of K_a in this paper was the overall average of the six determinations, which was $0.96 \pm (0.04) \times 10^{-5}$ M^{-1}.

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Host–Guest Complexation. 5. Convergent Functional Groups in Macrocyclic Polyethers[1,2]

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Abstract: Thirteen 2′-R-1′,3′-xylyl-*m*-crown-*n*-macrocyclic polyethers are reported where R = CO_2CH_3 (m = 15, n = 4; m = 18, n = 5; m = 21, n = 6; m = 30, n = 9); where R = CO_2H (m = 15, n = 4; m = 18, n = 5; m = 21, n = 6; m = 30, n = 9); where R = CH_2OH, CH_2OCH_3, Br, Cl, or CN (m = 18, n = 5). The pK_as in water at 22 °C of the cycles with R = CO_2H were found to be m = 15, n = 4, 4.8; m = 18, n = 5, 4.8; m = 21, n = 6, 3.8; m = 30, n = 9, 3.4; acyclic model compound 2,6-bis(methoxymethyl)benzoic acid, 3.3. In the smaller cycles, the carboxylic acid group is the most thoroughly hydrogen bonded. Association constants (K_a) were determined for complexation of *tert*-butylammonium thiocyanate with nine of the cycles in $CDCl_3$ at 22 °C. For the R groups in the 18-membered ring hosts, $CO_2CH_3 \gg H > CH_2OCH_3 \sim CH_2OH > CO_2H > CN$ in their ability to stabilize the complexes. When R = CO_2CH_3, the hosts changed in complexing power as follows: 18-membered $\gg$ 21-membered > 30-membered > 15-membered macrocycle. These results correlated with expectations based on examination of scale molecular models of the complexes. The anionic form of the four cyclic acids and their model compound were tested for their abilities to lipophilize Li^+, Na^+, K^+, and Ca^{2+} by distributing their host salts at 22 °C between CH_2Cl_2 and water. Maximum lipophilization occurred when hosts and guests were coupled as follows: Li^+, 18-membered ring; Na^+, 21-membered ring; K^+, 30-membered ring; Ca^{2+}, 18-membered ring. For all ions, the 15-membered ring host was poorer than the open-chain model. The *t*-$BuNH_4^+$ salts of the same host acids were distributed between D_2O and $CDCl_3$ at 22 °C. The distribution constants for the 2′-carboxylate-1′,3′-xylyl host salts (K_d = $[salt]_{CDCl_3}/[salt]_{D_2O}$) ranged from 0.7 to 0.02 in the order 18-crown-5 > 21-crown-6 > 30-crown-9 > open-chain model > 15-crown-5. The ^1H NMR spectra of the *t*-$BuNH_3^+$ complexes of the 1′,3′-xylyl-18-crown-5 hosts indicated a structure that placed the *t*-Bu protons in the shielding cone of the xylyl group.

One of the problems central to the design of host compounds is that of the placement of substituents in positions that converge on the functional or binding sites of guest compounds. Molecular model (Corey-Pauling-Koltun, or CPK) examination of macrocyclic polyethers containing a 1,3-xylyl unit as part of the large ring indicates that substituents attached to the 2 position of the aryl group are directed inward toward the hole of the cycle. Earlier work demonstrated that substituent variation in the 5′ position of 1′,3′-xylyl-18-crown-5 produced changes in $CDCl_3$ at 24 °C of association constants between cycles and the cations of inorganic and organic salts by factors as large as 54.[3] Effects of this magnitude, exerted by substituents both remote and divergent from the point of complexation, have been interpreted as evidence that the π system of 1,3-xylyl unit acts as a binding site.[3] The present study is concerned with the effects of convergent substituents on the binding properties of hosts containing the 2-substituted 1,3-xylyl unit.

Syntheses. New cycles **1–4** were prepared from dibromide **16** and the appropriate polyethylene glycols as starting materials. Moderately high dilution conditions were realized by slow, dropwise addition of an equimolar mixture of dibromide

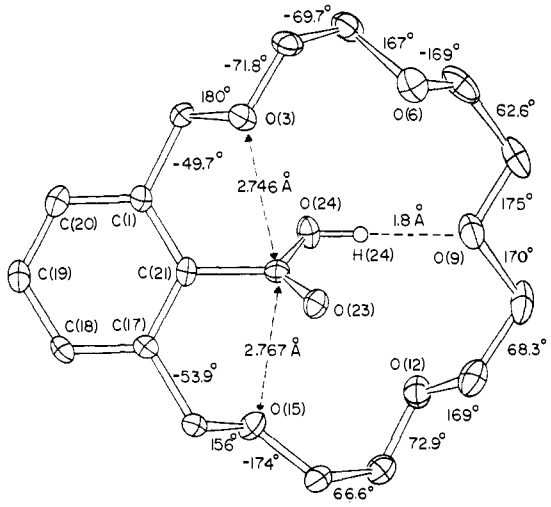
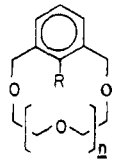
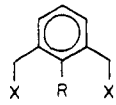


Figure 1.

16 and the appropriate polyethylene glycol[4] in tetrahydrofuran (THF) to a stirred mixture (under N_2) of sodium hydride and refluxing THF. The reactions were fast enough so that starting materials did not accumulate, and yields as high as 82% were obtained. Open-chain model compound **20** was prepared from **16** and $NaOCH_3$ in THF. Cycles **5–10** were prepared by conventional reactions from **1–4**, whereas **11** was already available.[3,4b] Cycles **12–14** were prepared from dibromides **17–19**, respectively, by adding the dibromide to the already prepared tetraethylene glycol sodium dialkoxide.[5] Attempts to convert chloride **13** to acid **6** failed.





	n	R		n	R	
1,	2	CO_2CH_3	8,	7	CO_2H	15, X = H, R = CO_2CH_3
2,	3	CO_2CH_3	9,	3	CH_2OH	16, X = Br, R = CO_2CH_3
3,	4	CO_2CH_3	10,	3	CH_2OCH_3	17, X = Br, R = Cl
4,	7	CO_2CH_3	11,	3	H	18, X = Br, R = Br
5,	2	CO_2H	12,	3	Br	19, X = Br, R = CN
6,	3	CO_2H	13,	3	Cl	20, X = OCH_3, R = CO_2H
7,	4	CO_2H	14,	3	CN	

All of the macrocycles except the two containing 15-membered rings (**1** and **5**) gave singlets for their $ArCH_2$ protons in their ^1H NMR spectra at ambient temperature. Compounds **1** and **5** gave an AB system for these protons. Thus at 25 °C, ring inversion is slow on the NMR time scale for **1** and **5** but not for their larger analogues. Molecular models (CPK) of **1** and **5** indicate that a considerable steric barrier inhibits ring inversion.

Acidity of Carboxyl-Containing Cycles and an Acyclic Model. The pK_as (±0.2) of the four cyclic and one acyclic carboxylic acids were determined with a pH meter in water at 22 °C with LiOH and HCl solutions. Table I records the results.

The open-chain model compound (**20**) and the largest cycle (**8**) containing 30 ring atoms (9 O's) have essentially the same pK_as and are about 1.5 units more acidic than the smallest cycles, **5** and **6**. Molecular models (CPK) suggest that two effects are responsible for these acidity differences. (1) The structures of **5** and **6** are relatively rigid, and their carboxyl groups hydrogen bond to the transannularly located ether oxygens. Although transannular hydrogen bonds can form in models of **7** and **8**, many more conformations are frozen out in the resulting structures. The open-chain model compound possesses only benzyl ether oxygens whose intramolecular hydrogen bonding to the carboxyl group is sterically inhibited by the inability of the carboxyl group to become coplanar with the aryl ring. Thus **5** and **6** are uniquely stabilized by internal hydrogen bonding. (2) Molecular models of the carboxylate anions of the cycles indicate that those of **5** and **6** are more rigidly located in the center of the macrocycle. Thus steric inhibition of solvation of the anion in the smaller rings should be more prominent than in the larger rings or the open-chain model.

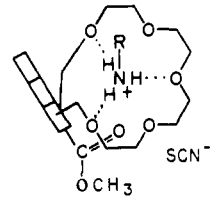
Table I. Variation of Acidity with Ring Size

Compd No.	Ring size	pK_a
5	15	4.8
6	18	4.8
7	21	3.8
8	30	3.4
20	0	3.3

Support for this interpretation is found in the x-ray crystal structure (Figure 1) of **6** taken at 93 K.[6a] The three atoms involved in the hydrogen bond, O(24)-H(24)···O(9), describe a 174° bond angle, the O(24)-H(24) bond distance is 0.88 Å, and the H(24)···O(9) is 1.84 Å. As expected from model examination, the ether oxygens generally turn inward, the methylenes outward, and the OCH_2CH_2O units describe gauche conformations with dihedral angles that vary from 63° to 70°. The benzyl ether oxygens (as in CPK models) contact the carboxyl carbon in such a way that one lone pair of each oxygen points toward the carbonyl carbon along the axis of its π system. This arrangement coupled with the shorter than usual van der Waals contacts of 2.75 and 2.77 Å suggests the presence of attractive dipole-dipole O···C=O interactions.[7] The correspondence between the x-ray structure and CPK model structure is remarkably good, and emphasizes the profit of scale molecular model examination in host design.

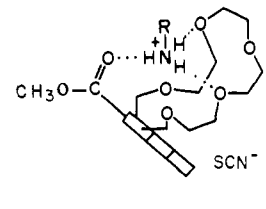
Association Constants for Complexation of *tert*-Butylammonium Thiocyanate and the Structures of the Complexes. Association constants (K_a) for nine of the cycles with *t*-$BuNH_3^+SCN^-$ in $CDCl_3$ at 24 °C were determined by the extraction-^1H NMR spectral technique (scale C).[4b] Table II records the calculated values of K_a (corrected to scale A),[4b] the observed values of the molar ratios of guest to host in the $CDCl_3$ layer at equilibrium (R), and the upfield chemical shifts relative to Me_4Si of the *t*-Bu protons of the complex in the $CDCl_3$ layer.

When R = CO_2CH_3, the hosts changed in complexing ability with changing ring size in the following order: 18-membered ≫ 21-membered > 30-membered > 15-membered. In CPK molecular models, the cycle containing the 18-membered ring provides the most ideal fit of host to guest, a fact which correlates with the ≥1.8 kcal/mol greater stability of its complex. In the complex's *nesting* conformation B, the ring



B

nesting conformation



C

perching conformation

Table II. Association Constants (K_a), Free Energies of Association, Molar Guest to Host Ratios (R), and Upfield Chemical Shifts (δ) of CH_3 Relative to Me_4Si for Complexes with *tert*-Butylammonium Thiocyanate in $CDCl_3$ at 24 °C

Host			Complex			
No.	Ring size	R group	K_a, M^{-1}	$-\Delta G$, kcal/mol	R	δ, ppm
1	15	CO_2CH_3	≲490	≲3.7	≤0.05	
2	18	CO_2CH_3	55 600	6.5	0.80	0.93
3	21	CO_2CH_3	3 000	4.7	0.23	1.05
4	30	CO_2CH_3	780	3.9	0.08	1.25
6	18	CO_2H	1 240	4.2	0.12	0.96
9	18	CH_2OH	2 300	4.6	0.19	0.95
10	18	CH_2OCH_3	2 500	4.6	0.20	0.93
11	18	H	3 300	4.8	0.25	0.96
14	18	CN	1 150	4.2	0.11	1.03

oxygens almost perfectly encircle (300 out of 360°) the NH_3^+ group which is bound by three $NH^+\cdots O$, two $N^+\cdots O$, one $N^+\cdots O{=}C$, and one $N^+\cdots\pi$aryl interactions. In the *perching* conformation C, the NH_3^+ group is far less deeply enveloped and is bound by two $NH^+\cdots O$, one $NH^+\cdots O{=}C$, and three $N^+\cdots O$ interactions. In B, two H's of the CH_3 groups of the guest lie in the shielding cone of the aryl group of the host, whereas in C, the aryl and CH_3 groups are distant from one another.

The chemical shift in $CDCl_3$ relative to Me_4Si of the *t*-Bu protons of *t*-$BuNH_2$ is δ 1.15 and that of its thiocyanate salt is δ 1.49. When solutions of **2, 3,** and **4** in $CDCl_3$ were used to extract *t*-$BuNH_3^+SCN^-$ into the organic phase, the ^1H NMR spectrum revealed that the *t*-Bu signal had moved upfield relative to that of uncomplexed salt by 0.56, 0.44, and 0.24 ppm, respectively. When 18-crown-6 was used as host in the extraction, an upfield shift of only 0.11 ppm was observed, but the signal remained significantly downfield from that observed for *t*-$BuNH_2$ in $CDCl_3$ in the absence of host. The upfield shift of the *t*-Bu signal in the complexes of *t*-$BuNH_3^+SCN^-$ with **2, 3,** and **4** relative to that for the complex with 18-crown-6 indicates that the *t*-Bu group of the guest lies within the shielding cone of the aryl ring in the complexes of **2, 3,** and **4.** These results provide evidence that the nesting conformation B contributes substantially to and probably dominates an equilibrium mixture between B and C. They also indicate that as the number of potential binding sites of the host exceed those of the guest as in the complexes of **3** and **4,** the complex is less rigid and less ordered, and the average distance between the *t*-Bu group of the guest and the face of the aryl group increases. This trend has also been observed by others[8] in the binding of *t*-$BuNH_3^+PF_6^-$ by 1′,3′-xylyl-18-crown-5 (**11**), 1′,3′-xylyl-21-crown-6, and 1′,3′-xylyl-30-crown-9.

For the R groups in the 18-membered ring hosts, $CO_2CH_3 \gg H > CH_2OCH_3 \sim CH_2OH > CO_2H > CN$ in their abilities to stabilize the complexes. In the CPK models of nesting conformations of these complexes, the plane of the aryl is tilted out of the best plane of the ether oxygens by about 30-60°. The angle decreases with changes in the R group in the order $CH_2OCH_3 \sim CH_2OH \sim CN > CO_2CH_3 \sim CO_2H > H$. Sterically all the R groups probably destabilize the complexes, but groups such as CO_2CH_3 and CH_2OCH_3 compensate by providing an extra $N^+\cdots O$ binding interaction site. The complex for **2** is 1.7 kcal/mol *more stable* than that for **11,** and that for **10** is 0.2 kcal/mol less stable than that for **11.** The electron pair of the linear and space-consuming cyano group is mislocated to act as a ligand, and with R = CN as in **14,** the complex is 0.6 kcal/mol less stable than when R = H as in **11.** When R = CO_2H as in **6,** the uncomplexed host is stabilized by an intramolecular hydrogen bond (see last section) which must be broken before complexation can occur. Thus the complex of **6** is less stable than that of **2** where R = CO_2CH_3 by 2.3 kcal/mol.

The data of Table II indicate that the chemical shifts of the *t*-Bu signals observed for the complexes of *t*-$BuNH_3^+SCN^-$ with all of the 18-membered cycles are remarkably similar. This fact indicates that in spite of the fact that K_a values vary considerably with variations of the substituent in the 2′ position, the structures of the complexes do not. This constancy of structure indicates that a single discrete conformation which is substituent independent dominates the complexes. The upfield shift of the *t*-Bu group in these complexes indicates that the nesting conformation applies.

Acid **6** formed a crystalline 1:1 salt with *tert*-butylamine when mixed in cyclohexane-dichloromethane. The x-ray crystal structure at 120 K of this complex proved to possess the perching conformation, two views of which are shown in Figures 2 and 3.[6b] Noteworthy features of this structure are as follows: (1) The complex is held together by one very short (1.70 Å) $NH^+\cdots\overline{O}$, two longer (2.21 Å) $NH^+\cdots O$ hydrogen bonds in a tripod arrangement, and by less important in-between $N\cdots O$ interactions, one of 3.11 and two of 3.49 Å distance (see Figure 2). (2) The *t*-Bu-N bond is only 3.4° from being perpendicular to the least-squares plane of the six oxygen atoms (see Figure 3). (3) The dihedral angles of H-N^+-C-C are about 60° (see Figure 2). (4) The six binding oxygens all turn inward and somewhat upward toward the N^+, and provide gauche O-C-C-O conformations with dihedral angles between the oxygens of 71 and 72°. (5) The rotations of the methyl groups of the *t*-Bu are frozen out and form an array of C-H bonds that resemble part of a chair cyclohexane ring (see Figure 3). Thus three C-H bonds possess axes parallel to the C-N bond axis and resemble axial H's. Six C-H bonds are equatorially arranged about the C of the N-C bond. (6) The plane of the aryl intersects the best plane of the six binding O's at an angle of less than 90°, and the aryl group partially covers the approach to the central hole of the guest from the side remote from the *t*-Bu group.[6b]

Examination of CPK molecular models of the complex of the perching structure conforms remarkably well to the observed x-ray structure. However, CPK models of the nesting structure appear equally attractive and resemble B except that the O contacting the N^+ from the carboxylic group carries a negative charge. The chemical shift in $CDCl_3$ of the *t*-Bu protons of the salt made from *t*-$BuNH_2$ and 2′-carboxy-1′,3′-xylyl-18-crown-5 (**6**) occurred at δ 1.07 ppm. The corresponding chemical shift in the complex between *tert*-butylammonium thiocyanate and **6,** formed by the extraction of a D_2O solution of *tert*-butylammonium thiocyanate with a $CDCl_3$ solution of **6**, was δ 0.96 ppm. Similarly, the chemical shift for the complex between *t*-$BuNH_3^+SCN^-$ and ester **2** was δ 0.93 ppm. The chemical shifts of the *t*-Bu protons in the complexes formed by extracting *t*-$BuNH_3^+ClO_4^-$, SCN^-, and picrate from D_2O into $CDCl_3$ solutions of 1′,3′-xylyl-18-crown-5 occurred at δ 0.86, 0.94, and 0.96 ppm, respectively. These last three chemical shifts vary only 0.1 ppm with vari-

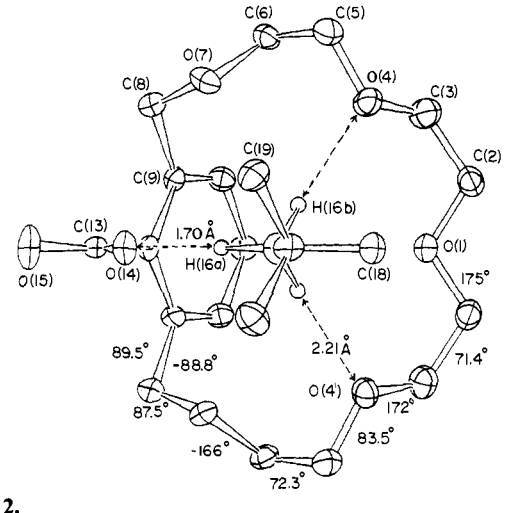


Figure 2.

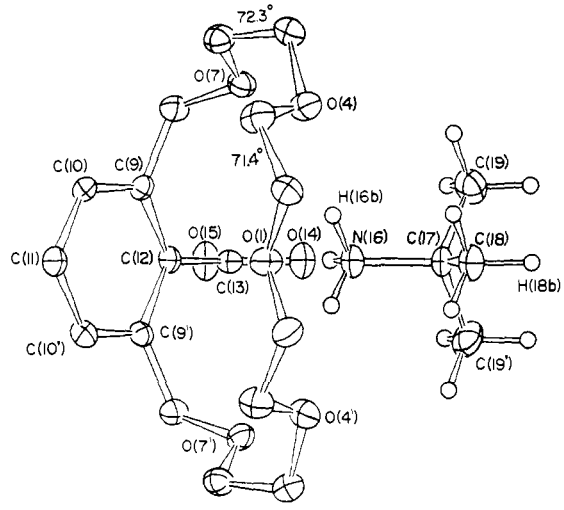
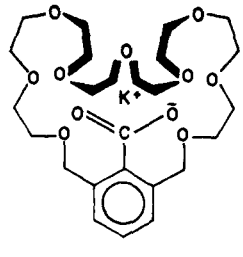


Figure 3.

ation in counterion. In contrast, the chemical shifts in $CDCl_3$ of the complex formed by extraction of t-$BuNH_3^+SCN^-$ in D_2O with 18-crown-6 in $CDCl_3$ gave δ 1.38 ppm. Uncomplexed t-$BuNH_3^+SCN^-$ in $CDCl_3$ gave δ 1.49 ppm, and t-$BuNH_3^+ClO_4^-$ gave δ 1.47 ppm. These results taken as a whole indicate that in $CDCl_3$ solution the salt formed from t-$BuNH_2$ and acid cycle **6** possesses a conformation in which the t-Bu protons are in the shielding cone of the aryl group of the host, which is only possible in the nesting conformation. Thus this conformation at least makes a substantial contribution to the equilibrium mixture of conformers in solution, in contrast to the crystalline complex which possesses the perching structure.

Lipophilization of Ions with Anionic Ligand Assemblies. The charged naturally occurring ionophores such as the antibiotics of the nigericin group selectively ion pair, complex, and lipophilize metal ions.[9] The anionic forms of host acids **5–8** and **20** were tested roughly for their abilities to lipophilize Li^+, Na^+, K^+, and Ca^{2+}. Their salts with the hosts were distributed at 22 °C between dichloromethane and water. Table III records the results.

Maximum lipophilization of each ion depended on the ring size of the host: for Li^+, 18-membered; for Na^+, 21-membered; for K^+, 30-membered; for Ca^{2+}, 18-membered. For all ions, the 15-membered ring host **5** was poorer than the open-chain host **20.** For the monovalent cations and the restricted series of anions of **5–8,** the maximum lipophilization occurs with different host-guest combinations, the larger rings better lipophilizing the larger ions. The effects are not dramatic, possibly because of cancellation in the large number of parameters that contribute to the distribution coefficients of the salts. Structure F is visualized for the potassium salt of **8.**



F

Rough distribution constants (K_d) for the *tert*-butylamine salt complexes of **5–8** and **20** between D_2O and $CDCl_3$ were determined at 22 °C: for **5,** ~0.02; for **6,** 0.7; for **7,** 0.36; for **8,** 0.27; for **20,** ~0.06. These results suggest that the salt of **6** is the best organized of the complexes to bury the hydrophilic sites of both host and guest in a lipophilic skin of C–H bonds. The observed order was predicted in advance of experiment by molecular model (CPK) examination of the complexes.

Table III. Distribution of Salts of Hosts between Water and Chloroform at 22 °C

	% salt in CH_2Cl_2 layer			
Salt of	Li^+	Na^+	K^+	Ca^{2+}
5	1.4	1.5	1.4	1.1
6	7.2	7.9	6.7	4.8
7	6.1	8.7	6.8	1.8
8	3.4	5.2	8.0	2.9
20	3.3	3.2	2.8	3.4

Experimental Section

General. All reactions with alkoxides or organometallics were run under nitrogen. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen. All temperatures were uncorrected. Melting points were taken on a Thomas-Hoover apparatus. Characterizing ^1H NMR spectra in $CDCl_3$ were recorded on a Varian T-60 spectrometer, and analytical spectra on a Varian HA-100 spectrometer. Infrared spectra were taken on a Beckman IR-5 spectrometer. All gel permeation chromatographs were run on an 18 ft by $\frac{3}{8}$ in. column of 200/400 Bio Beads SX-8 in THF as solvent, at ~400 psi and 3 mL/min. Gas-liquid partition chromatographs (GLC) were run on a 6 ft by $\frac{1}{4}$ in. 15% SE-30 on 60/80 firebrick. Mass spectra were taken on an AEI Model MS-9 double-focusing mass spectrometer at 70 eV.

Starting Materials. By the method published for the synthesis of mesitoic acid,[10] 2,6-dimethylbenzoic acid was prepared (80%) from 2,6-dimethylbromobenzene, except that 1,2-dibromoethane was used in place of bromoethane, mp 114–116 °C (lit.[11] mp 115 °C). The substance 2,6-dimethylbromobenzene was made from 2,6-dimethylaniline (41%) by the procedure[12] for the synthesis of *o*-bromotoluene, bp 78–81 °C (7 Torr) (lit.[13] bp 203–204 °C). From 2,6-dimethylaniline (Eastman) was prepared (27%) 2,6-dimethylchlorobenzene (bp 74–78 °C at 13 Torr, lit.[13] bp 184–185 °C) by a procedure similar to that for the preparation of *o*-chlorotoluene[14] except that the mixture of diazotized aniline and cuprous chloride was kept at 0 °C for 3 h before warming. Methyl 2,6-dimethylbenzoate (**15**) was prepared as follows. A solution of 3.0 g (20 mmol) of 2,6-dimethylbenzoic acid in 15 mL of thionyl chloride was stirred at 25 °C for 10 h and cooled to 0 °C, and 50 mL of absolute methanol was slowly added. The mixture was stirred at 25 °C for 3 h and distilled to give 3.2 g (~100%) of **15,** bp 90–93 °C (4 Torr), lit.[15] bp 109 °C (19 Torr). From 2,6-dimethylaniline was prepared[16] (25%) 2,6-dimethylbenzonitrile, mp 89–90 °C (lit.[16] mp 89–89.5 °C).

Brominations by *N*-Bromosuccinimide (NBS). The 2-substituted 1,3-xylene was dissolved in CCl_4 (dried over CaH_2), and 2.2 equiv of

NBS and a trace of dibenzoyl peroxide were added to the solution. The resulting mixture was warmed at reflux with stirring under a drying tube until all the NBS was consumed (3-12 h). The mixture was filtered, the filtrate was washed with water and evaporated in vacuo, and the residue was crystallized from cyclohexane. The methyl 2,6-bis(bromomethyl)benzoate (**16**) was obtained in 46% yield: mp 77-79 °C; ^{1}H NMR δ 3.9 (s, 3, CH_3), 4.5 (s, 4, $ArCH_2$), 7.2 (m, 3, ArH). Anal. Calcd for $C_{10}H_{10}Br_2O_2$: C, 37.30; H, 3.13. Found: C, 37.16; H, 3.23.

The 2,6-bis(bromomethyl)chlorobenzene (**17**) was obtained in 22% yield, mp 84-88 °C (lit.[17] 86-87 °C). The 2,6-bis(bromomethyl)-bromobenzene, **18** (55%),[5] gave mp 101-103 °C (lit.[17] mp 97-98 °C). The 2,6-bis(bromomethyl)benzonitrile[18] was not purified but was used directly in the ring-closing reaction (see below).

Ring-Forming Reactions. Cycles **1-10** and **12-14** were produced from dibromides **16-19** and oligoethylene glycols[19] by two methods. In method A, tetraethylene glycol in THF (0.025 M) was metalated with 2.5 equiv of NaH, and a solution (0.025 M) of dibromide in THF was added dropwise over 3 h at 25 °C to the stirred mixture under nitrogen. The resulting mixture was stirred for 12 h at 25 °C, quenched with excess water, filtered, and evaporated in vacuo. The residue was distributed between aqueous hydrochloric acid and CH_2Cl_2, and the aqueous solution was extracted twice with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered, and evaporated in vacuo, and the residue was purified by chromatography on silica gel with CH_2Cl_2 or acetone in CH_2Cl_2 as eluting agent. When necessary, monomers were separated from oligomers by gel permeation chromatography. Analytical samples were prepared by GLC where retention times are indicated.

In method B, an equimolar solution (0.02 M) of dibromide and oligoethylene glycol in THF was added dropwise with stirring under nitrogen over about a 3-h period to a refluxing mixture of 3 equiv of NaH (if the NaH were in solution, it would be 0.02 M). The mixture was stirred at 25 °C for 12 h, and the product isolated and purified as in method A.

Pentaethylene Glycol and Other Glycols.[19] To a solution of 48 g (0.86 mol) of potassium hydroxide in 200 mL of ethylene glycol was added 84 g (0.43 mol) of 1,8-dichloro-3,6-dioxaoctane. The mixture was refluxed at ~120 °C for 24 h, cooled, and filtered. The precipitate was washed with acetone (2 × 50 mL) and the filtrate distilled under vacuum (105 °C 12 mm) to remove acetone and ethylene glycol. The residue was fractionally distilled through a 12-in. Vigreux column. A center cut of pentaethylene glycol (43.3 g, 43%) was collected at bp 173-174 °C (0.6 mm) (reported bp 174-176 °C (0.14 mm)).[20] The diol was found to be 99% pure by GLC analysis on a F and M Model 720 instrument fitted with a 6 ft by 0.25 in. column packed with 20% SE-30 on 60-80 mesh Chromosorb W. The following retention times were observed with a flow rate of 60 mL/min and an oven temperature of 240 °C: triethylene glycol, 2.2 min; tetraethylene glycol, 4.2 min; and pentaethylene glycol, 8.5 min. The neat IR spectrum exhibited an absorption at 3350 cm^{-1} (br, OH bonded). The ^{1}H NMR spectrum (100 MHz) in $CDCl_3$ (~20% v/v) exhibited absorptions at δ 3.62 (m, OCH_2) and 3.80 (s, OH).

Hexaethylene Glycol. To 408.98 g (3.854 mol) of stirred diethylene glycol (Eastman, dried over activated 4 Å molecular sieves) was added 12.62 g (0.5490 mol) of freshly cut sodium metal. The mixture was stirred at room temperature under a nitrogen atmosphere until alkoxide formation was complete (several hours). Diethylene glycol ditosylate (101.7 g, 0.2455 mol) was then added and the reaction mixture was heated on a steam bath for 13 h. Vacuum distillation of the product yielded a viscous, yellow liquid (ca. 190-210 °C (0.1 mm)) (filtration for removal of sodium tosylate was necessary several times during the course of the distillation). The product was further fractionated through a 6-in. Vigreux column to yield fraction 1 (4.04 g, 160-175 °C (0.05 mm)) and fraction 2 (25.91 g, 175-177 °C (0.05 mm), lit.[20a] bp 203-205 °C (0.3 mm)). GLC (3.5 ft × 0.25 in. 15% SE-30 on 60/80 mesh firebrick) indicated that fraction 1 was >95% pure and fraction 2 was pure: yield 29.75 g (43%); NMR ($CDCl_3$, 60 MHz) δ 3.02 (s, 2 H), 3.67 (s, 24 H).

Hexaethylene Glycol Ditosylate. Separate solutions of 28.24 g (0.1001 mol) of hexaethylene glycol in 250 mM of pyridine (freshly distilled from calcium hydride) and 56.28 g (0.2954 mol) of *p*-toluenesulfonyl chloride in 250 mL of pyridine were cooled to −20 °C. The solutions were then combined and maintained at −20 °C for 74 h. The reaction mixture was then poured into 700 mL of ice/water, and this mixture was extracted successively with three 350-mL volumes of dichloromethane. The combined organic phases were successively washed with three 500-mL volumes of ice-cold 6 N aqueous HCl and 350 mL of saturated aqueous ammonium chloride. After drying of the organic phase over anhydrous magnesium sulfate and filtration, removal of solvent under reduced pressure yielded a viscous, yellow oil. Decolorization with Norite A or by filtration of a solution of the oil through silica gel failed: yield 53.65 g (90.8%); NMR ($CDCl_3$, 60 MHz) was indicative of >99% purity, δ 2.42 (broad s, 6 H, $ArCH_3$), 3.57 (s, 8 H, $-OCH_2CH_2O-$), 3.60 (s, 8 H, $-OCH_2CH_2O-$), 3.53-3.82 (m, 4 H, $TsOCH_2CH_2O-$), 3.98-4.27 (m, 4 H, $TsOCH_2CH_2O-$), 7.28 (V_A), and 7.73 (V_B) (AA'BB', 8 H, J_{AB} = 8 Hz, ArH).

Results of Ring-Closing Reactions. Diazomethane was added to the reaction mixtures before isolation in the preparations of **2** and **3** of the 2'-carbomethoxy-1',3'-xylyl-*m*-crown-*n*-cyclic ether esters to esterify any hydrolyzed ester.

Cycle **1**, 2'-carbomethoxy-1',3'-xylyl-15-crown-4, was prepared by method B, 34%, as an oil: gel permeation retention volume 139 mL (an additional 10% of what is probably dimer, gel permeation retention volume 109 mL, was also obtained); GLC retention time at 275 °C, 8 min; ^{1}H NMR δ 3.9 (s, 3, CH_3), 3.0-3.7 (m, 12, CH_2CH_2), 4.2, 4.9 (d of d, J = 12 Hz, 4, $ArCH_2$), 7.3 (m, 3, ArH); IR 1730 cm^{-1} (neat). Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.71; H, 7.09.

Cycle **2,** 2'-carbomethoxy-1',3'-xylyl-18-crown-5 (method B), was an oil (82%): gel permeation retention volume 132 mL; GLC retention time at 285 °C, 15 min; ^{1}H NMR δ 3.9 (s, 3, CH_3), 3.4-3.6 (m, 16, CH_2CH_2), 4.6 (s, 4, $ArCH_2$), 7.3 (m, 3, ArH); IR 1730 cm^{-1} (neat). Anal. Calcd for $C_{18}H_{26}O_7$: C, 61.00; H, 7.39. Found: C, 60.81; H, 7.47.

Cycle **3,** 2'-carbomethoxy-1',3'-xylyl-21-crown-6 (method B), was an oil (68%): gel permeation retention volume 127 mL; GLC retention time at 305 °C, 12 min; ^{1}H NMR δ 3.9 (s, 3, CH_3), 3.5 (m, 20, CH_2CH_2), 4.5 (s, 4, $ArCH_2$), 7.2 (m, 3, ArH); IR 1725 cm^{-1} (neat). Anal. Calcd for $C_{20}H_{30}O_8$: C, 60.29; H, 7.59. Found: C, 60.20; H, 7.82.

Cycle **4,** 2'-carbomethoxy-1',3'-xylyl-30-crown-9 (method B), was an oil (34%): gel permeation retention volume 116 mL; ^{1}H NMR δ 3.9 (s, 3, CH_3), 3.6 (m, 32, CH_2CH_2), 4.6 (s, 4, $ArCH_2$), 7.4 (m, 3, ArH); IR 1730 cm^{-1} (neat). Anal. Calcd for $C_{26}H_{42}O_{11}$: C, 58.85; H, 7.98. Found: C, 58.64; H, 8.07.

Cycle **12,** 2'-bromo-1',3'-xylyl-18-crown-5, was prepared by method A as an oil (7%) with the modification that dimethylformamide was used as solvent: ^{1}H NMR δ 3.5 and 3.6 (two peaks, 16, CH_2CH_2), 4.67 (s, 4, $ArCH_2$), 7.25 (m, 3, ArH); mass spectrum *m/e* 374 (M^+ for ^{78}Br), 376 (M^+ for ^{81}Br). Anal. Calcd for $C_{16}H_{23}BrO_5$: C, 51.21; H, 6.18. Found: C, 51.22; H, 6.30.

Cycle **13,** 2'-chloro-1',3'-xylyl-18-crown-5, was prepared by method A as an oil (53%): ^{1}H NMR δ 3.4-3.7 (m, 16, CH_2CH_2), 4.6 (s, 4, $ArCH_2$), 7.2 (m, 3, ArH). Anal. Calcd for $C_{16}H_{23}ClO_5$: C, 58.09; H, 7.01. Found: C, 57.89; H, 7.06.

Cycle **14,** 2'-cyano-1',3'-xylyl-18-crown-5, was prepared by method A as an oil (10%): gel permeation retention volume 132 mL; GLC retention time at 280 °C, 13 min; ^{1}H NMR δ 3.5-3.6 (m, 16, CH_2CH_2), 4.7 (s, 4, $ArCH_2$), 7.4 (m, 3, ArH); IR 2220 cm^{-1} (neat). Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21. Found: C, 63.43; H, 7.04.

Hydrolyses of 2'-Carbomethoxy-1',3'-xylyl-*m*-crown-*n*-cyclic Polyethers 1-4 to 2'-Carboxy-1',3'-xylyl-*m*-crown-*n*-cyclic Polyethers 5-8. The ester cycles were refluxed in excess 0.1 M sodium hydroxide in 95% ethanol for 12 h. The solvent was evaporated in vacuo, and the residue was dissolved in water. For **5** and **6,** the basic aqueous solution was washed with $CHCl_3$ and acidified with hydrochloric acid, and the mixture was extracted with CH_2Cl_2. For **6** and **7,** the original basic solution was acidified with hydrochloric acid and extracted with CH_2Cl_2. The organic layer was evaporated, and the residue was crystallized from CH_2Cl_2-pentane.

Cycle **5,** 2'-carboxy-1',3'-xylyl-15-crown-4, mp 106-112 °C (~100%), gave ^{1}H NMR δ 3.1-3.8 (m, 12, CH_2CH_2), 4.2 and 4.9 (doublet of doublets, J = 13 Hz, 4, $ArCH_2$), 7.2 (m, 3, ArH); IR 1730 cm^{-1} (KBr). Anal. Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 60.93; H, 6.83.

Cycle **6,** 2'-carboxy-1',3'-xylyl-18-crown-5, mp 100-101 °C (~100%), gave ^{1}H NMR δ 3.9-4.0 (s, 16, CH_2CH_2), 4.5 (s, 4, $ArCH_2$), 7.0 (m, 3, ArH); IR 1720 cm^{-1} (KBr). Anal. Calcd for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11. Found: C, 60.03; H, 7.09.

Cycle **7**, 2′-carboxy-1′-3′-xylyl-21-crown-6, mp 86–95 °C (~100%), gave ^{1}H NMR δ 3.7 (m, 20, CH_2CH_2), 4.6 (s, 4, $ArCH_2$), 7.3 (m, 3, ArH); IR 1730 cm^{-1} (KBr). Anal. Calcd for $C_{19}H_{28}O_8$: C, 59.39; H, 7.34. Found: C, 59.55; H, 7.56.

Cycle **8**, 2′-carboxy-1′,3′-xylyl-30-crown-9, oil (~100%), gave ^{1}H NMR δ 3.7 (m, 32, CH_2CH_2), 4.7 (s, 4, $ArCH_2$), 7.3 (m, 3, ArH); IR 1730 cm^{-1} (neat). Anal. Calcd for $C_{25}H_{40}O_{11}$: C, 58.12; H, 7.81. Found: C, 58.43, 57.72; H, 8.04, 7.95.

2′-Hydroxymethyl-1′,3′-xylyl-18-crown-5 (9) **and 2′-Methoxymethyl-1′,3′-xylyl-18-crown-5 (10).** To a solution of 700 mg (2 mmol) of methyl ester cycle **2** in 25 mL of anhydrous ether was added ca. 200 mg of lithium aluminum hydride. The mixture was stirred for 4 h under a drying tube. Excess acetone was added, and the mixture was partitioned between CH_2Cl_2 and dilute hydrochloric acid. The aqueous phase was washed with CH_2Cl_2, and the combined organic phases were evaporated to give 530 mg (80%) of **9**: ^{1}H NMR δ 3.5 (m, 16, CH_2CH_2), 4.7 (s, 6, $ArCH_2$), 7.1 (m, 3, ArH); mass spectrum *m/e* 308 ($M^+ - 18$), 326 (M^+) absent.

A mixture of 310 mg (1.0 mmol) of **9**, 150 mg (3 mmol) of 50% NaH in oil and 0.5 mL (ca. 8 mmol) of methyl iodide in 50 mL of THF was stirred at 25 °C for 4 h. Water was added to decompose the excess NaH, the solvent was evaporated, and the residue was chromatographed on silica gel with acetone in CH_2Cl_2 as eluting agent to give 180 mg (50%) of **10**, mp 62–69 °C. Recrystallization of this material from pentane gave mp 70–71 °C; ^{1}H NMR δ 3.4 (s, 3, OCH_3), 3.6 (broad s, 16, CH_2CH_2), 4.0–5.2 (broad m with s at 4.9, 6, $ArCH_2$), 7.2 (s, 3, ArH). Anal. Calcd for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29. Found: C, 63.41; H, 8.21.

2,6-Bis(methoxymethyl)benzoic Acid (20). To a solution of 3.2 g (10 mmol) of methyl 2,6-bis(bromomethyl)benzoate (**16**) in 200 mL of THF were added 1.2 g (25 mmol) of 50% NaH in oil and 1.0 g (31 mmol) of absolute methanol. The mixture was stirred at 25 °C for 24 h and evaporated in vacuo, and the residue was distributed between water and CH_2Cl_2. The organic layer was dried and evaporated, and the residue was refluxed for 24 h in 250 mL of 95% ethanol containing 4 g of sodium hydroxide. The solvent was evaporated in vacuo, and the residue was distributed between CH_2Cl_2 and hydrochloric acid. The organic layer was dried and evaporated in vacuo, and the residue was molecularly distilled (130 °C at 100 μ) to give 1.0 g (50%) of **20**, which solidified on standing: mp 54–62 °C; ^{1}H NMR δ 3.3 (s, 6, OCH_3), 4.5 (s, 4, $ArCH_2$), 7.2 (m, 3, ArH); IR 1700 cm^{-1} (mull). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.93; H, 6.86.

Crystalline Salt of *tert*-Butylamine and 2′-Carboxy-1′,3′-xylyl-18-crown-5 (6). To a solution of 82 mg (0.24 mmol) of **6** in cyclohexane–dichloromethane was added 50 μL (ca. 0.5 mmol) of *tert*-butylamine. Pentane was added to the cloud point. Slow evaporation of the solvent left a crystalline residue, mp 117–126 °C dec, of a 1:1 salt (^{1}H NMR of component peaks). The analytical sample was dried at 20 °C and 100 μ for 1 h (higher temperatures decomposed the salt). Anal. Calcd for $C_{21}H_{35}NO_7$: C, 60.99; H, 8.53. Found: C, 60.80; H, 8.69.

Extraction Experiments Involving *tert*-Butylammonium Thiocyanate. To 0.60 mL of a 0.135 M solution of **2** (R = CO_2CH_3) in $CDCl_3$ in a stoppered vial was added 0.30 mL of a 1.00 M solution of *t*-$BuNH_3SCN$ in D_2O at 24 °C. This mixture was shaken for 1–2 min and then centrifuged to separate the layers. The $CDCl_3$ phase was carefully removed and transferred to an NMR tube. The value of R was determined from the integration of the *t*-Bu signal of the guest and that of the protons present in the macrocycle. The chemical shift (δ, from Me_4Si) of the *t*-Bu signal of the guest was also determined from the NMR spectrum of the complex. Values of K_a are based on $K_d = 5.2 \times 10^{-5}$ M^{-1}, and were obtained at concentrations of scale C,[4b] but were corrected to scale A by dividing by 2.[4b] Table II reports K_a values corrected to scale A.[4b]

Solutions of cycles **1** (0.132 M), **3** (0.135 M), **4** (0.137 M), **6** (0.143 M), 9 (0.137 M), **10** (0.136 M), **11** (0.130 M), and **14** (0.116 M) in $CDCl_3$ were then treated in the same manner. The observed R values and association constants appear in Table II along with the chemical shifts of the *t*-Bu group of the guest salt.

In a related extraction experiment, a 0.139 M solution of 18-crown-6 in $CDCl_3$ at 24 °C was shaken with a 0.10 M solution of *t*-$BuNH_3SCN$. The phases were separated as above and the organic phase analyzed by ^{1}H NMR. In this experiment,[4b] R = 0.51 leading to a calculated K_a = 3 000 000. The chemical shift of the *t*-Bu singlet of the complex appeared at δ 1.38 as compared to δ 1.49 for the uncomplexed salt.

Metal Cation Lipophilization. A solution of 0.05 mmol of host acid in 2.00 mL of CH_2Cl_2 was mixed with 1.00 mL of an aqueous salt solution of μ = 2.00 (2.00 M LiCl, NaCl, or KCl or 0.67 M $CaCl_2$), and 2 drops of 2.00 N LiOH, NaOH, or KOH (for Ca^{2+}, solid $Ca(OH)_2$) was added. The mixture was shaken and centrifuged, and the aqueous phase was tested to ensure that a pH of greater than 11 was maintained. The CH_2Cl_2 phase was removed with a syringe, filtered through a glass wool plug, and evaporated. The residue was dissolved in 50 μL of $CDCl_3$ containing 0.0147 mmol of toluene as an internal standard. The ^{1}H NMR spectrum was taken, and the peaks due to the CH_2CH_2 groups of the cycles (or the CH_3O groups of the open-chain model, **20**) were integrated against the methyl group peak of toluene to determine the amount of extracted salt. The relative numbers are accurate to about 10%. Table III records the results.

Rough distribution constants (K_d) for the complexes of **5–8** and **20** between D_2O and $CDCl_3$ were determined at 22 °C as follows (complex in $D_2O \rightleftarrows$ complex in $CDCl_3$). A 0.5 M solution of the acid host in 0.10 mL of $CDCl_3$ was made 0.7 M in $(CH_3)_3CNH_2$, and the resulting solution was shaken with 0.10 mL of D_2O. The layers were separated, and the protons of the host and guest (plus free amine) were counted in their ^{1}H NMR spectra in each layer under identical conditions for each complex. Values of K_a were calculated from the relative amounts of host in each layer. Excess $(CH_3)_3CNH_2$ was observed in each layer.

Determination of pK_as of Acids 5–8 and 20. These determinations were made with a pH meter with 0.1 mmol of acid in 20–30 mL of water at 22 °C titrated with 0.10 N hydrochloric acid and with 0.10 N lithium hydroxide. Plots of pH vs. milliliters of titrant were made, and the pK_as were determined as the midpoint of the titration curve (average of two determinations, ±0.2).

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