(9) This system deserves a thorough study because of its unusual character. The mechanisms of eq 1 and 2 could be differentiated through kinetic studies. Conformational reorganizations undoubtedly accompany the monoanion going to the dianion (the C–O⁻ groups should move from mutually convergent to divergent positions). This change should be detectable by ^{1}H NMR spectral changes.
(10) R. P. Bell, "The Proton in Chemistry", Cornell University Press, Ithaca, N.Y., 1959, p 120.
(11) (a) M. Calvin and R. Wilson, *J. Am. Chem. Soc.*, **67**, 2003–2007 (1945); (b) F. J. C. Rossotti and H. Rossotti, "The Determinations of Stability Constants", McGraw-Hill, New York, 1961; (c) L. G. van Uitert, W. C. Fernelius, and B. E. Douglas, *J. Am. Chem. Soc.*, **75**, 451–455, 457–460, 2736–2738 (1953).
(12) Since CPK models provide only one metal of a diameter of about 2.5 Å, a series of graded ball bearings has been inserted into the cycles to estimate the diameters of the cavities.
(13) M. Newcomb, S. S. Moore, and D. J. Cram, *J. Am. Chem. Soc.*, **99**, 6405–6410 (1977).
(14) W. Braker, E. J. Pribyl, J. T. Sheehan, E. R. Spitzmiller, and W. A. Lott, *J. Am. Chem. Soc.*, **69**, 3072–3078 (1947).
(15) W. Baker, K. M. Buggle, J. F. W. McOmie, and D. A. M. Watkins, *J. Chem. Soc.*, 3594–3603 (1958).

Host–Guest Complexation. 16. Synthesis and Cation Binding Characteristics of Macrocyclic Polyethers Containing Convergent Methoxyaryl Groups[1,2]

Karl E. Koenig, George M. Lein, Peter Stuckler,[3] Takahiro Kaneda, and Donald J. Cram*

Contribution from the Department of Chemistry, University of California, Los Angeles, California 90024. *Received November 2, 1978*

Abstract: The syntheses and free energies of association of 12 new macrocyclic ligand systems (hosts) with alkali metal and ammonium and alkylammonium picrates in $CDCl_3$ are reported at 25 °C. Ten of the hosts were composed of 4-methylanisole units (abbreviated AN) incorporated into the macroring by substitution at their 2,6 positions by CH_2O (MO) units, or by direct attachment to other AN units at *their* 2,6 positions. The macrorings were completed with CH_2CH_2 (E) units and additional ether oxygens (O). Their structures were AN(MOEO)$_2$E (**22**), AN(MOEOE)$_2$O (**23**), AN(MOEOEO)$_2$E (**24**), AN(MOEOM)$_2$AN (**31**), AN(MOEOEOM)$_2$AN (**32**), ANAN(MOEO)$_2$E (**33**), ANAN(MOM)$_2$ANAN (**35**), ANAN(MSM)$_2$ANAN in which S is sulfur (**36**), ANANAN(MOE)$_2$O (**37**), and ANANAN(MOM)$_2$AN (**38**). The other two ligand systems were (AN)$_2$DP(OEOEO)$_2$E (**39**) and DP(OEOEO)$_2$E (**40**), in which DP = 5,5′-dimethyldiphenyl substituted in the 2,2′ positions with O and the 3,3′ positions with either H or 2-methoxy-5-methylphenyl (AN) groups. These systems were compared with model macrocyclic ethers not containing anisole units. Generalizations are as follows. The $-\Delta G_{av}°$ of association of hosts (kcal/mol) in $CDCl_3$ with Li^+, Na^+, K^+, Rb^+, Cs^+, and NH_4^+ picrates allowed the hosts to be graded as general ligand systems as follows: ANANAN(MOE)$_2$O (10.2); dicyclohexano-18-crown-6 (9.3); (AN)$_2$DP(OEOEO)$_2$E (9.0); 2,3-naphtho-18-crown-6 (8.7); ANAN(MOEO)$_2$E (8.2); DP(OEOEO)$_2$E (7.1); AN(MOEOE)$_2$O (7.0); AN(MOEOEO)$_2$E (6.6); ANANAN(MOM)$_2$AN (5.8); 1,3-benzo-18-crown-5 (5.7); AN(MOEO)$_2$E (5.5); AN(MOEOEOM)$_2$AN (5.0); AN(MOEOM)$_2$AN (4.5); ANAN(MOM)$_2$ANAN (4.4); ANAN(MSM)$_2$ANAN (4.1). General ion selectivity of each ligand system was measured by the difference in free energies between the best and poorest bound of the picrate salts, $-\Delta(\Delta G_{max})$ (kcal/mol). The order was as follows: ANANAN(MOE)$_2$O (5.3), $Na^+ > Li^+$; (AN)$_2$DP(OEOEO)$_2$E (4.8), $K^+ > Li^+$; 2,3-naphtho-18-crown-6 (4.8), $K^+ > Li^+$; 1,3-benzo-18-crown-5 (4.2), $NH_4^+ > Li^+$; dicyclohexano-18-crown-6 (4.1), $K^+ > Li^+$; ANANAN(MOM)$_2$AN (3.8), $Na^+ > Li^+$; ANAN(MOEO)$_2$E (3.3), $K^+ > Li^+$; AN(MOEOEO)$_2$E (3.2), $Cs^+ > Li^+$; AN(MOEOE)$_2$O (3.1), $K^+ > Li^+$; DP(OEOEO)$_2$E (2.6), $K^+ > Li^+$; AN(MOEOEOM)$_2$AN (1.6), $K^+ > Li^+$; ANAN(MSM)$_2$ANAN (1.1), $K^+ > NH_4^+$; AN(MOEO)$_2$E (1.0), $K^+ > Li^+$; AN(MOEOM)$_2$AN (0.9), $K^+ > Li^+$. These results demonstrate that, when the oxygens of anisole units are held in sterically enforced conformations which make the unshared electron pairs provide the lining of partially spherical cavities, the anisole units become better and more selective complexers of anions than the now classic crown ether compounds. Such conformations are observed only when *m*-teranisyl units are incorporated in macroring systems.

Aryl units possess certain properties useful in the design and synthesis of host compounds. Aromatic nuclei and their attached atoms ordinarily are coplanar and tend to rigidify molecules of which they are a part. They possess many substitutable positions for placement of functional groups in desired positions of hosts. The electronic character of aromatic systems can be varied over a wide range by attachment of appropriate substituents. Aryl units provide hosts with physical properties that aid experimental manipulation and detection. Their magnetic ring currents are sometimes useful in the determination of the structures of complexes in solution. Aryl–aryl bonds are stable to most chemical reagents and to irradiation. Appropriately substituted polyaryl units possess enforced conformations that provide hosts with desired symmetry properties. Polyaryl units incorporated in macrocycles can be used to prevent cavities designed for guest complexation from being blocked by flexible chains folding back on themselves.

This paper reports the synthesis and ligand properties of 12 new hosts designed to bind metal and ammonium cations. The binding sites are $ArOCH_3$ and CH_2OCH_2 units strung together in various combinations that provide differing degrees of enforced molecular organization. The overall goal of the research was to identify structural parameters that control the complementary relationships between potential ligand systems and metal, ammonium, and alkylammonium cations. A second goal was to develop feasible methods of synthesizing rigid polyaryl systems, and a third was to determine the utility of Corey–Pauling–Koltun (CPK) molecular models in predicting and correlating the binding properties of molecules.

Results

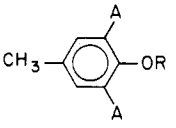
Design and Synthesis of Ligand Systems. The new macrocycles studied all contain one to four 4-methylanisole groups incorporated into the major ring system by substitution in their

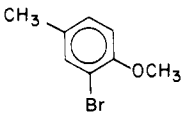
0002-7863/79/1501-3553$01.00/0 © 1979 American Chemical Society

2,6 positions or on their OCH_3 carbons. In CPK molecular models of the hosts reported, the OCH_3 groups of the anisole units tend to converge on the center of the macrocycle. In all of them, the unshared electron pairs of the oxygens are potential binding sites for cations. The degree of enforced convergence and the conformations of the CH_3O groups depend on the cycle size and the numbers and placements of the aryl units with respect to one another. The methyl groups in the divergent 4 positions of the benzene rings serve as blocking groups that prevent unwanted substitution reactions from occurring during syntheses.

Compounds **1–7** served as starting materials for those cycles

	R	A
1	H	CH_2OH
2	CH_3	CH_2OH
3	CH_3	CH_2Br
4	CH_3	CHO
5	H	CHO
6	CH_2OCH_3	CHO
7	CH_2OCH_3	CH_2OH

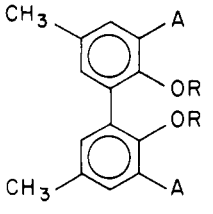




8

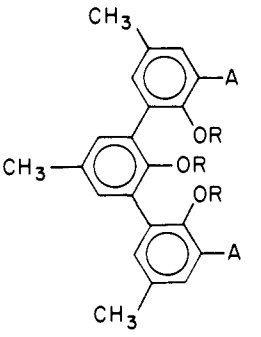
whose 4-methylanisole groups were not bonded directly to one another. Formylation[4] of *p*-cresol in the presence of base gave diol **1** (45%), which was selectively methylated ($(CH_3)_2SO_4$) to give diol **2** (84%). The two hydroxymethyl groups of **2** were converted with $SOBr_2$ to the bromomethyl groups of **3** (~100%). Compounds **2** and **3** served as starting materials for ring closures (see below). Since we wished ultimately to compare the binding properties of $ArOCH_3$ with those of ArOH units, compound **7**, which contained the easily hydrolyzable $ArOCH_2OCH_3$ group, was desired. Attempts to prepare **7** directly from **1** gave unwanted cycles and polymers. Accordingly, **2** was oxidized (MnO_2)[5] to dialdehyde **4** (78%) which was demethylated (BBr_3) to give **5** (82%), which in turn was methoxymethylated ($ClCH_2OCH_3$) to provide **6** (91%). This compound was reduced ($NaBH_4$) to **7** (89%).

The accumulative effect of anisole units bound directly to one another in the cycles on the binding properties of hosts appeared worth examining. To prepare the desired biphenyl compounds, two molecules of **8** were coupled by lithiation and oxidation ($CoCl_2$)[6] to give **9**[7] (42%), which was readily demethylated (BBr_3) to give **10**[7] (99%). Compound **9** was also dilithiated ($(CH_3)_2NCH_2CH_2N(CH_3)_2$-BuLi) and the resulting organometallic was carbonated to give diacid **11** (66%), reduction (BH_3·THF) of which gave diol **12** (100%). This diol with HBr gave dibromide **13** (90%), which, with thiourea as nucleophile, led to dithiol **14** (92%). Compounds **12–14** were used in the ring closures (see below).



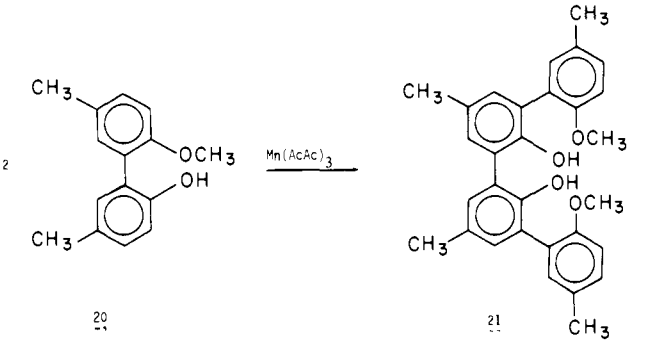
	R	A
9	CH_3	H
10	H	H
11	CH_3	CO_2H
12	CH_3	CH_2OH
13	CH_3	CH_2Br
14	CH_3	CH_2SH

In connection with the preparation of hosts containing *m*-terphenyl units, the reported[8] oxidation of *p*-cresol with $FeCl_3$·$6H_2O$ to give **15** was studied in detail. Yields as high as 39% were realized. The three hydroxyl groups of **15** were methylated ($(CH_3)_2SO_4$) to provide **16** (71%), which was dilithiated ($(CH_3)_2NCH_2CH_2N(CH_3)_2$-BuLi) and carbonated to provide diacid **17** (93%). Reduction of this diacid with BF_3·THF gave the desired diol **18** (93%), which, with PBr_3, gave dibromide **19**. Both **18** and **19** provided materials useful for ring-closing reactions.

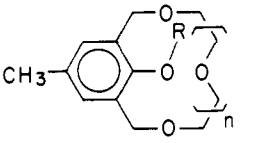


	R	A
15	H	H
16	CH_3	H
17	CH_3	CO_2H
18	CH_3	CH_2OH
19	CH_3	CH_2Br

The all-meta tetraaryl unit **21** was prepared as follows. The biphenyl derivative **10** was monomethylated with 1 equiv of $(CH_3)_2SO_4$ and K_2CO_3 to give **20**[9] (90%), which, with $Mn(acac)_3$,[10] gave **21** (50%).

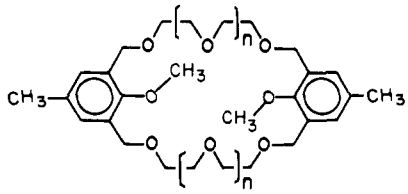


Macroring systems **22–24** containing one anisole unit each were prepared by high-dilution cyclization reactions[11] in which an equimolar amount of a reactive bisbenzyl bromide and a poly(ethylene glycol)[12] in the same dry THF solution were added slowly in such a way as to be further diluted by THF in the reflux return of a boiling mixture of NaH in THF. The diol and dibromide did not react with one another in the absence of base. When the mixture contacted the NaH, the diol formed the dialkoxide immediately, which in turn reacted rapidly with the dibromide before the reactants accumulated. By this technique, **22**, **23**, and **24** were prepared from dibromide **3** and



	n	R	Line formula
22	2	CH_3	$AN(MOEO)_2E$
23	3	CH_3	$AN(MOEOE)_2O$
24	4	CH_3	$AN\{MOEOEO\}_2E$
25	2	CH_2OCH_3	
26	3	CH_2OCH_3	
27	4	CH_2OCH_3	
28	2	H	
29	3	H	
30	4	H	

tri-, tetra-, and pentaethylene glycols[12] in 58, 49, and 59% yields, respectively. The same dibromide (**3**) with ethylene glycol gave **31** (14%), and with diethylene glycol gave **32** (26%)



31 n = 0, AN(MOEOM)$_2$AN
32 n = 1, AN(MOEOEOM)$_2$AN

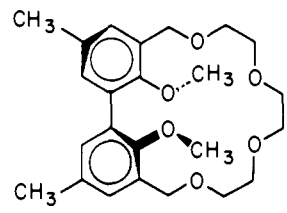
by the same technique. This yield pattern again illustrates the generalization that in oligomeric series the larger the number of bonds that must be made in a cyclization, the lower the yield of cycle. Higher cyclic oligomers and polymers produced in these and the other cyclization reactions described below were separated by gel permeation chromatography.

Cycles **25**, **26**, and **27** were prepared by the reactions of diol **7** and triethylene glycol, tetraethylene glycol, and pentaethylene glycol ditosylates reacting in the presence of NaH in THF under relatively low dilution conditions to give yields of 29, 34, and 34%, respectively. The acetal linkages of **25**, **26**, and **27** readily hydrolyzed in the presence of acid (pH 1) to produce macrocyclic phenols **28**, **29**, and **30** in essentially quantitative yields. After the appearance of our communication on the preparation and binding properties of the anisole unit containing cycles, others announced the synthesis and study of analogues of **22** and **23** in which hydrogen or nitro was substituted for the aryl methyl groups, and where R was either methyl or hydrogen. Interestingly, the authors found that the *O*-methyl groups could be removed from the anisole-containing cycles by heating them with LiI in pyridine to give the corresponding cyclic phenols.[13]

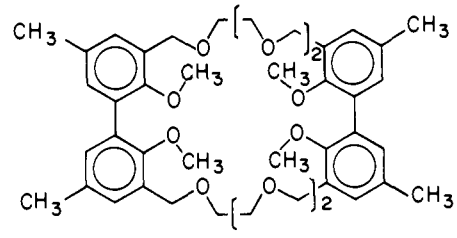
The multiplicity of the ArCH_2O proton chemical shifts in the ^{1}H NMR spectra of the 15-membered rings of **22** and **25** and of 18-membered cycle **26** indicated that the CH_3O or CH_3OCH_2O groups could not pass through the center of their macrorings rapidly enough on the instrument's time scale at ambient temperature to provide equivalent environments for these methylene protons. Equivalent magnetic environments were observed for all four benzyl protons in **23**, **24**, and **27–32** at ambient temperature. These observations correlate with expectations based on an examination of CPK molecular models of cycles **22–32**, and provide calibration for predicting from molecular model examination when cycles of these types should and should not undergo ring inversion rapidly on the ^{1}H NMR time scale at ordinary temperatures.

Macrocycle **33**, which contains the *o,o'*-dianisyl unit, was produced in 32% yield by the reaction (high dilution) of dibromide **13** with triethylene glycol and NaH. When diethylene glycol and **13** were used, cycle **34** containing two *o,o'*-dianisyl units was obtained (26%). The much more compact cycle **35**, which also contains two *o,o'*-dianisyl units, was prepared from dibromide **13**, diol **12**, and NaH in 18% yield. Its dithia analogue **36** was prepared in 18% yield from dibromide **13**, dithiol **14**, and NaH.

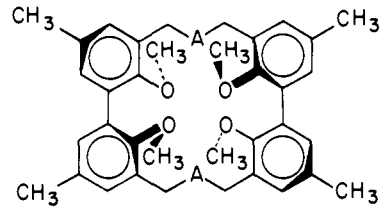
Molecular models of **33** suggest that at ambient temperature the two aryl groups cannot rotate with respect to one another. Therefore, the compound is probably chiral. Although the methoxyl groups can pass through the center of the macroring in molecular models of **33**, the poly(ethylene glycol) bridge is not long enough to allow the biaryl group as a whole to rotate through the macroring. Furthermore, the macroring is not large enough to allow the two aryl groups to rotate 180° with respect to one another *except by the two ortho methoxyl groups passing one another*. The conformation drawn for **33**



33, ANAII(MOEO)$_2$E



34, ANAN(MOEOEOM)$_2$ANAN

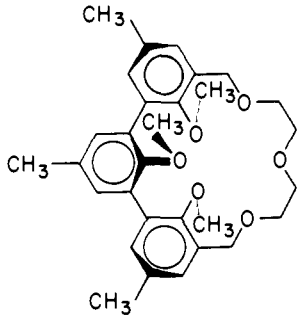


35, A = O; ANAN(MOM)$_2$ANAN
36, A = S; ANAN(MSM)$_2$ANAN

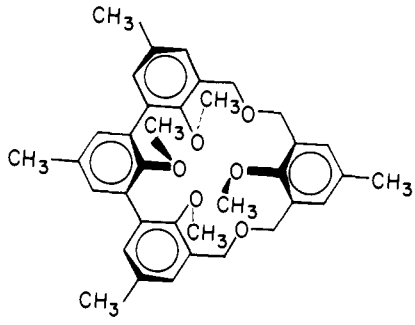
appears to be the most stable from models, and allows an all-gauche conformation for the poly(ethylene glycol) bridge. The compound in this conformation possesses a C_2 axis. In the ^{1}H NMR of **33** at 30 °C, the ArCH_2O protons appear as an A_2B_2 quartet. This suggests that the aryl groups are unable to pass one another at a rate rapid enough on the ^{1}H NMR time scale to average the chemical shifts of their benzyl protons.

Molecular models of **34** indicate that the central hole *is large enough* for one aryl to rotate 180° with respect to its attached aryl in such a way that *only ortho H and OCH_3 groups have to pass one another* for stereoisomer interconversion. That such rotations occur readily at room temperature is demonstrated by the observation that at 30 °C the ArOCH_3 protons in the ^{1}H NMR of the compound appear as a singlet. Thus these aryl–aryl rotations appear to be fast on the ^{1}H NMR time scale, and enantiomers and a meso form are probably in equilibrium at ambient temperature.

Molecular models of **35** and **36** indicate that, although the central rings are barely large enough to allow CH_3O groups to pass through the central hole, aryl groups cannot rotate 180° with respect to their attached aryl groups *without two ortho methoxyl groups* passing one another. In the synthesis of **35**, a mixture of stereoisomers was produced, as shown by the broad melting range of the material (correct analysis and molecular weight) and by its complex ^{1}H NMR spectrum. These isomers were not separated, but the sample obtained was undoubtedly a mixture of meso and racemic stereoisomers. In the synthesis of **36**, only one isomer was obtained. Its ^{1}H NMR spectrum provides an A_2B_2 splitting pattern for its ArCH_2S protons, which is predicted for either the meso or racemic diastereomers of the substance. In molecular models, either form can be assembled easily, but the racemic form appears considerably less sterically compressed, and the compound isolated



37, ANANAN(MOE)$_2$O



38, ANANAN(MOM)$_2$AN

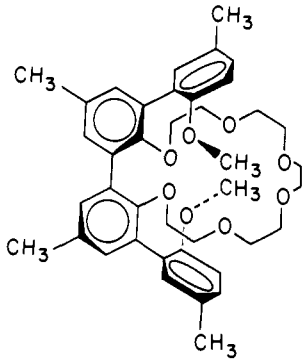
probably has that structure. Compound **37** contains the stereochemically interesting *m*-teranisyl unit. The macrocycle was prepared by the high-dilution method from dibromide **19**, diethylene glycol, and NaH in 49% yield. It was prepared by the same method without high dilution in 17% yield, and from diol **18** and diethylene glycol ditosylate without high dilution in 28% yield. In principle, two diastereomeric products might have been produced, since the central hole is much too small in any conceivable conformation to allow two methoxyl groups attached to adjacent aryls to pass one another. The ^{1}H NMR spectrum of the compound isolated demonstrated that it possessed the meso structure, **37.** The inner and outer $ArCH_3$ and $ArOCH_3$ possessed different chemical shifts, and the $ArCH_2O$ groups exhibited the anticipated A_2B_2 quartet. This structure was confirmed by an X-ray analysis of its crystalline complex with $(CH_3)_3CNH_3ClO_4$.[14]

Molecular model (CPK) examination of structure **37** indicates that it possesses little strain and allows an all-gauche arrangement for the OCH_2CH_2O groups. The structure contains a mirror plane. All oxygens face inward and their electron pairs converge on the center of the macroring. The three CH_3O groups possess enforced conformations that direct the methyl groups away from the center of the macroring along axes roughly normal to the best plane of the six oxygens.

A chiral structure diastereomeric to **37** can also be assembled with CPK molecular models. In this isomer, the two chiral elements arising from restricted rotation about the two Ar–Ar bonds are in a configuration which places the three oxygens of the $ArOCH_3$ groups almost on one line and the three oxygens of the $OCH_2CH_2OCH_2CH_2O$ group on a second line. The electron pairs of these oxygens do not converge on a spherical cavity as they do in structure **37**. This chiral structure, which is considerably more strained than its meso diastereomer (structure **37**), is unlikely to be formed in a ring closure and certainly not by a metal ion templated process.

Compound **38** contains four convergent anisole units, one of which is separated from the other three by two CH_2OCH_2 bridges. The compound was prepared by two methods, both involving high dilution. In the first, dibromide **19** and diol **2** with NaH gave **38** in 14% yield. In the second, dibromide **3** and diol **18** gave **38** in a 24% yield. Both samples possessed the same physical properties and ^{1}H NMR spectrum.

Molecular models (CPK) of only two reasonable structures can be constructed for compound **38**. Both possess the same configuration for the *m*-teranisyl unit found in simpler macrocycle **37**, and both contain a mirror plane. In the structure formulated (referred to as A), the methoxyl groups lying in the mirror plane are syn to one another, as are the two methoxyl groups on each side of that plane. In a second structure (referred to as B), the methoxyl groups lying in the mirror plane are anti to one another, whereas the two methoxyls on each side of the mirror plane are syn. In A, the methoxyl of the MANM group can essentially occupy the center of the hole. In B, the electron pairs of all six oxygens converge on the center of the hole and the methyls of the $ArOCH_3$ groups extend outward



39, (AN)$_2$DP(OEOEO)$_2$E

away from it. By careful conformational manipulation of the molecular models, A and B can be interconverted without breaking bonds by passing the OCH_3 group of the isolated anisyl unit through the center of the ring. It therefore seems probable that, at ambient temperature, A and B are in equilibrium with one another and that equilibration is fast even on the ^{1}H NMR time scale. No studies have yet been made of the temperature dependence of the ^{1}H NMR spectrum of this compound.

Macrocycle **39** was prepared in 39% yield by treating tetraaryl diol **21** with KOH and pentaethylene glycol ditosylate.[12] Molecular models of **39** indicate that the macroring is too small to allow the two central aryloxy units to rotate with respect to one another unless the two aryloxy oxygens can pass one another. It is not yet known whether this happens at ambient temperature. The models indicate that in an unstrained conformation the unshared electron pairs of eight oxygens neatly converge on a hole to provide a hexagonal bipyramidal arrangement of oxygens. For comparison purposes, cycle **40** was prepared (41%) from diol **10**, KOH, and pentaethylene glycol ditosylate.[12]

Determinations of Association Constants and Free Energies of Association between Ligand Systems and Metal and Ammonium Picrates. The association constants (K_a) of the macrocyclic ligand systems and metal, ammonium, or alkylammonium picrates in $CDCl_3$ at 24–26 °C were determined. The extraction technique was used in which Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and *t*-$BuNH_3^+$ picrates in aqueous solution were extracted with $CDCl_3$ both in the presence and absence of host. The amounts of picrate ion in both aqueous and $CDCl_3$ layers were determined from their extinction coefficients at 380 nm after appropriate dilution in CH_3CN.[15] The extraction constants (K_e) and distribution constants (K_d) were calculated from experimental measurements, in particular from *R* values, which are the molar ratios of picrate ion to host in the organic layer at equilibrium. Values of K_a, the host-guest association constant, were calculated from K_e and K_d and the definitions and relationships of eq 1–5 in which H is host.

$$[M^+Pic^-]_{CDCl_3} + [H] \overset{K_a}{\rightleftharpoons} [M^+ \cdot H \cdot Pic^-]_{CDCl_3} \quad (1)$$

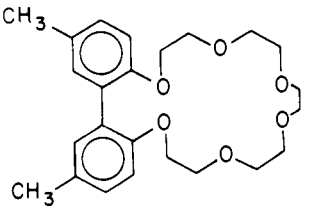
$$[M^+]_{H_2O} + [Pic^-]_{H_2O} + [H]_{CDCl_3} \overset{K_e}{\rightleftharpoons} [M^+ \cdot H \cdot Pic^-]_{CDCl_3} \quad (2)$$

$$[M^+]_{H_2O} + [Pic^-]_{H_2O} \overset{K_d}{\rightleftharpoons} [M^+Pic^-]_{CDCl_3} \quad (3)$$

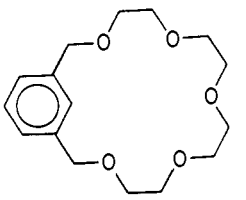
$$K_a = K_e/K_d \quad (4)$$

$$\Delta G^\circ = -RT \ln K_a \quad (5)$$

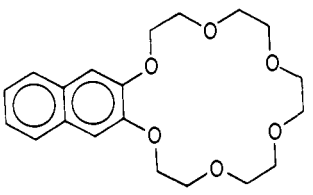
Complexation data for ligand systems **22–24**, **31–33**, and **35–43** are reported in Table I. Crown compounds **41–43** are



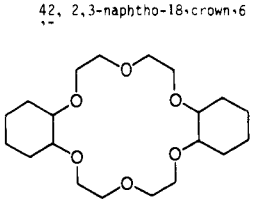
40, DP(OEOEO)$_2$E



41, 1,3-benzo-18-crown-5



42, 2,3-naphtho-18-crown-6



43, Dicyclohexano-18-crown-6

included for comparison purposes. Hosts 1,3-benzo-18-crown-5[15a] and 2,3-naphtho-18-crown-6[16] were available from earlier studies. The sample of dicyclohexano-18-crown-6 used is the commercial mixture rich in the cis,cis,syn and cis,cis,anti isomers. Values of K_a for 2,3-naphtho-18-crown-6 binding some of the picrate salts are slightly different from those reported previously[16] because of improvements in technique (see Experimental Section). Values of K_a calculated from extinction coefficients obtained from the aqueous and $CDCl_3$ layers agree well with one another as well as with values determined by ^1H NMR techniques when R values lie between 0.1 and 0.7. Values of R determined in $CDCl_3$ are more reliable when $R < 0.1$, and those determined in H_2O are more accurate with $R > 0.7$, since small differences between large numbers are not involved in these respective calculations of K_a and ΔG°. The values for all parameters reported in Table I were calculated from R values measured in $CDCl_3$ for all complexing partners when $R < 0.1$, and when none of the R values measured in $CDCl_3$ reached 0.5. When all R values for a particular host binding all ions except Li^+ were greater than 0.1 and at least one R value was greater than 0.5, the R, K_a, and ΔG° values were calculated from measurements on the aqueous layer. A random error analysis was made that included all of the physical measurements that contributed to $-\Delta G^\circ$ values.[15b] For the R values used, the precisions varied between ±1.4 and ±2.0% of the $-\Delta G^\circ$ values. Although the technique could be refined, particularly by increasing the volumes and amounts of hosts and guests used, finer distinctions are not needed for these investigations.

Discussion

Correlations between Structures of Ligand Systems and Their Free Energies of Association with Metal and Unsubstituted Ammonium Picrates. A context for discussion of structure-binding relationships is provided by the breadth of the free-energy scale involved. The total spread in $-\Delta G^\circ$ values between the best and poorest partner combinations that were measured for all ligand systems and Li^+, Na^+, K^+, Rb^+, Cs^+, and NH_4^+ picrates is about 9.8 kcal/mol. The best combination involved ANANAN(MOE)$_2$O binding Na^+ ($-\Delta G^\circ$ = 12.5 kcal/mol). The poorest involved 1,3-benzo-18-crown-5 binding Li^+ ($-\Delta G^\circ$ = 2.7 kcal/mol). The greatest spread in $-\Delta G^\circ$ values (8.3 kcal/mol) for any individual ion complexing the different ligand systems is with Na^+ complexing ANANAN(MOE)$_2$O ($-\Delta G^\circ$ = 12.5 kcal/mol) vs. AN-AN(MSM)$_2$ANAN ($-\Delta G^\circ$ = 4.2 kcal/mol). The maximum spread in $-\Delta G^\circ$ values for any individual ligand system complexing any of the six different ions is 5.3 kcal/mol. The host is ANANAN(MOE)$_2$O, which complexes Na^+ with $-\Delta G^\circ$ = 12.5 and Li^+ with $-\Delta G^\circ$ = 7.2 kcal/mol. These data indicate that, among the 15 ligand systems and 6 ions examined, the most vs. the least structural recognition of any host for any guest involves 9.8 kcal/mol free energy difference. Maximum structural differentiation of ligand system by a particular ion (Na^+) amounts to 8.3 kcal/mol, whereas maximum structural differentiation of ion by a particular ligand system (ANANAN(MOE)$_2$O) is 5.3 kcal/mol.

Table I characterizes each ligand system by the parameter $-\Delta G_{av}^\circ$, in which the $-\Delta G^\circ$ values associated with the five or six ions for which data was obtained are averaged. This parameter allows the hosts to be arranged in decreasing order of their *general complexing ability* in terms of $-\Delta G_{av}^\circ$ values (kcal/mol) as follows: ANANAN(MOE)$_2$O (10.2); dicyclohexano-18-crown-6 (9.3); (AN)$_2$DP(OEOEO)$_2$E (9.0); 2,3-naphtho-18-crown-6 (8.7); ANAN(MOEO)$_2$E (8.2); DP(OEOEO)$_2$E (7.1); AN(MOEOE)$_2$O (7.0); AN-(MOEOEO)$_2$E (6.6); ANANAN(MOM)$_2$AN (5.8); 1,3-benzo-18-crown-5 (5.7); AN(MOEO)$_2$E (5.5); AN-(MOEOEOM)$_2$AN (5.0); AN(MOEOM)$_2$AN (4.5); AN-AN(MOM)$_2$ANAN (4.4); ANAN(MSM)$_2$ANAN (4.1); ANAN(MOEOM)$_2$ANAN (too low to measure). *This order dramatically illustrates the importance of ligand organization to ion binding.* The best and poorest of the ligand systems contain both dianisyl and ethyleneoxy units, but differ in the numbers and particularly in the arrangements of these units.

Table I also characterizes each ligand system by the parameter $-\Delta(\Delta G^\circ)_{max}$, which indexes its general specificity toward the five or six ions in terms of the maximum difference in its free energies of association. This parameter allows the hosts to be arranged in decreasing order of their general ion specificities in free energy terms (kcal/mol) as follows: AN-ANAN(MOE)$_2$O (5.3), $Na^+ > Li^+$; (AN)$_2$DP(OEOEO)$_2$E (4.8), $K^+ > Li^+$; 2,3-naphtho-18-crown-6 (4.8), $K^+ > Li^+$;

Table I. Equilibrium and Free Energy Parameters for Association between Hosts and Metal or Ammonium Picrates in $CDCl_3$ at 25 °C

ligand system structure	no.	M^+ of M^+ picrate$^-$	R_{CDCl_3}[b]	$K_a \times 10^{-3}$, M^{-1}	$-\Delta G°$, kcal/mol	$-\Delta G_{av}°$,[c] kcal/mol	$-\Delta(\Delta G°)_{max}$[d] kcal/mol
AN(MOEO)$_2$E	**22**[e]	Li	0.0012	3.8	4.89	5.5	1.0
		Na	0.0545	14	5.66		
		K	0.012	21	5.90		
		Cs	0.0027	5.0	5.05		
		NH_4	0.0038	4.2	4.95		
AN(MOEOE)$_2$O	**23**[e]	Li	0.0031	9.9	5.46	7.0	3.1
		Na	0.017	47	6.38		
		K	0.32	1800	8.54		
		Cs	0.053	115	6.91		
		NH_4	0.18	370	7.60		
AN(MOEOEO)$_2$E	**24**[e]	Li	0.000 91	2.9	4.73	6.6	3.2
		Na	0.017	46	6.37		
		K	0.082	180	7.18		
		Cs	0.19	650	7.94		
		NH_4	0.091	130	6.98		
1,3-benzo-18-crown-5	**41**[e]	Li	0.0004	0.1	2.73	5.7	4.2
		Na	0.000 65	1.7	4.41		
		K	0.053	109	6.88		
		Rb	0.027	66	6.58		
		Cs	0.025	51	6.43		
		NH_4	0.081	115	6.91		
AN(MOEOM)$_2$AN	**31**[e]	Li	0.0028	0.86	4.01	4.5	0.9
		Na	0.0008	2.0	4.51		
		K	0.0022	3.9	4.90		
		Rb	0.0011	2.4	4.62		
		Cs	0.0010	1.9	4.48		
		NH_4	0.0017	1.9	4.48		
AN(MOEOEOM)$_2$AN	**32**[e]	Li	0.000 18	0.56	3.75	5.0	1.6
		Na	0.001 95	5.0	5.05		
		K	0.004 95	8.8	5.39		
		Rb	0.0027	5.9	5.15		
		Cs	0.003 25	6.1	5.17		
		NH_4	0.0075	8.5	5.37		
ANAN(MOEO)$_2$E	**33**[f]	Li	0.019	57	6.49	8.2	3.3
		Na	0.32	2460	8.73		
		K	0.617	15 900	9.83		
		Rb	0.314	1920	8.58		
		Cs	0.169	514	7.80		
		NH_4	0.242	606	7.90		
		CH_3NH_3	0.229	150	7.07		
		t-BuNH_3	0.389	33.5	6.18		
ANAN(MOM)$_2$ANAN	**35**[e]	Li	too low	too low	too low	4.4	
		Na	0.0025	6.2	5.18		
		K	0.0015	2.4	4.62		
		Rb	0.0004	0.81	3.97		
		Cs	0.0004	0.70	3.88		
		NH_4	0.0017	1.90	4.48		
		CH_3NH_3	0.0024	0.70	3.88		
		t-BuNH_3	0.0020	0.040	2.19		
ANAN(MSM)$_2$ANAN	**36**[e]	Li	0.0003	0.92	4.04	4.1	1.1
		Na	0.0005	1.20	4.20		
		K	0.0012	1.90	4.48		
		Rb	0.0009	1.80	4.45		
		Cs	0.0005	0.80	3.96		
		NH_4	0.0003	0.30	3.38		
		CH_3NH_3	0.0005	0.15	2.97		
		t-BuNH_3	0.0007	0.01	1.36		
ANANAN(MOE)$_2$O	**37**[f]	Li	0.053	179	7.17	10.2	5.3
		Na	0.895	1 460 000	12.51		
		K	0.916	1 150 000	12.37		
		Rb	0.702	45 700	10.46		
		Cs	0.418	3680	8.97		
		NH_4	0.639	14 500	9.78		
		CH_3NH_3	0.473	990	8.19		
		t-BuNH_3	0.694	420	7.68		

Table I (*continued*)

ligand system structure	no.	M^+ of M^+ picrate$^-$	R_{CDCl_3}[b]	$K_a \times 10^{-3}$, M^{-1}	$-\Delta G°$, kcal/mol	$-\Delta G_{av}°$,[c] kcal/mol	$-\Delta(G°)_{max}$,[d] kcal/mol
ANANAN(MOM)$_2$AN	**38**[e]	Li	0.002 88	0.81	3.97	5.8	3.8
		Na	0.131	486	7.76		
		K	0.0373	66.2	6.58		
		Rb	0.004 23	8.7	5.38		
		Cs	0.004 89	8.8	5.39		
		NH_4	0.009 22	10.3	5.48		
		CH_3NH_3	0.0235	7.7	5.31		
		t-BuNH_3	0.003 95	0.073	2.54		
dicyclohexyl-18-crown-6	**43**[f]	Li	0.053	192	7.20	9.3	4.1
		Na	0.308	2340	8.68		
		K	0.809	200 000	11.32		
		Rb	0.636	5050	9.14		
		Cs	0.497	1790	8.53		
		NH_4	0.768	67 100	10.67		
		CH_3NH_3	0.705	8310	9.43		
		t-BuNH_3	0.569	132	6.98		
(AN)$_2$DP(OEOEO)$_2$E	**39**[f]	Li	0.032	103	6.84	9.0	4.8
		Na	0.679	49 500	10.50		
		K	0.838	328 000	11.63		
		Rb	0.485	1900	8.57		
		Cs	0.225	312	7.50		
		NH_4	0.443	2680	8.78		
		CH_3NH_3	0.416	606	7.90		
		t-BuNH_3	0.351	22.8	5.95		
DP(OEOEO)$_2$E	**40**[e]	Li	0.0069	22.0	5.92	7.1	2.6
		Na	0.055	166	7.12		
		K	0.314	1700	8.49		
		Rb	0.136	185	7.18		
		Cs	0.0552	51.7	6.43		
		NH_4	0.166	315	7.50		
		CH_3NH_3	0.0402	13.9	5.65		
		t-BuNH_3	0.0709	1.66	4.39		
2,3-naphtho-18-crown-6	**42**[f]	Li	0.007 04	22.5	5.94	8.7	4.8
		Na	0.226	1220	8.31		
		K	0.740	85 900	10.8		
		Rb	0.524	11 300	9.63		
		Cs	0.262	1250	8.33		
		NH_4	0.575	9850	9.55		
		CH_3NH_3	0.315	334	7.53		
		t-BuNH_3	0.534	105	6.85		

[a] AN = 4-methylanisole substituted in 2,6 positions; M = CH_2; O = oxygen; S = sulfur; E = CH_2CH_2; DP = 5,5′-dimethyldiphenyl substituted in the 2,2′ positions with 0 and 3,3′ positions with either H or 2-methoxy-5-methylphenyl groups. [b] Ratio of picrate to host in $CDCl_3$ phase at equilibrium obtained by direct measurement, or calculated by difference from measurements made on aqueous phase. [c] Average-$\Delta G°$ values of each host binding Li^+, Na^+, K^+, Rb^+, Cs^+, and NH_4^+ (Rb^+ missing in a few cases). [d] $-\Delta(\Delta G°)_{max}$ for each host equals the highest $-\Delta G°$ value minus the lowest $-\Delta G°$ value among the Li^+, Na^+, K^+, Rb^+, Cs^+, or NH_4^+ picrate$^-$ possible partners. [e] Based on ϵ values obtained by UV measurements on $CDCl_3$ layer. [f] Except for Li^+ picrate$^-$, based on ϵ values calculated from UV measurements on H_2O layer.

1,3-benzo-18-crown-5 (4.2), $NH_4^+ > Li^+$; dicyclohexano-18-crown-6 (4.1), $K^+ > Li^+$; ANANAN(MOM)$_2$AN (3.8), $Na^+ > Li^+$; ANAN(MOEO)$_2$E (3.3), $K^+ > Li^+$; AN(MOEOEO)$_2$E (3.2), $Cs^+ > Li^+$; AN(MOEOE)$_2$O (3.1), $K^+ > Li^+$; DP(OEOEO)$_2$E (2.6), $K^+ > Li^+$; AN(MOEOEOM)$_2$AN (1.6), $K^+ > Li^+$; ANAN(MSM)$_2$ANAN (1.1), $K^+ > NH_4^+$; AN(MOEO)$_2$E (1.0), $K^+ > Li^+$; AN(MOEOM)$_2$AN (0.9), $K^+ > Li^+$. There is a partial correlation between this order and the order based on the $-\Delta G_{av}°$ parameter, particularly toward the top of the scale. The ion most poorly complexed, with one exception (NH_4^+), is Li^+. The ions best complexed were K^+ (ten cases), Na^+ (two cases), NH_4^+ (one case), and Cs^+ (one case). Hosts for binding K^+ and Na^+ ions are easier to design than those that complex better the larger or smaller ions.

Each of the six ions can be characterized by the difference in $-\Delta G°$ values between their best and poorest ligand systems. The six ions are arranged in decreasing order of the $-\Delta(\Delta G°)$ involved (kcal/mol) as follows: Na^+ (8.3), ANANAN(MOE)$_2$O > ANAN(MSM)$_2$ANAN; K^+ (7.9), ANANAN(MOE)$_2$O > ANAN(MSM)$_2$ANAN; NH_4^+ (7.3), dicyclohexano-18-crown-6 > ANAN(MOM)$_2$ANAN; Rb^+ (6.5), ANANAN(MOE)$_2$O > ANAN(MOM)$_2$ANAN; Cs^+ (5.1), ANANAN(MOE)$_2$O > ANAN(MOM)$_2$ANAN; Li^+ (4.5), dicyclohexano-18-crown-6 > 1,3-benzo-18-crown-5. This order indicates that, in discriminating between hosts, $Na^+ > K^+ > NH_4^+ > Rb^+ > Cs^+ > Li^+$. More interestingly, ANANAN(MOE)$_2$O is the best of the ligand systems for Na^+, K^+, Rb^+, and Cs^+, and dicyclohexano-18-crown-6 is the best for NH_4 and Li^+. The poorest ligand systems are also rich in anisyl units. Thus, for Na^+ and K^+, ANAN(MSM)$_2$ANAN is the poorest; for NH_4^+, Rb^+, Li^+, and Cs^+, ANAN(MOM)$_2$ANAN is the poorest.

These different ways of viewing the results clearly indicate that anisyl units are capable of providing superb binding sites in certain assemblages and very poor in others. Examinations of CPK molecular models of the hosts containing these units indicate that only when the unshared electron pairs of the anisyl's oxygens are forced to line the cavities of the host prior to complexation can they exceed the binding abilities of ordinary ether oxygens. Thus sterically enforced conformations of the aryl groups that support these oxygens are a necessary

Table II. Differences in Free Energies of Association of Hosts with Ammonium, Methylammonium, and *tert*-Butylammonium Picrates in $CDCl_3$ at 25 °C

ligand system	$-(\Delta G°)_{NH_4^+}$, kcal/mol	$-(\Delta G°)_{CH_3NH_3^+}$, kcal/mol	$-(\Delta G°)_{t\text{-}BuNH_3^+}$, kcal/mol	$-\Delta(\Delta G°)_{CH_3NH_3^+}^{NH_4^+}$, kcal/mol	$-\Delta(\Delta G°)_{t\text{-}BuNH_3^+}^{CH_3NH_3^+}$, kcal/mol
ANANAN(MOE)$_2$O	9.8	8.2	7.7	1.6	0.5
ANANAN(MOM)AN	5.5	5.3	2.5	0.2	2.8
ANAN(MOEO)$_2$E	7.9	7.1	6.2	0.8	0.9
ANAN(MOM)$_2$ANAN	4.5	3.9	2.2	0.6	1.7
ANAN(MSM)$_2$ANAN	3.4	3.0	1.4	0.4	1.6
(AN)$_2$DP(OEOEO)$_2$E	8.8	7.9	6.0	0.9	2.0
DP(OEOEO)$_2$E	7.5	5.6	4.4	1.9	1.2
2,3-naphtho-18-crown-6	9.5	7.5	6.9	2.0	0.7
dicyclohexano-18-crown-6	10.7	9.4	7.0	1.2	2.5

condition for good binding. The method used here to generate the required enforced conformations made use of aryl-aryl bonds. Molecular model examination indicates that *the larger the number of m-polyanisyl units strung together in the proper configurations in a macrocycle, the more the oxygen's electron pairs are forced to converge on a central cavity.* As the anisyl units become more separated from one another by spacers, their conformations become more flexible and experimentally their binding abilities decrease.

The following comparisons illustrate this generalization. The following hosts all contain 6 ether oxygens and all possess 18-membered rings. The three hosts AN(MOEOE)$_2$O, AN-AN(MOEO)$_2$E, and ANANAN(MOE)$_2$O provide $-\Delta G_{av}°$ values (kcal/mol) of 7.0, 8.2, and 10.2, respectively. Each additional *m*-anisyl unit bonded to the others in the macroring provides 1.2–2 kcal/mol of binding potential. However, when a fourth anisyl unit was added, separated by spacers from the other three as in ANANAN(MOM)$_2$AN, $-\Delta G_{av}°$ decreased dramatically to 5.8 kcal/mol. Models indicate that this host has two conformations, the most relaxed of which places a methoxyl group close to the center of the cavity. Hosts AN-(MOEOM)$_2$AN and ANAN(MOEO)$_2$E are isomers of one another, yet the former provides $-\Delta G_{av}°$ of 4.5, and the latter, 8.2 kcal/mol. In models of the better binder, the anisyl oxygens are better organized in a convergent conformation. In the poorer binder, many more conformations are available, several of which possess no central cavity at all. Hosts ANAN-(MOM)$_2$ANAN and ANANAN(MOM)$_2$AN are isomeric, and provide $-\Delta G_{av}°$ values of 4.4 and 5.8 kcal/mol, respectively. In models, the former host possesses a large number of conformations, many of which place methoxyl groups in the central cavity. The latter host possesses only two reasonable conformations, one of which places one methoxyl group not far from the center of the cavity, and the other which places all six oxygens in a beautifully convergent arrangement. If the latter conformation were enforced, ANANAN(MOM)$_2$AN should be a superb ligand system whose oxygen lone pairs provide a hemispheric nest with a diameter of about 2.8 Å.

Host ANANAN(MOE)$_2$O is the best ligand system so far prepared that contains only oxygen binding sites. Thus its structure deserves special examination. In models, the three aliphatic oxygens (OCH_2CH_2O groups gauche) and the central methoxyl oxygen are nearly coplanar. The outer methoxyl oxygens lie below this plane to form the floor of a nest which is not far from being hemispheric. The diameter of the central hole can vary from a minimum of about 2.0 Å to a maximum of about 3.0 Å by varying the dihedral angles between the planes of the three aryl groups bound to one another. This structural feature explains why the substance is such a good complexer of Na^+, K^+, and Rb^+, whose diameters are 1.9, 2.66, and 2.96 Å, respectively. The fact that ANANAN-(MOE)$_2$O binds K^+ better than dicyclohexano-18-crown-6 probably reflects the superior (nonplanar) ligand organization in the former compound. The methoxy aryl oxygens should be intrinsically poorer ligands for cations than purely aliphatic oxygens because of the electron-withdrawing effect of the attached aryl groups. This purely electronic effect is more than compensated for in ANANAN(MOE)$_2$O by its organization.

The two extra anisyl groups in (AN)$_2$DP(OEOEO)$_2$E as compared to DP(OEOEO)$_2$E lead to an increase in the $-\Delta G_{av}°$ of binding of 1.9 kcal/mol. The former compound also binds Na^+ and K^+ better than dicyclohexano-18-crown-6. These effects are attributed to the presence and placement of the two extra *o*-methoxyl groups in (AN)$_2$DP(OEOEO)$_2$E. A molecular model of the substance indicates that, although these *o*-methoxylphenyl groups have several conformations available, one of the least hindered of them involves location of one of the methoxyl oxygens just above and the other just below the best plane of the macroring.

Correlations between Structures of Ligand Systems and Their Free Energies of Association with Ammonium and Alkylammonium Picrates. For nine of the ligand systems, the $-\Delta G°$'s of association were determined for NH_4^+, $CH_3NH_3^+$, and *t*-$BuNH_3^+$ picrates, Table II reports these values, as well as those for the $-\Delta(\Delta G°)_{CH_3NH_3^+}^{NH_4^+}$ and $-\Delta(\Delta G°)_{t\text{-}BuNH_3^+}^{CH_3NH_3^+}$ parameters.

In complexing NH_4^+, the hosts arranged in decreasing order of their values of $-(\Delta G°)_{NH_4^+}$ (kcal/mol) are as follows: dicyclohexano-18-crown-6 (10.7); ANANAN(MOE)$_2$O (9.8); 2,3-dinaphtho-18-crown-6 (9.5); AN$_2$DP(OEOEO)$_2$E (8.8); ANAN(MOEO)$_2$E (7.9); DP(OEOEO)$_2$E (7.5); ANA-NAN(MOM)$_2$AN (5.5); ANAN(MOM)$_2$ANAN (4.5); ANAN(MSM)$_2$ANAN (3.4). Nearly the same order is followed with $CH_3NH_3^+$ as guest, except that the relative positions of (AN)$_2$DP(OEOEO)$_2$E and 2,3-naphtho-18-crown-6 are inverted. The same general order is observed for $-\Delta(\Delta G°)_{NH_4^+}^{CH_3NH_3^+}$ values. The better binding hosts provide $-\Delta(\Delta G°)_{NH_4^+}^{CH_3NH_3^+}$ values that range from 2.0 to 1.2, and the poorer from 0.9 to 0.2 kcal/mol. If, in $CDCl_3$, three of the hydrogens of NH_4^+ in the complexes hydrogen bond oxygens, one hydrogen is left free to ion pair the picrate ion through a hydrogen bond. With $CH_3NH_3^+$, no fourth hydrogen is available in the complex, and the ion pair is more separated. In the better binding hosts, the positive charge is probably more delocalized onto the oxygens of the host and the complexes are more perfectly structured. Thus the positive charge is more deeply buried in a lipophilic skin, part of which is the CH_3 of $CH_3NH_3^+$. In the poorer binding hosts, the positive charge is more localized on the NH_3^+ group, and the complexes are less structured and more adaptive to minimizing the distance between plus and minus charges. As a result, charge separation is less, and $-\Delta(\Delta G°)_{NH_4^+}^{CH_3NH_3^+}$ values are smaller. In the extreme, possibly with ANAN(MOM)$_2$-ANAN and ANAN(MSM)$_2$ANAN, the complexes are held together by only two hydrogen bonds, and $CH_3NH_3^+$ provides

one hydrogen bond through which it can form a contact ion pair with picrate ion.

In complexing t-$BuNH_3^+$ ion, the hosts show a slightly different order than with the other two ions. Their rank in terms of decreasing $-\Delta G°_{t\text{-}BuNH_3^+}$ values (kcal/mol) is as follows: ANANAN(MOE)$_2$O (7.7); dicyclohexano-18-crown-6 (7.0); 2,3-naphtho-18-crown-6 (6.9); ANAN(MOEO)$_2$O (6.2); (AN)$_2$DP(OEOEO)$_2$E (6.0); DP(OEOEO)$_2$E (4.4); ANANAN(MOM)AN (2.5); ANAN(MOM)$_2$ANAN (2.2); ANAN(MSM)$_2$ANAN (1.4). The striking feature of the data is the discontinuity in values between the first six and the last three hosts. This was not observed with NH_4^+ and $CH_3NH_3^+$, and is attributed to the greatly increased bulk of the $(CH_3)_3C$ as compared to the CH_3 group. Thus the $(CH_3)_3C$ group sterically inhibits gathering the partners and, ion pairing and solvating the complex by $CDCl_3$. The greater lipophilic character of the $(CH_3)_3C$ vs. the CH_3 group also provides a poorer local dielectric medium for charge separation.

The sum of these effects is most visible in the $-\Delta(\Delta G°)_{t\text{-}BuNH_3^+}^{CH_3NH_3^+}$ values (kcal/mol). The hosts fall in the following order: ANANAN(MOM)AN (2.8); dicyclohexano-18-crown-6 (2.5); (AN)$_2$DP(OEOEO)$_2$E (2.0); ANAN(MOM)$_2$ANAN (1.7); ANAN(MSM)$_2$ANAN (1.6); DP(OEOEO)$_2$E (1.2); ANAN(MOEO)$_2$E (0.9); 2,3-naphtho-18-crown-6 (0.7); ANANAN(MOE)$_2$O (0.5). These values measure the extent of structural recognition the hosts show for $CH_3NH_3^+$ vs. t-$BuNH_3^+$ ion in complexation. As expected, this order bears little relationship to the order of overall binding ability of any of the ions.

Interestingly, ANANAN(MOE)$_2$O, which is the best overall host in this study, showed the lowest $-\Delta(\Delta G°)_{t\text{-}BuNH_3^+}^{CH_3NH_3^+}$ value of 0.5 and ANANAN(MOM)$_2$AN the highest of 2.8 kcal/mol. The X-ray structure of the t-$BuNH_3^+ClO_4^-$ complex of ANANAN(MOE)$_2$O indicates that complexation occurs from the side of the macroring from which the two OCH_3 groups protrude.[14] The complex almost possesses a C_2 axis. Two of the NH···O contact sites involve the benzyl oxygens, and the third hydrogen bond appears to involve all three of the CH_3O oxygens (a trifurcated hydrogen bond). Molecular models of the complex indicate little steric interference between the OCH_3 groups of the host and the CH_3 groups of the guest. The opposite side of the complexed cation is relatively available to $CDCl_3$ and picrate$^-$. If the complex of *tert*-butylammonium picrate and ANANAN(MOM)$_2$AN is similarly held together, two CH_3O groups protrude from each side of the macroring, and all of the oxygens are covered with a "skin" of CH bonds. Furthermore, two CH_3 groups of the t-Bu lie in the face of the benzene ring of the M$_2$AN group. These factors in sum are probably responsible for the high $-\Delta(\Delta G°)_{t\text{-}BuNH_3^+}^{CH_3NH_3^+}$ value (2.8 kcal/mol) for ANANAN(MOM)$_2$AN. In molecular models of complexes of dicyclohexano-18-crown-6 and of (AN)$_2$DP(OEOEO)$_2$E, steric interactions between the CH_3 groups of $(CH_3)_3C$ and parts of the host are visible, and $-\Delta(\Delta G°)_{t\text{-}BuNH_3^+}^{CH_3NH_3^+}$ values are 2.5 and 2.0 kcal/mol, respectively. Host (AN)$_2$DP(OEOEO)$_2$E is potentially chiral and is a possible candidate for examination of chiral recognition of the enantiomers of racemic amine salts. The low $-\Delta(\Delta G°)_{t\text{-}BuNH_3^+}^{CH_3NH_3^+}$ value of 0.7 kcal/mol for 2,3-naphtho-18-crown-6 correlates with the absence of steric interactions in molecular models of the complex.

These studies provide several generalizations important to host design. (1) In an envisioned complex, enforced conformations in the host, itself, that provide a desired complementary relationship between host and guest are a necessary condition for a high binding free energy. (2) Hosts with specialized and limited conformational mobility can be designed that will complex metal ions of widely differing diameters with high binding free energies. (3) Hosts can be designed with so little conformational mobility that they show high structural recognition in complexation. (4) Although aryl groups attached to oxygen ordinarily decrease their ability to act as good ligands, proper organization of the oxygens can more than compensate for this electronic effect.

Experimental Section

General. All chemicals were reagent grade. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use. Dimethylformamide (DMF) was distilled from 4 Å molecular sieves and stored over them. Carbon tetrachloride was stored over CaH_2. Diethyl ether was distilled from $LiAlH_4$ immediately prior to use. Dichloromethane was fractionally distilled before use. Melting points were measured on a Thomas-Hoover apparatus, and were uncorrected. Mass spectra were run on either a CEC MS-21 or an AEI MS-9 machine. Infrared spectra were taken on a Perkin-Elmer Model 297 spectrometer, and ^{1}H NMR spectra were taken on either a Varian HA-100, Varian T-60, or Bruker WP-200 spectrometer with chemical shifts given in δ (ppm) from internal $(CH_3)_4Si$. Ultraviolet measurements were made at 24–26 °C with a Beckman DU spectrometer equipped with a Gilford Model 252 modernization system. Gel permeation chromatographic runs were made on column A, 3/8 in. (o.d.) by 20 ft column of Styragel 100 Å beads (Waters Associates Inc.), 37–75 μm particle size, exclusion limit 1500 molecular weight in THF at a flow rate of 4 mL min^{-1} and a pressure of 400–600 psi; column B, same as A except column was 10 ft long; column C, same size as A but packed with 60 Å Styragel packed in CH_2Cl_2, mesh size 37–75 μm, exclusion limit 500 molecular weight run at a flow rate of 4 mL min^{-1} and a pressure of 750–900 psi; column D, same as A except CH_2Cl_2 was used as the mobile phase. Sodium hydride was used as a 50% dispersion in mineral oil.

2,6-Bis(hydroxymethyl)-4-methylphenol (1). To a solution of 20 g (0.185 mol) of p-cresol and 30 g (0.217 mol) of K_2CO_3, stirred under N_2 at 50 °C, in 300 mL of water was added 60 mL (0.74 mol) of 37% aqueous formaldehyde. The solution was stirred at 50 °C for 3.5 h, the oil bath was removed, and CO_2 was bubbled through the yellow solution until it turned very cloudy. The mixture was extracted twice with ethyl acetate, the combined extracts were dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was recrystallized from 50 mL of $CHCl_3$ at −20 °C to give 13.9 g (45%) of product: mp 123–124 °C; M$^+$ *m/e* 168; ^{1}H NMR (100 MHz, $(CD_3)_2CO$), δ 2.18 (s, CH_3, 3 H), 4.66 (s, CH_2O, 4 H), 6.86 (s, ArH, 2 H). Anal. ($C_9H_{12}O_3$) C, H.

2,6-Bis(hydroxymethyl)-4-methylanisole (2). A mixture of 23 g (0.137 mol) of 2,6-bis(hydroxymethyl)-4-methylphenol, 28 g (0.20 mol) of K_2CO_3, 19 g (0.15 mol) of $(CH_3)_2SO_4$, and 700 mL of reagent acetone was stirred under N_2 at 25 °C for 24 h. The resulting mixture was filtered, and the solvent was evaporated from the filtrate under reduced pressure. The residue was shaken with $CHCl_3$ and water, and the $CHCl_3$ layer was washed with water and dried ($MgSO_4$). Evaporation of the solvent gave a residue that was recrystallized at −20 °C from a minimum amount of $CHCl_3$ to give 21 g (84%) of product, mp 103–104 °C. This material gave M$^+$ *m/e* 182; ^{1}H NMR (100 MHz, $CDCl_3$), δ 2.30 (s, CH_3, 3 H), 3.78 (s, CH_3O, 3 H), 4.64 (s, CH_2O, 4 H), 7.10 (s, ArH, 2 H). Anal. ($C_{10}H_{14}O_3$) C, H.

2,6-Bis(bromomethyl)-4-methylanisole (3). To a solution stirred at 25 °C under N_2 of 10 g (0.055 mol) of 2,6-bis(hydroxymethyl)-4-methylanisole in 350 mL of $CHCl_3$ was added over a 5-min period a solution of $SOBr_2$ (15 g, 0.072 mol) in 50 mL of $CHCl_3$. The solution was stirred for 1 h and washed with a saturated aqueous $NaHCO_3$ solution and then with water saturated with Na_2SO_3. The organic layer was dried ($MgSO_4$), and the solvent was evaporated to give 16.9 g (~100%) of product as an oil, which solidified on standing, mp 66–68 °C. This material gave M$^+$ *m/e* 306 (^{79}Br); ^{1}H NMR (100 MHz, $CDCl_3$) δ 2.26 (s, CH_3, 3 H), 3.94 (s, CH_3O, 3 H), 4.46 (s, CH_2O, 4 H), 7.12 (s, ArH, 2 H). Anal. ($C_{10}H_{12}Br_2O$), C, H.

2-Methoxy-5-methylisophthalaldehyde (4). A mixture of 1 g (5.5 mmol) of 2,6-bis(hydroxymethyl)-4-methylanisole, 50 mL of pure THF, and 4 g (56 mmol) of activated MnO_2[5] was heated at reflux for 2 h during which all starting material was consumed (TLC, silica gel, CH_2Cl_2). The cooled mixture was filtered through Celite, and the solvent was evaporated under reduced pressure. The residue was recrystallized from 1:1 (v) CCl_4–cyclohexane to give 0.75 g (78%) of product as white needles, mp 88–89 °C. This material gave M$^+$ *m/e*

178; IR (CCl_4) 1670 cm^{-1} (C=O); ^1H NMR (100 MHz, $CDCl_3$) δ 2.38 (s, CH_3, 3 H), 4.04 (s, CH_3O, 3 H), 7.83 (s, ArH, 2 H), 10.36 (s, CHO, 2 H). Anal. ($C_{10}H_{10}O_3$) C, H.

The same compound was prepared in 93% yield by oxidizing 2,6-bis(hydroxymethyl)-4-methylanisole (0.50 g, 2.7 mmol) with pyridinium chlorochromate (2 g, 9.3 mmol) in 100 mL of CH_2Cl_2 at 25 °C for 2 h, mp 88–89 °C.

2-Hydroxy-5-methylisophthalaldehyde (5). To a solution stirred under N_2 at −78 °C of 12.3 g (0.069 mol) of 2-methoxy-5-methylisophthalaldehyde in 200 mL of CH_2Cl_2 was added in one portion 4.75 mL (0.050 mol) of BBr_3. The stirred, colored, heterogeneous mixture was allowed to warm to 25 °C. After 1.5 h of additional stirring, the reaction was 91% complete (^1H NMR), and side reactions were starting. The mixture was shaken with water, the organic layer was treated with activated charcoal, dried ($MgSO_4$), and filtered, and the solvent was evaporated from the filtrate under reduced pressure. The solid residue was recrystallized from CCl_4 at 0 °C to give 4.0 g (82%) of product: mp 129–130 °C; M^+ *m/e* 164; IR (CCl_4) 1670, 1640 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 2.33 (s, CH_3, 3 H), 7.69 (s, ArH, 2 H), 10.14 (s, CHO, 2 H). Anal. ($C_9H_8O_3$) C, H.

2-Methoxymethoxy-5-methylisophthalaldehyde (6). To a brilliant red solution of 3 g (0.018 mol) of 2-hydroxy-5-methylisophthalaldehyde in 150 mL of pure, dry DMF stirred under N_2 at 25 °C was added 1.8 g (0.037 mol) of NaH in two portions. The mixture was stirred for 10 min, and 4 mL (0.0605 mol) of chloromethyl methyl ether was added in one portion. The solution was stirred for 1 h, and 2 mL of water was carefully added. The mixture was shaken with 200 mL of CH_2Cl_2 and 200 mL of H_2O, and the organic layer was washed with six successive 200-mL portions of water. The organic layer was dried, and the solvent was evaporated under reduced pressure. The residue (3.8 g) was chromatographed on a dry silica gel column (1.5 by 14 in.) with CH_2Cl_2. The column filtrate was evaporated under reduced pressure to give 3.38 g (91%) of product: mp 92–94 °C; M^+ *m/e* 208; IR (CCl_4) 1690 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 2.38 (s, CH_3, 3 H), 3.55 (s, CH_3O, 3 H), 5.14 (s, OCH_2O, 2 H), 7.84 (s, ArH, 2 H), 10.25 (s, CHO, 2 H). Anal. ($C_{11}H_{12}O_4$) C, H.

1-Methoxymethoxy-2,6-bis(hydroxymethyl)-4-methylbenzene (7). To a solution stirred under N_2 at 25 °C of 4.9 g (0.0235 mol) of 2-methoxymethoxy-5-methylisophthalaldehyde in 150 mL of pure THF was added 1 g (0.0262 mol) of $NaBH_4$ in three portions over a 5-min period. The mixture was stirred for 2.5 h, and 2 mL of H_2O was carefully added. After H_2 evolution ceased, the solvent was evaporated under reduced pressure, the residue was shaken with 200 mL of CH_2Cl_2 and 200 mL of water, and the CH_2Cl_2 layer was dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give 4.4 g (89%) of product, pure enough for use in the cyclization reactions. A small portion was recrystallized from CCl_4–cyclohexane at 0 °C to give material: mp 82–83 °C; M^+ *m/e* 212; ^1H NMR (100 MHz, $CDCl_3$) δ 2.24 (s, CH_3, 3 H), 3.30 (broad s, OCH_2O, 2 H), 3.52 (s, CH_3O, 3 H), 4.49 (s, CH_2, 4 H), 4.88 (s, OCH_2O, 2 H), 7.05 (s, ArH, 2 H). Anal. ($C_{11}H_{16}O_4$) C, H.

2-Bromo-4-methylanisole (8). To a solution stirred at −40 °C under N_2 of 47 g (0.382 mol) of 4-methylanisole in 50 mL of $CHCl_3$ was added dropwise (20 min) 61 g (0.382 mol) of Br_2 in 10 mL of $CHCl_3$. The solution was allowed to come to 25 °C over a 30-min period and was washed with H_2O saturated with $NaHSO_3$. The organic layer was dried and evaporated under reduced pressure to give 75 g (99%) of product used directly in the next step. The material gave M^+ *m/e* 200 (^{79}Br); ^1H NMR (100 MHz, $CDCl_3$) δ 2.20 (s, CH_3, 3 H), 3.74 (s, CH_3O, 3 H) 6.68–7.27 (m, ArH, 3 H). Anal. (C_8H_9BrO) C, H.

2,2′-Dimethoxy-5,5′-dimethyl-1,1′-diphenyl (9). To a solution stirred under N_2 at −60 °C composed of 100 g (0.50 mol) of 2-bromo-4-methylanisole in 200 mL of anhydrous Et_2O was added slowly via a syringe 208 mL (0.5 mol) of BuLi in hexane (2.4 M). The cooling bath was removed, and the reaction mixture was stirred for 20 min. If precipitation of any Li salt occurred, a minimum amount of dry ether was added to produce a homogeneous solution. This solution was added at such a rate as to maintain reflux to a mixture stirred under N_2 of 8 g (~60 mmol) of anhydrous $CoCl_2$[6] (dried at 140 °C for 24 h at 0.01 mm) in 100 mL of anhydrous ether. During the addition of the first 10 mL, the initial blue color of $CoCl_2$ disappeared and a black precipitate formed. The mixture was stirred for 8 h at 25 °C, refluxed for 2 h, quenched with water, and filtered. The organic phase was washed with water and dried (Na_2SO_4), and the solvent was evaporated to give a colorless liquid that was distilled at 80 °C (0.02 Torr). The residue was distilled through a short-path column at 120–135 °C (0.02 Torr) to give an oil, which in pentane at −20 °C gave crystals of product: 25.0 g (42%); mp 63–64 °C (lit. 61 °C);[7] M^+ *m/e* 242; ^1H NMR (60 MHz, $CDCl_3$) δ 2.30 (s, CH_3, 6 H), 3.84 (s, CH_3O, 6 H), 6.70–7.23 (m, ArH, 6 H). Anal. ($C_{16}H_{18}O_2$) C, H.

5,5′-Dimethyl-2,2′-dihydroxydiphenyl (10). To a stirred solution of 8.3 g (34.3 mmol) of 5,5′-dimethyl-2,2′-dimethoxydiphenyl in 300 mL of CH_2Cl_2 under N_2 at −78 °C was added 3.3 mL (8.59 g, 34.3 mmol) of BBr_3. The reaction mixture was allowed to warm to 25 °C and stirred for 2 days. The mixture was then shaken with 300 mL of water, the organic layer was washed with two 300-mL portions of water and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to yield 7.3 g (99%) of product as an oil. An analytical sample was prepared by recrystallizing the material from CH_2Cl_2 at −20 °C: mp 154–155 °C (lit.[7] 154 °C); M^+ *m/e* 214; ^1H NMR (60 MHz, $CDCl_3$) δ 2.33 (s, $ArCH_3$, 6 H), 5.30 (broad s, ArOH, 2 H), 6.83–7.16 (m, ArH, 6 H). Anal. ($C_{14}H_{14}O_2$) C, H.

2,2′-Dimethoxy-5,5′-dimethyl-1,1′-diphenyl-3,3′-dicarboxylic Acid (11). To a mixture stirred under N_2 at 25 °C of 3.4 mL (8.24 mmol) of BuLi (2.4 M in hexane), 50 mL of dry Et_2O, and 0.96 g (8.3 mmol) of tetramethylethylenediamine was added dropwise a solution of 1.0 g (4.12 mmol) of 2,2′-dimethoxy-5,5′-dimethyl-1,1′-diphenyl in 20 mL of dry THF. The solution became dark yellow and cloudy after 30 min. The mixture was stirred for 3 h and transferred under N_2 to a stirred mixture of dry ice and dry ether. The ether phase was acidified with 6 N HCl in water and the acid product extracted with ethyl acetate. The organic phase was dried (Na_2SO_4), the solvent evaporated under reduced pressure, and the white residual solid washed with 300 mL of pentane to give product that was recrystallized from CH_2Cl_2 at −20 °C to yield 1.32 g (66%): mp 224–225 °C; M^+ *m/e* 330; ^1H NMR (60 MHz, $CDCl_3$) δ 2.57 (s, $ArCH_3$, 6 H), 3.55 (s, OCH_3, 6 H), 7.75 (d, d, J = 17, 2 Hz, ArH, 4 H). Anal. ($C_{18}H_{18}O_5$) C, H.

By the usual procedure (CH_3OH–H_2SO_4), the diester of this diacid was prepared as a colorless oil (96%) which was molecularly distilled, M^+ *m/e* 358. Anal. ($C_{20}H_{22}O_6$) C, H.

3,3′-Bis(hydroxymethyl)-2,2′-dimethoxy-5,5′-dimethyl-1,1′-diphenyl (12). To a solution stirred under N_2 at 25 °C of 1.62 g (4.9 mmol) of 2,2′-dimethoxy-5,5′-dimethyl-1,1′-diphenyl-3,3′-dicarboxylic acid (4.9 mmol) in 20 mL of dry THF was added dropwise 11 mL (11 mmol) of THF·BH_3 (1 M in THF). Instantaneously H_2 was evolved and the mixture became cloudy. It was stirred for 6 h, 3 h at 25 °C and 3 h at reflux. Water was cautiously added to destroy excess reagent, 10 mL of H_2O saturated with K_2CO_3 was added, and the mixture was stirred for 10 h. The phases were separated, the aqueous phase was extracted with Et_2O, and the combined organic phases were dried with Na_2SO_4. The solvent was evaporated at reduced pressure and the residual oil, 1.5 g (~100%), was pure enough for use in the next step. An analytical sample was prepared by silica gel dry column chromatography (silica gel, ethyl acetate, R_f 0.40 on plates) to provide a white foam: M^+ *m/e* 302; ^1H NMR (60 MHz, $CDCl_3$) δ 2.33 (s, CH_3, 6 H), 2.50 (broad s, OH, 2 H), 3.40 (s, OCH_3, 6 H), 4.73 (s, $ArCH_2$, 4 H), 7.16 (m, ArH, 4 H). Anal. ($C_{18}H_{22}O_4$) C, H.

3,3′-Bis(bromomethyl)-2,2′-dimethoxy-5,5′-dimethyl-1,1′-diphenyl (13). A mixture of 11 g (36.2 mmol) of 3,3′-bis(hydroxymethyl)-2,2′-dimethoxy-5,5′-dimethyl-1,1′-diphenyl and 100 mL of 40% aqueous HBr was heated to reflux for 30 min. The still heterogeneous mixture was maintained at 50 °C for 2 h, cooled to 25 °C, and extracted with 300 mL of ether. The ether phase was washed with aqueous $NaHCO_3$ and dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residual oil was recrystallized from Et_2O at −20 °C to give 14.0 g (90%) of product: mp 103–104 °C; M^+ *m/e* 426 (^{79}Br); ^1H NMR (60 MHz, $CDCl_3$) δ 2.30 (s, CH_3, 6 H), 3.47 (s, CH_3O, 6 H) 4.60 (s, CH_2Br, 4 H), 7.16 (m, ArH, 4 H). Anal. ($C_{18}H_{20}O_2Br_2$) C, H.

3,3′-Bis(thiomethyl)-2,2′-dimethoxy-5,5′-dimethyl-1,1′-diphenyl (14). A mixture of 3.2 g (7.5 mmol) of 3,3′-bis(bromomethyl)-2,2′-dimethoxy-5,5′-dimethyl-1,1′-diphenyl, 1.26 g (16.5 mmol) of thiourea, 40 mL of EtOH, and 2 mL of water was refluxed for 3 h. The solvent was evaporated at reduced pressure and the residual solid was extracted with CH_2Cl_2. The residual bis(thiouranium salt) was refluxed under N_2 in 100 mL of 5 N NaOH in water for 1 h. The mixture was cooled, acidified with 20% aqueous HCl, and extracted with three 250-mL portions of Et_2O. The organic phase was washed with water, dried (Na_2SO_4), and evaporated. The resulting colorless oil was crystallized from pentane at −20° to give 2.30 g (92%) of product (bad odor): mp 79–80 °C; M^+ *m/e* 334; ^1H NMR (60 MHz, $CDCl_3$)

δ 1.90 (t, J = 9 Hz, SH, 2 H), 2.28 (s, CH_3, 6 H), 3.43 (s, OCH_3, 6 H), 3.77 (d, J = 9 Hz, CH_2S, 4 H), 7.13 (m, ArH, 4 H). Anal. ($C_{18}H_{22}O_2S_2$) C, H.

2,6-Bis(2′-hydroxy-5′-methylphenyl)-4-methylphenol (15). In a 5-gal glass water bottle was placed a mixture of 15 L of water and 100 g (0.93 mol) of *p*-cresol, which was agitated by bubbling N_2 through it. After the *p*-cresol had dissolved, a hot solution of $FeCl_3{\cdot}6H_2O$ (1.0 kg, 3.7 mol) in 2 L of water was added and mixed with a stream of N_2. The resulting green suspension was allowed to stand at room temperature for 1 month. Most of the liquid was decanted from the crude product that crystallized on the bottom of the bottle, and the remaining mixture was filtered, washed with water, and dried, wt 85.3 g (tan powder). This material was refluxed for 15 min in 853 mL of cyclohexane, the mixture was cooled and filtered, and the product was washed with 512 mL of hexane to give 42.5 g of crude product. This material was stirred vigorously in a mixture of 85 g of 85% KOH and 1.7 L of water at 25 °C for 1 h. The resulting brown suspension was washed with two 340-mL portions of Et_2O to give a clear, brown, aqueous solution, which was acidified with 255 mL of concentrated hydrochloric acid. The mixture was extracted with 850 mL of Et_2O, and the organic layer was washed with two 340-mL portions of water and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave 40.0 g of pale tan solid. This material was dissolved in 120 mL of acetone to which was added 400 mL of cyclohexane. The solution was concentrated on a rotoevaporator until crystals appeared. The mixture was cooled, and the product was filtered with the aid of 400 mL of petroleum ether (bp 30–60 °C), washed with an additional 400 mL of petroleum ether, and dried to give 34.2 g (35%) of product **15**, mp 194–197 °C (lit.[8] mp 197 °C). This material gives the following R_f values on precoated TLC plates, silica gel 60 F-254 (E. Merck): 0.80 (THF); 0.32 hexane–ethyl acetate; 2:1 v/v); 0.12 (1,2-dichloroethane). The yield of **15** varied with the reaction times and weights of $FeCl_3{\cdot}6H_2O$ used as follows: 1 week, 1 kg, 25%; 15 days, 1 kg, 30%; 1 month, 400 g, 27%; 1 month, 1 kg, 35%; 2 months, 1 kg, 39%; 4 months, 400 g, 39%; 1 year, 400 g, 39%. This material gave M^+ m/e 320.

2,6-Bis(2′-methoxy-5′-methylphenyl)-4-methylanisole (16). A solution of 62.1 g of 85% KOH (0.942 mol) in 42 mL of water was mixed under N_2 with a solution of 10.0 g (31.3 mmol) of 2,6-bis(2-hydroxy-5-methylphenyl)-4-methylphenol. To the vigorously stirred mixture was added dropwise 49.5 g (0.393 mol) of $(CH_3)_2SO_4$ over a 10-min period. The mixture was refluxed for 1 h and evaporated under reduced pressure. The residue was shaken with a mixture of water and Et_2O, and the organic layer was washed with water, dried ($MgSO_4$), and evaporated to give a residue which was recrystallized from EtOH to give pale yellow crystals, 8.3 g (71%), mp 95–101 °C. A small amount of material was recrystallized from EtOH to give product: mp 104–105.5 °C; M^+ m/e 362; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.30 (s, outer $ArCH_3$, 6 H), 2.34 (s, inner $ArCH_3$, 3 H), 3.18 (s, inner OCH_3, 3 H), 3.76 (s, outer OCH_3, 6 H), 6.83–7.12 (m, ArH, 8 H). Anal. ($C_{24}H_{26}O_3$) C, H.

2,6-Bis(3-carboxy-2-methoxy-5-methylphenyl)-4-methylanisole (17). To a solution stirred under N_2 at 25 °C of 2.0 g (5.52 mmol) of 2,6-bis(2-methoxy-5-methylphenyl)-4-methylanisole in 50 mL of anhydrous Et_2O were added 2.4 mL (11.04 mmol) of tetramethylethylenediamine followed by 5.2 mL (11.04 mmol) of a 2.1 M solution of BuLi in hexane. The solution (orange) was stirred under N_2, and a precipitate started to appear after 1 h. After a total of 3 h of stirring, CO_2 was vigorously bubbled through the mixture for 0.5 h while 25 mL of dry THF was added to replace the Et_2O evaporated by the escaping CO_2. The resulting mixture was stirred for 14 h, acidified to pH 2 with concentrated hydrochloric acid, and shaken with 100 mL of water and 100 mL of ethyl acetate. The aqueous layer was washed with two 100-mL portions of ethyl acetate, and the combined organic layers were washed with two 100-mL portions of water and one 100-mL portion of brine. The organic layer was dried ($MgSO_4$), the solvent was evaporated under reduced pressure, and the resulting solid was stirred for 1 h with 100 mL of pentane to dissolve any monoacid and filtered to give 2.3 g (93%) of diacid product as a white solid. This material was pure enough (^{1}H NMR) for use directly in the next step. A sample was recrystallized from CH_3OH–H_2O to give product: mp 225–228 °C; M^+ m/e 450; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.37 (s, $ArCH_3$, 9 H), 3.19 (s, inner OCH_3, 3 H), 3.63 (s, outer OCH_3, 6 H), 7.23 (s, ArH, 2 H), 7.40 (d, J_{meta} = 2.4 Hz, ArH, 2 H), 8.00 (d, J_{meta} = 2.4 Hz, ArH, 2 H). Anal. ($C_{26}H_{26}O_7$) C, H.

2,6-Bis(3-hydroxymethyl-2-methoxy-5-methylphenyl)-4-methylanisole (18). To a solution stirred under N_2 at 25 °C of 1.0 g (2.22 mmol) of 2,6-bis(3-carboxy-2-methoxy-5-methylphenyl)-4-methylanisole in 30 mL of dry THF was added by syringe through a septum 6.6 mL (6.6 mmol) of 1 M $BH_3{\cdot}$THF. The mixture was stirred under N_2 for 3 h at 25 °C and for 3 h at reflux. The excess $BH_3{\cdot}$THF was destroyed by the careful addition of water, and 15 mL of water saturated with K_2CO_3 was added. The mixture was stirred for 14 h and shaken with 50 mL of Et_2O. The aqueous layer was extracted with two 50-mL portions of Et_2O, and the organic layers were combined and washed with two 50-mL portions of water and 50 mL of brine. The solution was dried ($MgSO_4$), and the solvent was evaporated and dried at 25 °C (0.1 mm) to give the product (0.90 g, 96%) as a white foam pure enough for use in the next step. A small sample was purified by thick layer chromatography on a silica gel plate with 25% EtOAc in Et_2O (v) as developer (R_f 0.6); M^+ m/e 422; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.34 (s, outer $ArCH_3$, 6 H), 2.36 (s, inner $ArCH_3$, 3 H), 3.22 (s, inner CH_3O, 3 H), 3.50 (s, outer CH_3O, 6 H), 4.74 (s, $ArCH_2$, 6 H), 7.12–7.15 (m, ArH, 6 H). Anal. ($C_{26}H_{30}O_5$) C, H.

2,6-Bis(3-bromomethyl-2-methoxy-5-methylphenyl)-4-methylanisole (19). To a solution of 5.0 g (11.8 mmol) of 2,6-bis(3-hydroxymethyl-2-methoxy-5-methylphenyl)-4-methylanisole in 300 mL of benzene was added 1.15 mL (11.8 mmol) of PBr_3. The reaction mixture was stirred at 25 °C for 14 h and then shaken with 200 mL of Et_2O and 200 mL of $NaHCO_3$-saturated water. The organic layer was washed with a second 200-mL portion of $NaHCO_3$-saturated water, 200 mL of water, and 200 mL of brine and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and dried at 25 °C (0.01 mm) for 24 h to give 6.3 g (97%) of product as a foam, pure to TLC; M^+ m/e 546 (^{79}Br); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.33 (s, outer $ArCH_3$, 6 H), 2.37 (s, inner $ArCH_3$, 3 H), 3.19 (s, inner CH_3O, 3 H), 3.56 (s, outer CH_3O, 6 H), 4.63 (s, $ArCH_2$, 4 H), 7.14–7.19 (m, ArH, 6 H). Anal. ($C_{26}H_{28}O_3Br_2$) C, H.

5,5′-Dimethyl-2-hydroxy-2′-methoxydiphenyl (20). A mixture of 7.3 g (34 mmol) of 5,5′-dimethyl-2,2′-dihydroxydiphenyl, 600 mL of acetone, and 4.8 g (35 mmol) of K_2CO_3 (anhydrous) was stirred under N_2 for 0.5 h, 6.45 g (4.8 mL, 52 mmol) of $(CH_3)_2SO_4$ was added, and the mixture was stirred for 14 h (TLC on SiO_2 plates showed only one spot with CH_2Cl_2). Concentrated aqueous NH_4OH (50 mL) was added, and the mixture was stirred for 10 h. The reaction mixture was acidified with 63 mL of concentrated HCl and shaken with 500 mL of water and 300 mL of ether. The aqueous layer was extracted with two 300-mL portions of ether, the combined ether layers were washed with 300 mL of water and 300 mL of brine and dried ($MgSO_4$), and the ether was evaporated under reduced pressure. The residue was dissolved in 80 mL of hot petroleum ether and crystallized at −20 °C to give 6.9 g (90%) of product: mp 76–77 °C (lit.[9] 79–80 °C); M^+ m/e 228; ^{1}H NMR (200 MHz) δ 2.33 (s, $ArCH_3$, 3 H), 2.35 (s, $ArCH_3$, 3 H), 3.86 (s, CH_3O, 3 H), 6.18 (s, OH, 1 H), 6.90–7.19 (m, ArH, 6 H). Anal. ($C_{15}H_{16}O_2$) C, H.

5,5′-Dimethyl-3,3′-bis(2-methoxy-5-methylphenyl)-2,2′-dihydroxydiphenyl (21). A solution of 5,5′-dimethyl-2-hydroxy-2′-methoxydiphenyl (3.7 g, 16.2 mmol) in 55 mL of CH_3CN was flushed with N_2. To this solution was added 6.8 g (19.4 mmol) of $Mn(acac)_3$,[10] and the reaction mixture was heated at reflux for 5 h. The solvent was evaporated under reduced pressure. The residue was dissolved in 300 mL of CH_2Cl_2, the solution was washed with three 330-mL portions of 2 N HCl solution and 300 mL of water and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was chromatographed on 400 g of silica gel with 1:1 (v) CCl_4–CH_2Cl_2 as carrier. Unreacted starting material (~50%) eluted first followed by 900 mg (25%) of product as a glass: M^+ m/e 454; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.34 (s, $ArCH_3$, 6 H), 2.37 (s, $ArCH_3$, 6 H), 3.81 (s, CH_3O, 6 H), 6.50 (s, OH, 2 H), 6.88–7.19 (m, ArH, 10 H). Anal. ($C_{30}H_{30}O_4$) C, H.

18-Methoxy-16-methyl-3,6,9,12-tetraoxabicyclo[12.3.1]octadeca-1(18),14,16-triene (22). Procedure A.[11] To a refluxing mixture stirred under N_2 of 150 mL of dry THF and 1.3 g (0.027 mol) of NaH was added dropwise over a 2.5-h period a solution of 3.0 g (9.74 mmol) of 2,6-bis(bromomethyl)-4-methylanisole and 2.4 g (10 mmol) of triethylene glycol in 50 mL of dry THF. After the addition was complete, the mixture was allowed to cool to 25 °C and stirred for 12 h. Water (2 mL) was added, the solvent was evaporated under reduced pressure, and the residue was shaken with CH_2Cl_2 and H_2O. The organic layer was washed with water, dried, and evaporated, and the residue was submitted to gel permeation chromatography on column A. Cycle **22** eluted with a retention volume of 168 mL of THF.

Evaporation of the solvent under reduced pressure gave 1.7 g (58%) of **22** as a viscous oil, which was film dried at 0.01 mm and 40 °C for 12 h. This material gave M^+ *m/e* 296; ^1H NMR (100 MHz, $CDCl_3$) δ 2.28 (s, CH_3, 3 H), 3.36 (m, CH_2OCH_2, 12 H), 3.86 (s, CH_3O, 3 H), 4.54 (d of d, J = 7.9, 13 Hz, $ArCH_2O$, 4 H), 7.02 (s, ArH, 2 H). Anal. ($C_{16}H_{24}O_5$) C, H.

21-Methoxy-19-methyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]heneicosa-1(21),17,19-triene (23). Procedure A was applied to 3.0 g (9.74 mmol) of 2,6-bis(bromomethyl)-4-methylanisole, 1.94 g (10 mmol) of tetraethylene glycol,[12] 1.3 g (27 mmol) of NaH dispersion, and 200 mL of dry THF. The product gave a 75-mL THF retention volume on gel permeation chromatographic column B, and was an oil which solidified: wt 1.61 g (49%); mp 70–72 °C; M^+ *m/e* 340; ^1H NMR (100 MHz, $CDCl_3$) δ 2.27 (s, CH_3, 3 H), 3.50 (m, CH_2OCH_2, 16 H), 4.04 (s, OCH_3, 3 H), 4.50 (s, $ArCH_2$, 4 H), 7.02 (s, ArH, 2 H). Anal. ($C_{18}H_{28}O_6$) C, H.

22-Methoxy-24-methyl-3,6,9,12,15,18-hexaoxabicyclo[18.3.1]tetracosa-1(24),20,22-triene (24). Procedure A was applied to 3.0 g (9.74 mmol) of 2,6-bis(bromomethyl)-4-methylanisole, 2.4 g (10 mmol) of pentaethylene glycol,[12] 1.3 g (27 mmol) of NaH, and 200 mL of THF. The product gave a 79-mL THF retention volume on gel permeation chromatographic column B, and was isolated as an oil that crystallized to give 1.91 g (59%): mp 71–73 °C; M^+ *m/e* 384; ^1H NMR (100 MHz, $CDCl_3$) δ 2.26 (s, CH_3, 3 H), 3.56 (m, CH_2OCH_2, 20 H), 3.94 (s, CH_3O, 3 H), 4.50 (s, $ArCH_2$, 4 H), 7.06 (s, ArH, 2 H). Anal. ($C_{20}H_{32}O_7$) C, H.

23,24-Dimethoxy-10,21-dimethyl-3,6,14,17-tetraoxatricyclo[17.3.1.1^{8,12}]tetracosa-1(23),8,10,12(24),19,21-hexaene (31). Procedure A was applied to 3.0 g (9.74 mmol) of 2,6-bis(bromomethyl)-4-methylanisole, 0.62 g (10 mmol) of ethylene glycol, 1.3 g (27 mmol) of NaH, and 200 mL of THF. The product eluted from gel permeation chromatographic column A at 183 mL of THF gave a white solid: 297 mg (14%); mp 148–151 °C; M^+ *m/e* 416; ^1H NMR (100 MHz, $CDCl_3$) δ 2.24 (s, CH_3, 3 H), 3.36 (s, CH_3O, 6 H), 3.60 (s, CH_2OCH_2, 8 H), 4.36 (s, $ArCH_2$, 8 H), 6.98 (s, ArH, 4 H). Anal. ($C_{24}H_{32}O_6$) C, H.

29,30-Dimethoxy-13,27-dimethyl-3,6,9,17,20,23-hexaoxatricyclo[23.3.1.1^{11,15}]triconta-1(29),11,13,15(30),25,27-hexaene (32). Procedure A was applied to 3.0 g (9.74 mmol) of 3,6-bis(bromomethyl)-4-methylanisole, 1.06 g (10 mmol) of diethylene glycol, 1.3 g (27 mmol) of NaH, and 200 mL of THF. The product was eluted from gel permeation chromatographic column A at 170 mL of THF to give 635 mg (26%) of solid product: mp 88–90 °C; M^+ *m/e* 504; ^1H NMR (100 MHz, $CDCl_3$) δ 2.22 (s, CH_3, 6 H), 3.52 (s, CH_3O, 6 H), 3.60 (s, CH_2OCH_2, 16 H), 4.44 (s, $ArCH_2$, 8 H), 7.06 (s, ArH, 4 H). Anal. ($C_{28}H_{40}O_8$) C, H.

18-Methoxymethoxy-16-methyl-3,6,9,12-tetraoxabicyclo[12.3.1]octadeca-1(18),14,16-triene (25). Procedure B. A mixture of 0.50 g (2.36 mmol) of 1-methoxymethoxy-2,6-bis(hydroxymethyl)-4-methylbenzene, 240 mg (5.0 mmol) of NaH, and 350 mL of dry THF was stirred under N_2, at 25 °C, and 1.1 g (2.4 mmol) of triethylene glycol ditosylate[12] was added. The mixture was stirred under N_2 heated at reflux for 77 h, and cooled and 2 mL of water was added to destroy excess NaH. The solvent was evaporated under reduced pressure, the residue was shaken with CH_2Cl_2 and water, and the organic layer was washed with water. The organic layer was separated and dried and the solvent was evaporated under reduced pressure. The product was purified by gel permeation chromatography on column A, and was eluted at 188 mL of THF (retention volume). Evaporation of this eluate fraction under reduced pressure gave 0.22 g (29%) of macrocycle as a white solid, mp 76–78 °C, which gave rhombic crystals after recrystallization from Et_2O at 0 °C (same melting point): M^+ *m/e* 326; ^1H NMR (100 MHz, $CDCl_3$) δ 2.29 (s, CH_3, 3 H), 3.28 (m, OCH_2CH_2O, 12 H), 3.56 (s, CH_3O, 3 H), 4.10 (d, J = 12 Hz, $ArCH_2$, 2 H), 4.98 (d, J = 12 Hz, $ArCH_2$, 2 H), 5.12 (s, $ArOCH_2$, 2 H), 7.01 (s, ArH, 2 H). Anal. ($C_{17}H_{26}O_6$) C, H.

21-Methoxymethoxy-19-methyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]heneicosa-1(21),17,19-triene (26). Procedure B applied to 0.50 g (2.36 mmol) of 1-methoxymethoxy-2,6-bis(hydroxymethyl)-4-methylbenzene, 240 mg (5 mmol) of NaH, 350 mL of dry THF, and 1.2 g (2.4 mmol) of tetraethylene glycol ditosylate[12] gave product whose retention volume on gel permeation chromatographic column A was 178 mL of THF. Final purification was accomplished by thick layer chromatography on silica gel plates with 3% EtOH in $CHCl_3$ (v) (R_f 0.3) to give 372 mg (34%) of product: mp 63–65 °C: M^+ *m/e* 370; ^1H NMR δ 2.24 (s, CH_3, 3 H), 3.50 (m, OCH_2CH_2O, 16 H), 3.64 (s, CH_3O, 3 H), 4.08 (d, J = 10 Hz, $ArCH_2$, 2 H), 4.94 (d, J = 10 Hz, $ArCH_2$, 2 H), 5.28 (s, OCH_2O, 2 H), 7.00 (s, ArH, 2 H). Anal. ($C_{19}H_{30}O_7$) C, H.

24-Methoxymethoxy-22-methyl-3,6,9,12,15,18-hexaoxabicyclo[18.3.1]tetracosa-1(24),20,22-triene (27). Procedure B applied to 1.0 g (4.7 mmol) of 1-methoxymethoxy-2,6-bis(hydroxymethyl)-4-methylbenzene, 600 mg of NaH, 400 mL of dry THF, and pentaethylene glycol ditosylate[12] gave product whose retention volume on gel permeation column A was 178 mL of THF. The compound was purified by thick layer chromatography on silica gel, 3% EtOH in $CHCl_3$ (v), R_f ~2.0, to give 668 mg (34%) of product: mp 42–44 °C; M^+ *m/e* 414; ^1H NMR (100 MHz, $CDCl_3$) 2.28 (s, CH_3, 3 H), 3.58 (m, OCH_2CH_2O, CH_3O, 23 H), 4.52 (s, $ArCH_2$, 4 H), 5.10 (s, OCH_2O, 2 H), 7.08 (s, ArH, 2 H). Anal. ($C_{21}H_{34}O_8$) C, H.

18-Hydroxy-16-methyl-3,6,9,12-tetraoxabicyclo[12.3.1]octadeca-1(18),14,16-triene (28). Procedure C. To a solution stirred at 25 °C under N_2 of 220 mg (0.674 mmol) of cycle **25** in $CHCl_3$ and 10 mL of CH_3OH was added dropwise a concentrated hydrochloric acid solution until a pH of 1.0 was obtained. The mixture was stirred for 30 min and shaken with 100 mL of $CHCl_3$ and a saturated $NaHCO_3$ aqueous solution until the water layer remained basic. The organic layer was dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give 187 mg (98%) of product: mp 51–52 °C; M^+ *m/e* 282; ^1H NMR (100 MHz, $CDCl_3$) δ 2.19 (s, CH_3, 3 H), 3.57 (s, OCH_2CH_2O, 12 H), 4.54 (s, $ArCH_2$, 4 H), 6.84 (s, ArH, 2 H), 7.35 (broad s, OH, 1 H). Anal. ($C_{15}H_{22}O_5$) C, H.

21-Hydroxy-19-methyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]heneicosa-1(21),17,19-triene (29). Application of procedure C to 200 mg (0.55 mmol) of macrocycle **26** gave 178 mg (98%) of phenol cyclic product: mp 57–59 °C; M^+ *m/e* 326; ^1H NMR (100 MHz, $CDCl_3$) 2.20 (s, CH_3, 3 H), 3.63 (s, OCH_2CH_2O, 16 H), 4.58 (s, $ArCH_2$, 4 H), 6.86 (s, ArH, 2 H), 7.64 (s, OH, 1 H). Anal. ($C_{17}H_{26}O_6$) C, H.

24-Hydroxy-22-methyl-3,6,9,12,15,18-hexaoxabicyclo[18.3.1]tetracosa-1(24),20,22-triene (30). Application of procedure C to 270 mg (0.65 mmol) of macrocycle **27** gave phenolic cyclic product as an oil: 230 mg (95%); M^+ *m/e* 370; ^1H NMR (100 MHz, $CDCl_3$) δ 2.20 (s, CH_3, 3 H), 3.66 (m, OCH_2CH_2O, 20 H), 4.61 (s, $ArCH_2$, 4 H), 6.89 (s, ArH, 2 H), 7.66 (s, OH, 1 H). Anal. ($C_{19}H_{30}O_7$) C, H.

2,3,4,5-Di[1,3-(2-methoxy-5-methylbenzo)]-9,12,15,18-tetraoxacyclooctadeca-2,5-diene (33). Procedure A was applied to 3 g (7.05 mmol) of 3,3′-bis(bromomethyl)-2,2′-dimethoxy-5,5′-dimethyl-1,1′-diphenyl, 1 g (21 mmol) of NaH (suspension washed free of mineral oil with dry pentane), 700 mL of dry THF, and 1.06 g (7.05 mmol) of triethylene glycol. Addition of the dibromide and diol and refluxing of the mixture were adjusted to produce an additional 10:1 dilution factor. Gel permeation chromatographic column C was used for initial purification of the product, retention volume 160.5 mL of CH_2Cl_2. This material was chromatographed on 200 g of alumina with 97% CH_2Cl_2–3% CH_3OH (v) as eluting agent. The slowest moving band (220–320 mL) was collected, the solvent was evaporated, and the residue was crystallized to give 0.923 g (32%) of product: mp 95–97 °C; M^+ *m/e* 416; ^1H NMR (60 MHz, $CDCl_3$) δ 2.33 (s, CH_3, 6 H), 3.30 (s, CH_3O, 6 H), 3.66 (s, OCH_2CH_2O, 12 H), 4.30 (d, half of A_2B_2 q, J = 12 Hz, $ArCH_2O$, 2 H), 4.81 (d, half of A_2B_2 q, J = 12 Hz, $ArCH_2O$, 2 H), 7.16 (m, ArH, 4 H). Anal. ($C_{24}H_{32}O_6$) C, H.

2,3,4,5,6,7,17,18,19,20,21,22-Tetra[1,3′-(2-methoxy-5-methylbenzo)]-9,12,15,24,27,30-hexaoxacyclotriconta-2,5,17,20-tetraene (34). Procedure A was applied to 3.0 g (7.05 mmol) of 3,3′-bis(bromomethyl)-2,2′-dimethoxy-5,5′-dimethyl-1,1′-diphenyl and 748 mg (7.05 mmol) of diethylene glycol in 500 mL of dry THF which was added to 1.0 g (21 mmol) of NaH (50% oil dispersion washed with dry pentane) and 200 mL of dry THF over a 24-h period. The product was purified by gel permeation chromatography on column C, and gave a retention volume of 132 mL (was the second band). This band gave product that was chromatographed on alumina with Et_2O as solvent. The band with R_f 0.45 was collected, and the product was recrystallized from ether to give 692 mg (26%) of macrocycle: mp 116–119 °C; M^+ *m/e* 744; ^1H NMR (60 MHz, $CDCl_3$) δ 2.25 (s, CH_3, 12 H), 3.23 (s, OCH_3, 12 H), 3.70 (s, OCH_2CH_2O, 16 H), 4.58 (s, $ArCH_2O$, 8 H) 7.01 (m, ArH, 8 H). Anal. ($C_{44}H_{56}O_{10}$) C, H.

2,3,4,5,6,7,11,12,13,14,15,16-Tetra[1,3-(2-methoxy-5-methylbenzo)]-9,18-dioxacyclooctadeca-2,5,10,14-tetraene (35). Procedure A was applied to 2.03 g (4.75 mmol) of 3,3′-bis(bromomethyl)-2,2′-dimethoxy-5,5′-dimethyl-1,1′-diphenyl and 1.44 g (4.75 mmol) of 3,3′-bis(hydroxymethyl)-2,2′-dimethoxy-5,5′-dimethyl-1,1′-diphe-

nyl dissolved in 500 mL of dry THF by adding the solution to 810 mg (17 mmol) of NaH (50% oil dispersion, oil washed out with dry pentane) and 200 mL of refluxing dry THF. Addition time was 30 h. The product was initially purified by gel permeation chromatography on column C (second band, retention volume 153 mL), and was rechromatographed on 200 g of alumina with CH_2Cl_2 as solvent. The material that eluted between 270 and 720 mL was isolated and recrystallized from ether to give 473 mg (18%) of white crystals, mp 159–177 °C. A TLC run on an alumina plate with C_6H_6 as solvent gave two spots with R_f values of 0.18 and 0.07, which did not separate on preparative chromatography. This material is a mixture of isomers that arise due to restricted rotation of the aryl groups (see text): ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.30 (s, CH_3, 12 H), 2.95 (s, CH_3O, 12 H), 4.23 (d, half of A_2B_2 q, J = 12 Hz, $ArCH_2O$, 4 H), 4.78 (d, half of A_2B_2 q, J = 12 Hz, $ArCH_2O$, 4 H), 7.13 (m, ArH, 8 H), and additional signals at 2.36, 2.57, 3.12, 3.17, 3.37, 4.42, and 4.58. Anal. ($C_{36}H_{40}O_6$) C, H.

2,3,4,5,6,7,11,12,13,14,15,16-Tetra[1,3-(2-methoxy-5-methylbenzo)]-9,18-dithiacyclooctadeca-2,5,12,14-tetraene (36). Procedure A was applied to 3.2 g (7.5 mmol) of 3,3′-bis(bromomethyl)-2,2′-dimethoxy-5,5′-dimethyl-1,1′-diphenyl and 2.49 g (7.5 mmol) of 3,3′-bis(thiamethyl)-2,2′-dimethoxy-5,5′-dimethyl-1,1′-diphenyl in 500 mL of dry THF, added dropwise (30 h) to 1.5 g (20 mmol) of NaH in dry THF. The reaction mixture was refluxed for an additional 2 days. The product was subjected to gel permeation chromatography on column C, and had a retention volume of 150.5 mL of CH_2Cl_2 (second band). The product in this band was submitted to alumina–benzene chromatography. The desired product eluted between 180 and 410 mL to give 820 mg (18%) of crystalline solid: mp 197–200 °C; M^+ *m/e* 600; ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.33 (s, $ArCH_3$, 12 H), 3.00 (s, OCH_3, 12 H), 3.63 (d, half of A_2B_2 q, J = 14 Hz, SCH_2, 4 H), 4.01 (d, half of A_2B_2 q, J = 14 Hz, SCH_2, 4 H), 7.13 (m, ArH, 8 H). Anal. ($C_{36}H_{40}O_4S_2$) C, H.

2,3,4,5,6,7,8,9,10-Tri[1,3-(2-methoxy-5-methylbenzo)]-12,15,-18-trioxacyclooctadeca-2,5,8-triene (37), Procedure D. This reaction was carried out in an apparatus fitted with a high-dilution condenser–constant rate addition funnel combination containing a double thimble in the reflux return which diluted by a large factor the solution being added. This procedure was applied to 1.0 g (1.82 mmol) of 2,6-bis(3-bromomethyl-2-methoxy-5-methylphenyl)-4-methylanisole and 233 mg (2.0 mmol) of diethylene glycol dissolved in 50 mL of dry THF (the thimbles contained 20 mL of dry THF). This solution was added at a constant rate with stirring over a 7-h period to 350 mg (4.0 mmol) of NaH and 100 mL of dry THF at reflux under N_2. After the addition was complete, the reaction mixture was held at reflux for an additional 14 h and cooled, and the thimbles were emptied into the pot. The cooled reaction mixture was carefully treated with 0.5 mL of concentrated hydrochloric acid to decompose any excess NaH, and the solvent was evaporated under reduced pressure. The residue was shaken with 250 mL of CH_2Cl_2 and 200 mL of water, and the organic layer was washed with 200 mL of water, dried ($MgSO_4$), and evaporated under reduced pressure. The material was chromatographed on gel permeation column D, the desired product having a retention volume of 179 mL of CH_2Cl_2. Solvent was evaporated under vacuum from the band cut, and the solid residue was washed with two 5-mL portions of pentane to remove any residual mineral oil. The solid was recrystallized from 12 mL of 95% EtOH to give 439 mg (49%) of product: mp 208–209 °C; M^+ *m/e* 492; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.32 (s, outer $ArCH_3$, 6 H), 2.45 (s, inner OCH_3, 3 H), 2.56 (s, inner CH_3O, 3 H), 3.39 (s, outer CH_3, 6 H), 3.61 (s, OCH_2CH_2O, 8 H), 4.40 (AB q, J = 11.7 Hz, $ArCH_2O$, 2 H), 4.78 (AB q, J = 11.7 Hz, $ArCH_2O$, 2 H), 7.06 (s, ArH, 2 H), 7.08 (s, ArH, 2 H), 7.25 (s, ArH), 2 H). Anal. ($C_{30}H_{36}O_6$) C, H. This sample possessed the same properties (melting point, ^{1}H NMR) as did a sample synthesized (not under high-dilution conditions) by procedure A (17% yield), and as did a sample prepared by procedure B from ethylene glycol ditosylate and 2,6-bis(3-hydroxymethyl-2-methoxy-5-methylphenyl)-4-methylanisole in about 28% yield.

2,3,4,5,6,7,8,9,10,14,15,16-Tetra[1,3-(2-methoxy-5-methylbenzo)]-12,18-dioxacyclooctadeca-2,5,8,14-tetraene (38). Application of procedure D to 1.69 g (4.0 mmol) of 2,6-bis(3-hydroxymethyl-2-methoxy-5-methylphenyl)-4-methylanisole, 1.23 g (4.0 mmol) of 2,6-bis(bromomethyl)-4-methylanisole, 0.48 g (10 mmol) of NaH, and 750 mL of dry THF gave product (after a 31-h addition and an additional 5-h reflux time) whose retention volume on gel permeation chromatographic column D was 192 mL of CH_2Cl_2. The product was 0.549 g (24.2%), mp 173–177 °C, which after recrystallization from EtOH gave mp 176–179 °C and was homogeneous to TLC: M^+ *m/e* 568; ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.32 (s, $ArCH_3$, 9 H), 2.37 (s, $ArCH_3$, 3 H), 2.55 (s, inner OCH_3 in *m*-terphenyl unit, 3 H), 2.97 (s, outer OCH_3 in *m*-terphenyl unit, 6 H), 3.63 (s, OCH_3 of isolated anisole unit, 3 H), 4.67 (AB, ν_{AB} = 30.0 Hz, J_{AB} = 11.0 Hz, $ArCH_2O$, 4 H), 4.73 (AB, ν_{AB} = 32.5 Hz, J_{AB} = 13.0 Hz, $ArCH_2O$, 4 H), 7.0–7.2 (m, ArH, 8 H). Anal. ($C_{36}H_{40}O_6$) C, H.

Application of procedure D to 2,6-bis(3-bromomethyl-2-methoxy-5-methylphenyl)-4-methylanisole and 2,6-bis(hydroxymethyl)-4-methylanisole produced a 14% yield of the same macrocycle, **38**, with the same melting point and ^{1}H NMR spectrum as the other sample.

3,4,5,6-Bis[3-methyl-5-(2-methoxy-5-methylphenyl)benzo]-2,7,10,13,16,19-hexaoxacyclodocosa-3,5-diene (39). To a stirred solution of 600 mg (1.32 mmol) of 5,5′-dimethyl-3,3′-bis(2-methoxy-5-methylphenyl)-2,2′-dihydroxydiphenyl in 24 mL of pure THF stirred under N_2 was added 361 mg (5.5 mmol) of 85% KOH, and the mixture was stirred under N_2 at reflux for 0.5 h. A solution of 721 mg (1.32 mmol) of pentaethylene glycol ditosylate[12] in 64 mL of pure THF was added, and the mixture was stirred at reflux under N_2 for 48 h, at which time all starting materials had been consumed (TLC). The mixture was cooled and acidified with 6 N HCl, the solvent was evaporated under reduced pressure, and the residue was shaken with 200 mL of Et_2O and 100 mL of water. The organic layer was washed with 100 mL of water and 100 mL of brine and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was submitted to gel permeation chromatography on column D to give 400 mg (45%) of nearly pure product with a retention volume of 167 mL of CH_2Cl_2. This material was chromatographed on an alumina medium-pressure column with Et_2O as eluent to give 340 mg (39%) of product as a glass; M^+ *m/e* 656; ^{1}H NMR (200 MHz, $CDCl_3$), δ 2.30 (s, $ArCH_3$, 6 H), 2.33 (s, $ArCH_3$, 6 H), 2.88–3.69 (m, OCH_2CH_2O, 20 H), 3.75 (s, CH_3O, 6 H), 6.82–7.11 (m, ArH, 10 H). Anal. ($C_{40}H_{48}O_8$) C, H.

3,4,5,6-Bis(2-methylbenzo)-2,7,10,13,16,19-hexaoxacyclodocosa-3,5-diene (40). Essentially the same procedure described for the preparation of **39** was applied to 0.60 g (2.8 mmol) of 2,2′-dihydroxy-5,5′-dimethyldiphenyl, 1.53 g (2.8 mmol) of pentaethylene glycol ditosylate,[12] 0.47 g of 85% KOH (8.4 mmol), 250 mL of purified THF, and 9 mL of H_2O. The product gave a 182-mL CH_2Cl_2 retention volume on gel permeation column D, and was further purified by medium-pressure chromatography on silica gel with ether as eluent to yield 557 mg (48%) of cycle **40** as a solid. The material was recrystallized from 95% ethanol at −20 °C to yield 470 mg (41%) of product: mp 96.5–97.5 °C; M^+ *m/e* 416; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.30 (s, $ArCH_3$, 6 H), 3.48–4.17 (m, OCH_2CH_2O, 20 H), 6.82–7.09 (m, ArH, 6 H). Anal. ($C_{24}H_{32}O_6$), C, H.

Determination of Association Constants (K_a) for Metal Picrate Salts and Ligand Systems. This procedure is a modification of the one reported previously,[15a] and is more reproducible than the earlier method. The values of the distribution constants (K_d, see eq 3) of the picrate salts between water and $CDCl_3$ determined earlier were used here, as well as the method of calculating K_a (eq 1) values. Only the experimental means of determining the values of the extraction constant (K_e, see eq 2) were changed as follows.

All operations were conducted at 24–26 °C. Absorbances were determined at 380 nm with a Beckman DU spectrophotometer equipped with a Gilford Model 252 modernization system. Spectral grade solvents were used throughout. Picrate salts[15a] were dried under high vacuum before use. Aqueous solutions were prepared that were 0.0150 M in the picrate of Li^+, Na^+, K^+, NH_4^+, $CH_3NH_3^+$, and $(CH_3)_3CNH_3^+$ and 0.0100 M in the picrates of Rb^+ and Cs^+ (the latter are less soluble in water than the former). Into each of six 12-mL centrifuge tubes was transferred 0.50 mL of the appropriate picrate solution with a Labindustries Micropipettor. When Rb^+ or Cs^+ picrates were involved, 0.75-mL portions of each solution were added to 12-mL centrifuge tubes with a 1-mL graduated pipet. Aliquots (0.50 mL) of a previously prepared $CDCl_3$ solution that was 0.0150 M in host were added with volumetric pipets to each tube. The tubes were covered immediately with rubber septums to prevent evaporation and were centrifuged in a hand-worked machine for 10 s each to force the organic phase completely to the bottom of each tube. The two layers in each tube were mixed thoroughly using a Vortex Genie mixer for 1 min. The tubes were then placed in an International Clinical centrifuge for 10 min at high speed. Aliquots varying from 0.0050 to

Table III. Comparison of R, K_a, and $-\Delta G°$ Values Obtained from H_2O and $CDCl_3$ Layers at Equilibrium in Picrate Salt Extraction Experiments with 2,3-Naphtho-18-crown-6 as Host

picrate salt of	calcd for $CDCl_3$ layer			calcd for H_2O layer		
	R	$K_a \times 10^{-3}$, M^{-1}	$-\Delta G°$, kcal/mol	R	$K_a \times 10^{-3}$, M^{-1}	$-\Delta G°$, kcal/mol
Li^+	0.007 04	22.5	5.9	0.0154	50.5	6.4
Na^+	0.185	856	8.1	0.226	1220	8.3
K^+	0.720	66 200	10.7	0.740	85 900	10.8
Rb^+	0.560	15 400	9.8	0.524	11 300	9.6
Cs^+	0.287	1520	8.4	0.262	1250	8.3
NH_4^+	0.546	7580	9.4	0.575	9850	9.5
$CH_3NH_3^+$	0.308	316	7.5	0.315	334	7.5
t-$BuNH_3^+$	0.518	92	6.8	0.534	105	6.9

Table IV. Values of Extinction Coefficient (ϵ) in CH_3CN at 380 nm and Distribution Constants (K_d) for Picrate Salts between H_2O and $CDCl_3$ at 24–26 °C

picrate salt	ϵ, M^{-1} cm^{-1}	$K_d \times 10^3$, M^{-1}
Li^+	16 900	1.42
Na^+	16 900	1.74
K^+	16 900	2.55
Rb^+	16 900	4.57
Cs^+	16 900	5.41
NH_4^+	17 700	4.02
$CH_3NH_3^+$	17 400	14.5
t-$BuNH_3^+$	17 400	237

0.1000 mL of the organic phase (depending on its color intensity) were very carefully removed from each phase with a Hamilton Gastight syringe and transferred to 5-mL volumetric flasks which were brought to the mark with CH_3CN. From each of the aqueous phases was removed a 0.010-mL aliquot with a SM1 Micropipettor. The aqueous aliquots were also pipetted into 5-mL volumetric flasks which were brought to the mark with CH_3CN. The absorbance of each sample was then determined and the R and K_a values were calculated as before.[15a,17] The R, K_a, and $\Delta G°$ values of the standard compound 2,3-naphtho-18-crown-6 determined from the water and the $CDCl_3$ layers are listed in Table III to illustrate the type of agreement. The $CDCl_3$ layer was 0.0154 M in host and the temperature was 24–26 °C.

Equation 6 was employed for calculation of R_{CDCl_3} from the aqueous measurements. Definitions are as follows: A is the observed absorbance in the aqueous phase, D is the dilution factor, ϵ is the extinction coefficient of the picrate salt at 380 nm in CH_3CN, $[G_i^+]$, is the initial concentration of guest in the aqueous phase, V_{aq} is the volume of the aqueous phase, V_{org} is the volume of the organic phase, and $[H_i*]$ is the initial concentration of the host in the $CDCl_3$ phase.

$$R_{CDCl_3} = \frac{\{[G_i^+] - A(D/\epsilon)\}(V_{aq}/V_{org})}{[H_i*]} \quad (6)$$

Table IV records the values of ϵ and K_d from which R_{org}, K_e, and K_a were calculated.

References and Notes

(1) The authors thank the Division of Basic Sciences of the Department of Energy for a contract, AT(04-3)34, P.A. 218, which supported this research.
(2) Some of these results appeared in a communication: K. E. Koenig, R. C. Helgeson, and D. J. Cram, *J. Am. Chem. Soc.*, **98**, 4018–4020 (1976).
(3) This author thanks the NATO (DAAD) for a fellowship.
(4) W. J. Moran, E. C. Schreiber, E. Engel, D. C. Behn, and J. L. Yamins, *J. Am. Chem. Soc.*, **74**, 127–129 (1952).
(5) M. Harnfest, A. Bavley, and W. A. Lazier, *J. Org. Chem.*, **19**, 1608–1616 (1954).
(6) (a) G. Adda and R. Pallaud, *C. R. Acad. Sci., Ser. C*, **266**, 35–36 (1968); (b) L. F. Elsom, J. D. Hunt, and A. McKillop, *Organomet. Chem. Rev., Sect. A*, **8**, 135–152 (1972).
(7) O. R. Pummerer, H. Puttfargken, and P. Schopflocher, *Chem. Ber.*, **58**, 1808–1820 (1925).
(8) (a) K. Bowden and C. R. Reece, *J. Chem. Soc.*, 2249 (1950); (b) W. I. Taylor and A. R. Battersby, Eds., "Oxidative Coupling of Phenols", Marcel Dekker, New York, 1967; (c) R. A. Anderson, D. T. Dagleish, D. C. Nonhebel, and P. L. Pauson, *J. Chem. Res., (M)*, 0201–0209 (1977).
(9) N. Tsuĝi and K. Nagashima, *Tetrahedron*, 3017–3031 (1969).
(10) M. J. S. Dewar and T. Nakaya, *J. Am. Chem. Soc.*, **90**, 7134–7135 (1968).
(11) M. Newcomb, J. M. Timko, D. M. Walba, and D. J. Cram, *J. Am. Chem. Soc.*, **99**, 6392–6398 (1977).
(12) M. Newcomb, S. S. Moore, and D. J. Cram, *J. Am. Chem. Soc.*, **99**, 6405–6410 (1977).
(13) M. A. McKervey and D. L. Mulholland, *J. Chem. Soc., Chem. Commun.*, 438–439 (1977).
(14) The authors thank Professor K. N. Trueblood for this information in advance of publication.
(15) (a) S. S. Moore, T. L. Tarnowski, M. Newcomb, and D. J. Cram, *J. Am. Chem. Soc.*, **99**, 6398–6405 (1977); (b) R. C. Helgeson, G. R. Weisman, J. L. Toner, T. L. Tarnowski, Y. Chao, J. M. Mayer, and D. J. Cram, *ibid.*, in press.
(16) R. C. Helgeson, T. L. Tarnowski, J. M. Timko, and D. J. Cram, *J. Am. Chem. Soc.*, **99**, 6411–6418 (1977).
(17) The authors wish to thank Dr. John Toner and Dr. Lester Kaplan for refining this technique and applying it to standard hosts.