9 and 5.4, and in $CHCl_3$ saturated with water, 10.6 and 13.2, respectively. Therefore, the log K values for the interaction of the rigid ligands with the alkali metal ions are probably six or more log K units less in water than in $CHCl_3$ saturated with water. Thus, the classes of ligands listed in Table 1 could be useful in applications involving complexation of the alkali metal ions in aqueous solutions. Other classes of macrobicyclic ligands, such as cryptands with carbon bridgehead atoms (see Figure 1) prepared by Parsons and co-workers, also form strong complexes with the alkali metal ions.[9]

The rigid macrocyclic ligands owe their high affinity for the alkali metal ions to their highly preorganized and rigid structures. Cram has suggested that even though each oxygen atom in the anisyl groups of the spherands and spherand-containing macrocycles has a weak affinity for a metal ion, preorganization of the macrocycle brings all possible binding sites into the proper position for

† IBC Advanced Technologies, Inc.

‡ Brigham Young University.

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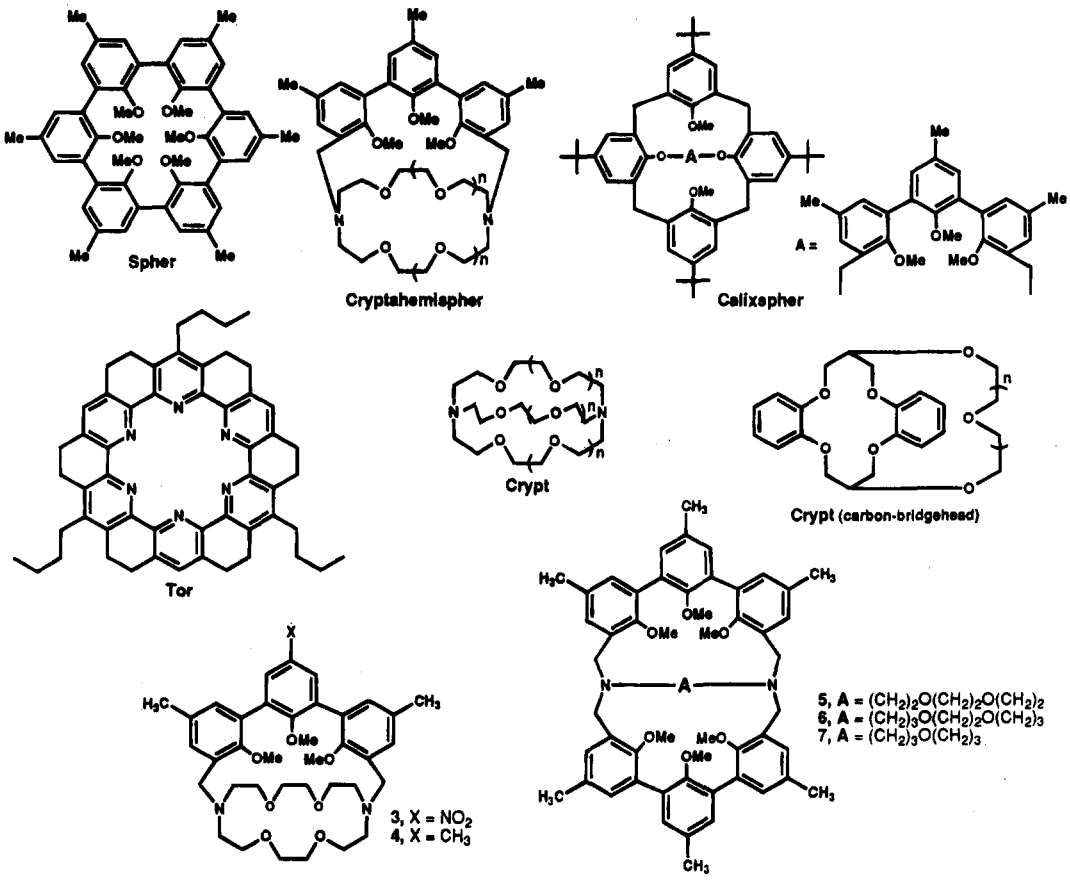


Figure 1. Structures of ligands.

Table 1. Reported Stability Constants (log *K*) for Alkali Metal Interaction with Various Rigid Ligands (Figure 1) in $CHCl_3$ Saturated with H_2O

				crypt[d]		cryptahemispher[e]	
cation	spher[a]	calixspher[b]	tor[c]	221	222	321	322
Li^+	>16.9		13.4				
Na^+	14.1	12.4	14.7	13.0	10.6	15.0	9.9
K^+		13.4	14.3	11.2	13.2	14.0	13.9
Rb^+					12.3		14.9
Cs^+							15.9

[a] Reference 1c. [b] Reference 3b. [c] Reference 4b. [d] Reference 5c. [e] References 2b and 2c.

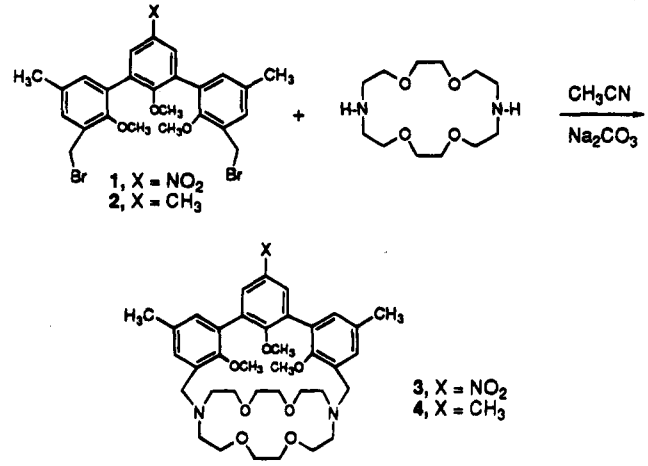
binding.[10] Rigidity in most of these ligands is provided by the aromatic rings. This lipophilic region encapsulates the metal ion, thereby helping to cause the high complex stability.

We herein report the preparation of three new rigid cryptaspherands (**5**–**7**) and a comparison of their affinities for certain alkali metal ions with that of cryptahemispherands **3** and **4**. The cryptaspherands are similar to the cryptahemispherands with the exception that one poly(ethylenedioxy) bridge of the cryptahemispherand has been replaced by a dimethylenetrianisyl bridge. This additional rigidity could increase their interactions with and selectivities for metal ions.

Results and Discussion

The first synthesis of the cryptahemispherands was carried out using the condensation of diacid dichlorides with appropriate diaza-crowns followed by a reduction step.[2a] The products were first isolated as hydroborane complexes and were purified using silica gel column chromatography. We prepared cryptahemispherands **3** and **4** from diaza-18-crown-6 and the appropriate bis-(bromomethyl)-substituted trianisyl compound (**1** or **2**) in acetonitrile as shown in Scheme 1. Preparation of starting materials **1** and **2** as well as the idea for this type of synthesis was patterned after the syntheses of cryptahemispherands by Cram and co-workers.[2b] According to those authors, it was impossible to purify the final free cryptahemispherand, such as **4**, on silica gel. Cryptahemispherands **3** and **4** produced a number of spots on silica gel TLC plates using various solvents. We believe that those spots are complexes of **3** or **4** with trace

Scheme 1. Preparation of Cryptahemispherands 3 and 4



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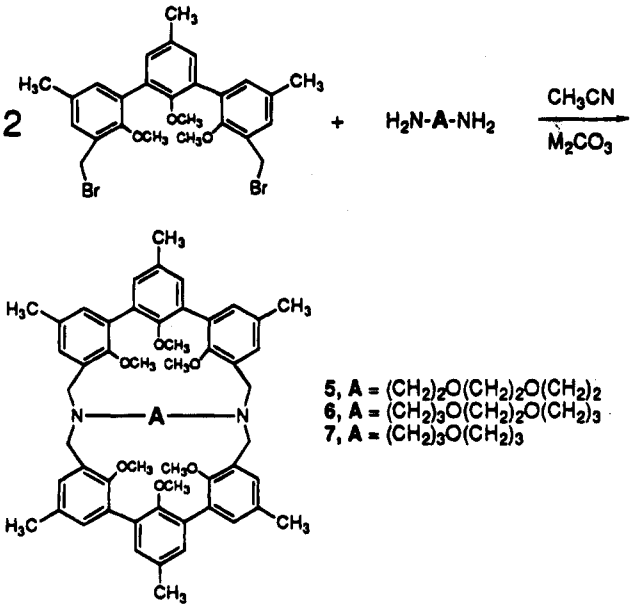
Scheme 2. Preparation of Cryptaspherands 5–7



cations which are present on silica gel or they could be inclusion complexes with the solvents. The cryptahemispherands gave only one TLC spot using water or CH_3OH as eluents because they form weaker cation complexes in those solvents. Free cryptahemispherands **3** and **4** were purified on silica gel using CH_3OH/NH_4OH as the eluent.

The synthesis of key starting compound **2** was performed as reported by two different authors.[1b,c,11] We found that the synthesis proposed by Reinhoudt and coworkers[11] for compound **2** is better because it is repeatable and purification of the products is easier. Synthesis of new starting compound **1** was performed using the published procedure[2b] except for the last step.

New cryptaspherands **5–7** (see Scheme 2) were prepared by a 2:1 cyclocondensation of compound **2** with the appropriate diamine in CH_3CN in the presence of an appropriate alkali metal carbonate. This 2:1 cyclocondensation is patterned after the synthesis of a variety of cryptands using a diamine and a dihalide or ditosylate.[12] These synthetic reactions are a great improvement on the usual method of preparation of the cryptands by first preparing a diaza-crown followed by a second reaction to connect the third arm. The pure, metal ion-free products were isolated by an aluminum oxide chromatographic process using nonpolar solvents. The nonpolar solvents do not extract the various trace metal ions from the aluminum oxide, resulting in a noncomplexed product. This greatly simplified the purification of these products.

Stability constants and enthalpy changes for the interactions of **3–7** with alkali metal ions were determined calorimetrically. Values of log K, ΔH, and ΔS for these interactions are given in Table 2.

Stability constants for the interaction of macrocyclic ligands with various metal ions in DMSO are usually

Table 2. Stability Constants and Thermodynamic Quantities Determined by Titration Calorimetry for Alkali Metal Cation Interactions with 3–7 in Chloroform–DMSO Mixtures[a]

ligand	cation	solvt[b] (v/v)	log K	ΔH (kJ·mol^{-1})	ΔS (J·mol^{-1}·K^{-1})
3	Cs^+	6C/4D	>5	−57.4(3)	
	K^+	6C/4D	>5	−54.8(2)	
	Na^+	6C/4D	3.60(5)	−17.2(4)	11.2
4	Cs^+	1C/1D	5.2(1)	−78.6(4)	−164.1
	K^+	1C/1D	5.4(1)	−59.6(3)	−96.5
	K^+	6C/4D	5.64(5)	−68.6(4)	−122.1
	Na^+	6C/4D	4.88(5)	−30.5(4)	−8.9
5	Cs^+	6C/4D	>5		
	K^+	6C/4D	4.8(1)	−29.7(4)	−7.7
	Na^+	6C/4D	NR		
6	Cs^+	1C/1D	3.82(4)	−12.1(1)	32.5
	K^+	1C/1D	NR		
	Na^+	1C/1D	NR		
7	Cs^+	1C/1D	2.80(3)	−10.5(1)	18.5
	K^+	1C/1D	NR		
	Na^+	1C/1D	NR		

[a] The uncertainty of each value in the last digit is given in parentheses. NR indicates that no reaction was observed. [b] C = chloroform, D = DMSO.

lower than those determined in H_2O.[6] Compounds **3–7** are soluble only in a mixture of $CHCl_3$ and no more than 50% DMSO. These DMSO–$CHCl_3$ mixtures were chosen for calorimetric measurements because the log K values were usually less than 6 and, therefore, amenable to determination by the calorimetric titration method. The usual NMR method to determine log K values in $CHCl_3$ saturated with D_2O was not used. The DMSO–$CHCl_3$ mixture should be similar to an H_2O–$CHCl_3$ mixture and therefore closer to what would be expected in H_2O rather than the H_2O-saturated $CHCl_3$.

As shown by CPK models, the cavity of the cryptaspherands is large and only Cs^+ (the largest alkali metal ion) is large enough to provide a close fit in the cavity. Indeed, for ligands **6** and **7**, stable complexes were observed with Cs^+ but those ligands did not interact with K^+ or Na^+ in our solvent system (Table 2). Ligand **5** also exhibited selectivity for Cs^+ over Na^+. Although the dimensions of the cavities of **5** and **7** are about the same, **5** has a much greater affinity for Cs^+. This could be a result of the additional oxygen donor atom in **5**. Ligands **5** and **6** have the same number of oxygen atoms but **6** has two propylene bridges in one of the arms. Macrocycles with propylene units between donor atoms always have weaker affinities for cations,[6] and likewise **6** formed a weaker complex with Cs^+ than did **5**.

The data in Table 2 also show that cryptahemispherands **3** and **4** are probably not selective for Cs^+ in this solvent system. These molecules have smaller cavity dimensions which more closely match K^+ and they are less rigid. It is interesting that **3** formed a weaker complex than **4** with Na^+. These two ligands should have the same cavity dimensions and the same number of oxygen donor atoms. The less negative ΔH value for complexation of Na^+ by **3** must be a result of the electron-withdrawing effect of the nitro group in **3**. In this case, the methoxy oxygen atom would have less affinity for the cation resulting in a less negative ΔH value. The positive ΔS values for the interaction of **3** with Na^+ indicates that the ligand is highly desolvated upon complexation. The ligand also has little conformation change because the methoxy oxygen atom is not strongly coordinated with the cation. The greater negative ΔH value for complexation of Na^+ by **4** shows an increased affinity of the ligand

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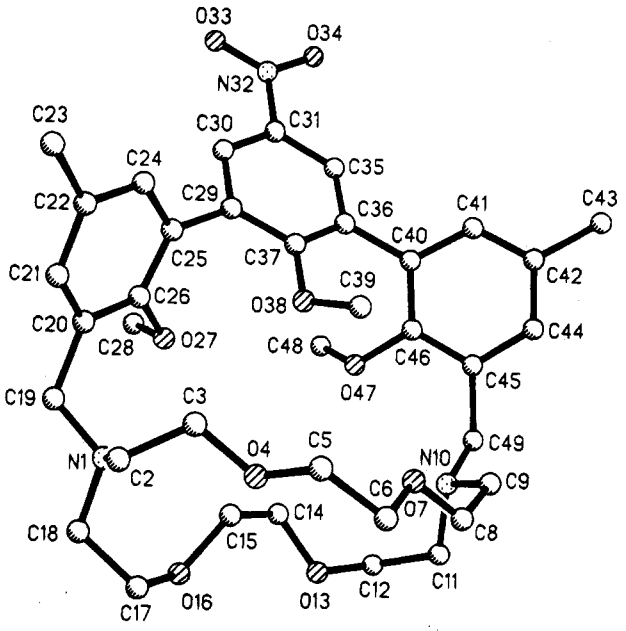

Figure 2.

for Na^+ presumably by the methoxy oxygen atom. The negative ΔS value indicates that there is a large conformational change in the ligand due to the increased coordination strength of the methoxy oxygen atom.

The structure of cryptahemispherand **3** has been established by an X-ray diffraction study (Figure 2). A direct comparison of the structures of **3** and **4** is not possible because the structure of uncomplexed **4** has not been reported, but Cram and co-workers[2a] have reported the structures of the Na^+, K^+, and Cs^+ complexes of **4**, and a comparison of **3** with the complexes of **4** is helpful. Replacing a CH_3 group of **4** with the NO_2 group on the middle benzene of the rigid preorganized spherand portion of the cryptahemispherand molecule (to form **3**) does not alter the structure of that portion of the molecule as will be shown below. However, the role of a cation in organizing the aza-crown portion of the macrocycle is evident in the conformational differences between the 18-membered rings of **3** and of complexed **4**. Since Cs^+ is the most complementary cation with **4**, the geometry of this complex is used in the comparison.

The major structural difference between uncomplexed **3** (Figure 2) and complexed **4** in the spherand-like module of the macrocycle is the N—N interatomic distance. These distances, 6.90 Å in **3** and 6.67 Å in complexed **4**,[2a] illustrate the attractive force of the Cs^+ for nitrogen atoms. The similarities of the spherand module in the uncomplexed **3** and complexed **4** are apparent in the orientation of the methoxy groups and also in the dihedral angles between the benzene rings. In both uncomplexed **3** and complexed **4**, the methoxy oxygens are oriented in such a way that their nonbonding electron pairs are pointing into the cavity. As a result, the methoxy carbon atoms of both compounds point out of the cavity with the carbons of the lateral benzenes directed out on one side of the aromatic framework and the methoxy carbon of the central benzene pointing out on the opposite side of this framework (Figure 2). The dihedral angles between the benzene groups range from 54.1° to 59.2° in **3** and from 55.7 to 56.5° in the Cs^+ complex of **4**. These similarities substantiate the statements of Cram and coworkers that this portion of the molecule is preorganized.[2a,10]

The 18 membered aza-crown ring in uncomplexed **3** is not preorganized, as was predicted by Cram.[2a] When an aza-crown ring forms a complex with a cation, the cation organizes the ring in such a way that the nonbonding electron pairs of the donor atoms point toward the cation in the cavity. As a result the X—C—C—X and C—X—C—C (X = O or N) torsion angles have values of approximately 60° and 180°, respectively. The metal ion—donor atom interatomic distances are approximately equal. In uncomplexed **3** only O4 is positioned so its nonbonding electron pair is pointed toward the potential cavity while the nonbonding electron pairs of the other oxygens are pointing in other directions, O7 up, O13 down, and O16 out of the potential cavity (see Figure 2). As a result, the X—C—C—X torsion angles range from 60° to 79° and the C—X—C—C torsion angles vary from 68° to 178°. The fact that the nonbonding electrons of the nitrogen atoms point toward the potential cavity of the molecule is a result of the rigidity of the spherand-like portion of the molecule. The effect of the Cs^+ is to organize the 18-membered ring with the Cs^+ being approximately equidistant from the donor oxygens (2.91 to 3.15 Å).[2a] The Cs^+—N interatomic distances are longer, 3.36 and 3.40 Å. This increase in interatomic distances is the result of the rigid spherand-like arm that joins the nitrogens. The longer Cs^+—N interatomic distance causes the 18-atom ring to be elliptical rather that circular.[2a] It is interesting to note one possible evidence of preorganization affecting the 18-membered ring of **3**. The least-squares plane of the donor atoms in the 18-membered ring is nearly parallel to the plane determined by the three methoxy oxygens of the spherand-like module. The dihedral angle between these planes is 2.8°. This allows a large entrance into the three-dimensional cavity of **3** for a cation.

The solid structure of **3** contains an ethanol of solvation. It lies below the aza-crown ring and is likely hydrogen bonded to O13. This is likely the reason that O13 points down in the structure. Unfortunately, the ethanol hydrogen atom could not be found so the presence of the H-bond could not be verified. However, the O15--O13 interatomic distance of 2.97 Å and the C25—O15—O13 angle of 105° are good evidence for the H-bond.

In summary, the spherand portions of **3** and complexed **4** are similar while the 18-membered rings differ considerably because of the organizing effect of Cs^+. Replacement of a methyl group by a NO_2 group (to form **3**) does not cause any significant structural differences in the spherand portion of the molecule. The less negative ΔH value for the complex of **3** compared to that of **4** with Na^+ is a result of the greater electron-withdrawing ability of the NO_2 group rather than the structural differences of the ligands. Experimental details, positional and thermal parameters, and structural data including bond lengths and bond angles for **3** are available.[13]

Experimental Section

Proton and carbon NMR spectra were obtained at 200 MHz in $CDCl_3$. Starting materials were purchased from Aldrich Chemical Co. unless otherwise stated. Compound **2** was

(13) X-ray structure data and experimental details are available from the Cambridge Crystallographic Data Centre. The coordinates, structural data, and experimental details can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 IEZ, U.K.

prepared as reported.[1b,c,11] Purities of all compounds were checked on TLC in two different solvent systems.

2,6-Bis[3-(bromomethyl)-2-methoxy-5-methylphenyl]-4-nitroanisole (1). 2,6-Bis[3-(methoxymethyl)-2-methoxy-5-methylphenyl]-4-nitroanisole[2b] (8 g, 16.6 mmol) was dissolved in 750 mL of $CHCl_3$. Anhydrous HBr gas was bubbled into the stirred solution for at least 2 h at rt. The progress of the reaction was checked by silica gel TLC (toluene/ethanol 100/1). Stirring was continued for 1 h, 1 L of water was added, and the mixture was stirred for 30 min. The separated organic layer was dried ($MgSO_4$), and the solvent was evaporated. The residue was chromatographed on silica gel using toluene/ethanol 100/1 to give 6.5 g (68%) of **1**: ^1H NMR δ 2.3 (6 H), 3.3 (s, 3 H), 3.57 (s, 6 H), 4.6 (s, 4 H), 7.1–7.3 (m, 4 H), 8.3 (s, 2 H). A satisfactory elemental analysis was obtained for **3**, a derivative of **1**.

36,37,38-Trimethoxy-5,15-dimethyl-10-nitro-22,25,30,-33-tetraoxa-1,19-diazapentacyclo[17.8.8.$1^{3,7}$.$1^{8,12}$.$1^{13,17}$]-octatriaconta-3,5,7(36),8,10,12(37),13,15,17(38)-nonaene (3) (Scheme 1). Compound **1** (1.88 g, 3.25 mmol) in 50 mL of CH_3CN and 0.85 g (3.24 mmol) of 1,7,10,16-tetraoxa-4,13-diazacyclododecane in 50 mL of CH_3CN were added simultaneously using syringe pumps over 6 h to the 200 mL of CH_3CN containing 15 g of powdered Na_2CO_3 under reflux. The mixture was stirred under reflux for 12 h. After cooling, the reaction mixture was filtered and the filtrate was evaporated. The residue was chromatographed on alumina (THF/ethanol) and then on a short silica gel column (CH_3OH/NH_4OH 50/1, 25/1, and 10/1) to give 1.12 g (51%) of **3**: ^1H NMR δ 2.35 (s, 6 H), 2.95 (s, 3 H), 3.5 (s, 3 H), 3.8 (s, 3 H), 2.5–3.9 (m, 26 H), 4.1 (d, 2 H, J = 10 Hz) 7.05–7.15 (m, 4 H), 8.3 (s, 2 H). Anal. Calcd for $C_{37}H_{49}N_3O_9$: C, 65.43; H, 7.37; N, 6.18. Found: C, 65.40; H, 7.15; N, 5.93.

36,37,38-Trimethoxy-5,10,15-trimethyl-22,25,30,33-tetraoxa-1,19-diazapentacyclo[17.8.8.$1^{3,7}$.$1^{8,12}$.$1^{13,17}$]-octatriaconta-3,5,7(36),8,10,12(37),13,15,17(38)-nonaene (4) (Scheme 1). Compound **2** (1 g, 1.8 mmol) in 60 mL of CH_3CN and 0.38 g (1.8 mmol) of 1,7,10,16-tetraoxa-4,13-diazacyclooctadecane in 60 mL of CH_3CN were added simultaneously using syringe pumps to 150 mL of CH_3CN containing 5 g of anhydrous Na_2CO_3 under reflux over a period of 24 h. The resulting mixture was stirred under reflux for 18 h. The solution was cooled and evaporated, CH_2Cl_2 was added, and the resulting solid was filtered. The solvent was removed under reduced pressure, and the residue was purified on alumina (THF/ethanol 5/1) and then on silica gel (CH_3OH/CH_2Cl_2 1/1, $CH_3OH/CH_2Cl_2/NH_4OH$ 20/20/2, 20/20/4, and 20/20/8) to give 0.41 g (35%) of **4**. **4** exhibited the same NMR spectra as that reported.[2a]

45,46,47,48,49,50-Hexamethoxy-5,10,15,23,28,33-hexamethyl-39,42-dioxa-1,19-diazaoctacyclo[17.17.8.-$1^{3,7}$.$1^{8,12}$.$1^{13,17}$.$1^{21,25}$.$1^{26,30}$.$1^{31,35}$]pentaconta-3,5,7(45),8,10,12-(46),13,15,17(47),21,23,25(48),26,28,30(49),31,33,35(50)-octadecaene (5) (Scheme 2). Compound **2** (1.1 g, 2.05 mmol) and 0.15 g (1.0 mmol) of 3,6-dioxa-1,8-octanediamine each in 30 mL of CH_3CN were added simultaneously using syringe pumps to a stirred mixture of 50 mL of CH_3CN and 4 g of Na_2CO_3 over a 12-h period under reflux. The resulting mixture was stirred under reflux for 36 h. The mixture was cooled and filtered, and the solvent was removed under reduced pressure. The residue was purified by alumina chromatography (toluene/ethanol 100/10 and then 50/1). The solvent was evaporated, and the residue was mixed with a small amount of CH_3OH and filtered to give 0.53 g (58%) of **5**: ^1H NMR δ 2.3–2.4 (few s, 18 H), 2.8 (s, 3 H), 2.92 (s, 3 H), 3.33 (s, 6 H), 3.72 (s, 6 H), 2.45–3.7 (m, 16 H), 3.94 (d, 2 H, J = 10 Hz), 4.3 (d, 2 H, J = 10 Hz), 6.9–7.2 (m, 12 H). Anal. Calcd for $C_{58}H_{68}O_8N_2$: C, 75.62; H, 7.44. Found: C, 75.80; H, 7.29.

47,48,49,50,51,52-Hexamethoxy-5,10,15,23,28,33-hexamethyl-40,43-dioxa-1,19-diazaoctacyclo[17.17.10.-$1^{3,7}$.$1^{8,12}$.$1^{13,17}$.$1^{21,25}$.$1^{26,30}$.$1^{31,35}$]dopentaconta-3,5,7(47),8,10,-12(48),13,15,17(49),21,23,25(50),26,28,30(51),31,33,35(52)-octadecaene (6) (Scheme 2). Macrocycle **6** was prepared as **5** above except 0.18 g (1.0 mmol) of 4,7-dioxa-1,10-decanediamine was used to give 0.51 g (53%) of **6**: ^1H NMR δ 1.5 (m, 4 H), 2.20–2.40 (few s, 18 H), 3.18 (s, 3 H), 3.25 (s, 3 H), 3.35 (s, 3 H), 3.6 (s, 3 H), 2.5–3.8 (m, 22 H), 4.2–4.4 (m, 4 H), 6.9–7.25 (m, 12 H). Anal. Calcd for $C_{60}H_{72}O_8N_2$: C, 75.92; H, 7.65. Found: C, 76.14; H, 7.44.

44,45,46,47,48,49-Hexamethoxy-5,10,15,23,28,33-hexamethyl-40-oxa-1,19-diazaoctacyclo[17.17.7.-$1^{3,7}$.$1^{8,12}$.$1^{13,17}$.$1^{21,25}$.$1^{26,30}$.$1^{31,35}$]nonatetraconta-3,5,7(44),8,-10,12(45),13,15,17(46),21,23,25(47),26,28,30(48),31,33,35-(49)-octadecaene (7) (Scheme 2). Macrocycle **7** was prepared as **6** above except 0.13 g (1.0 mmol) of 4-oxa-1,8-octanediamine was used to give 0.61 g (68%) of **7**: ^1H NMR δ 1.2–1.4 (m, 4 H), 2.30–2.38 (three s, 18 H), 2.82 (s, 3 H), 2.9 (s, 3 H), 3.08 (s, 6 H), 3.4 (s, 6 H), 2.8–3.7 (m, 12 H), 3.9 (d, 2 H, J = 11 Hz), 4.27 (d, 2H, J = 11 Hz), 6.9–7.2 (m, 12 H). Anal. Calcd for $C_{58}H_{68}O_7N_2$: C, 76.96; H, 7.57. Found: C, 77.04; H, 7.57.

Calorimetric Determinations. Values of log K, ΔH, and $T\Delta S$ for the complexes of **3–7** with the alkali metal ions were determined calorimetrically using a Tronac 450 isoperibol titration calorimeter.[14] Analysis of the raw data was done on a VAX computer using programs developed in our laboratory.[14]

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Note Added in Proof. New calixspherands with ethoxy instead of methoxy substituents have recently been reported.[15] These new calixspherands formed slightly more stable complexes with Na^+ and K^+ than those reported in Table 1.

Supplementary Material Available: ^1H NMR spectrum and MS for **1** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in microfiche version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.

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