Host-Guest Complexation. 42. Preorganization Strongly Enhances the Tendency of Hemispherands To Form Hemispheraplexes[1]

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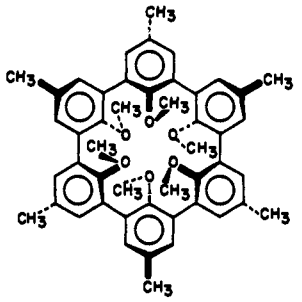
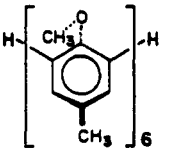
Abstract: The design and syntheses of four new macrocyclic host compounds (**1-4**, Chart I) are reported which contain three cyclic urea carbonyls and two anisyl-like oxygens alternately arranged to bind alkali metal or alkylammonium ion guests. The macroring systems are completed with a 1,3-xylyl bridging unit containing a methoxy in its 2- and a methyl in its 4-position (**1**, **2**) or a 3,5-dimethylphenyl group in its 2-position (**3**, **4**). Hosts **1-4** are rigidified further with a trimethylene bridge that spans the two aryl oxygens. Hosts **1** and **2** differ only by the absence in **1** and the presence in **2** of methyl groups in the positions para to the two aryl oxygens. Hosts **3** and **4** are diastereomers, whose interconvertibility by ring inversion is blocked by steric limitations imposed on the system by the two bridging units. The configurational identities of **3** and **4** were established from their crystal structures. Hosts **5-7** (Chart I) were also prepared. Macrocycle **5** resembles **4** except the aryl oxygen trimethylene bridge is replaced by hydrogens. In **6** and **7**, the trimethylene bridge is in place, but the 1,3-xylyl bridge is replaced by hydrogens. The crystal structures of the more conformationally mobile compounds **5** and **6** show that the dipoles of the carbonyl groups are better arranged to cancel one another than those of the more rigid hosts, **3** and **4**. The crystal structure of **2**·$(CH_3)_3CNH_3^+$ is exactly what was expected from molecular model examination. Free energies and association constants were determined for **1-4** and **7** binding Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and $(CH_3)_3CNH_3^+$ picrates at 25 °C in $CDCl_3$ saturated with D_2O. The resulting $-\Delta G°$ values ranged from 7.3 (**7** binding Li^+) to 16.7 kcal mol^{-1} (**3** binding Na^+). The $-\Delta G°$ values correlate with the degrees of preorganization of the hosts for binding. Cycle **2** was the strongest binding host. Diastereomer **3**, the second strongest complexing host, bound the eight guests 2.25 ± 0.75 (extremes) kcal mol^{-1} better than diastereomer **4**. The crystal structure of **3** shows its binding sites to be better organized for complexation than those of **4**. Host **2**, containing methyl groups para to the aryl oxygens, bound the eight guests an average of 3.7 kcal mol^{-1} better than **1** without the two methyl groups. This effect is attributed to greater steric inhibitions of solvation of the binding sites of **2** than of **1**. Host **7**, containing the trimethylene but lacking the xylyl bridge, bound the eight guests with $-(\Delta G°)_{av}$ = 7.5 kcal mol^{-1}, which is lower by 4.4-7.1 kcal mol^{-1} than the hosts containing the latter bridge. Host **3** was found to complex 1 mol of $(CH_3)_3C—O—N=O$ (^1H NMR). The $-\Delta G°$ value of known host **8** was used for comparisons.

A basic theme in this series of papers has been the correlation of the structures and binding free energies of a variety of hosts and guests. In excess of a thousand designed complexes have been examined.[2] Solvent and the number and character of binding sites in host and guest play prominent roles in determining the values of binding free energies. The geometric and electronic complementarity of host and guest are also important. A more subtle but equally significant determinant of binding power is the degree of preorganization. The principle of preorganization has been formulated as follows: the more highly hosts and guests are organized for binding and low solvation *prior* to complexation, the more stable are their complexes.[3a] This principle, although self-evident, gains force only in retrospect through exemplification.[4]

Spherand I is the most completely preorganized system reported to date. Its binding sites are conformationally organized for complexation and are desolvated during its synthesis. Podand II contains the same binding sites but exists in over a thousand conformations, only two of which can provide full ligation for sodium or lithium ions. During complexation of these ions, II must desolvate its binding sites and freeze out most of its conformations. As a result of the preorganization of I and the lack thereof in II, the free energy of formation of spheraplexes is 14-17 kcal mol^{-1} more negative than that for formation of the corresponding podaplexes.[2,3a]



I



II

Here, we report the design, synthesis, and binding free energies and association constants of **1-4** and **7** and the syntheses of **5** and **6**. We interpret the results in terms of the preorganization of these hemispherands, aided by the crystal structures of **3-6**[3b] and **2**·$(CH_3)_3CNH_3^+$, by their ^1H NMR spectra, and by comparisons of their binding free energies with those of reported host, **8**.[5] The latter lacks the rigidifying trimethylene bridge present in its analogue, **2** (Chart I).

Synthesis. Chart II traces the synthetic scheme used to prepare the key compounds **6**, **7**, and **25** needed to complete the syntheses of **1-4**. Nitration of salicylic acid gave 3-nitrosalicylic acid (20%),[6] which was methylated with dimethyl sulfate to provide the methyl ester of **9** (87%),[7] hydrolysis of which provided **9** (93%).[8] In a

(1) We warmly thank the National Science Foundation for Grant CHE 81-09532 and the U.S. Public Health Service for Grant GM 12640, for support of this work. K. M. Doxsee gratefully thanks the American Cancer Society for a postdoctoral fellowship.

(2) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1039-1057. In this paper, we suggest that complexes of podands, corands, cryptands, spherands, and cavitands be called podaplexes, coraplexes, cryptaplexes, spheraplexes, and caviplexes, respectively.

(3) (a) Cram, D. J.; Lein, G. M. *J. Am. Chem. Soc.* **1985**, *107*, 3657-3668. (b) Goldberg, I.; Doxsee, K. M. *J. Inclusion Phenom.* **1986**, *4*, 303-322.

(4) For a balanced and comprehensive review of the development of the field of host-guest chemistry, see: Stoddart, F. J. *Annu. Rep., Prog. Chem., Sect. B*: **1983**, *80*, 353-378.

(5) Cram, D. J.; Dicker, I. B.; Lauer, M.; Knobler, C. B.; Trueblood, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7150-7167.

(6) Meldrum, A. N.; Hirve, N. W. *J. Indian Chem. Soc.* **1928**, *5*, 95-101.

(7) Richtzenhain, H.; Nippus, P. *Chem. Ber.* **1949**, *82*, 408-417.

(8) Simonsen, J. L.; Rau, M. G. *J. Chem. Soc.* **1917**, *111*, 220-236.

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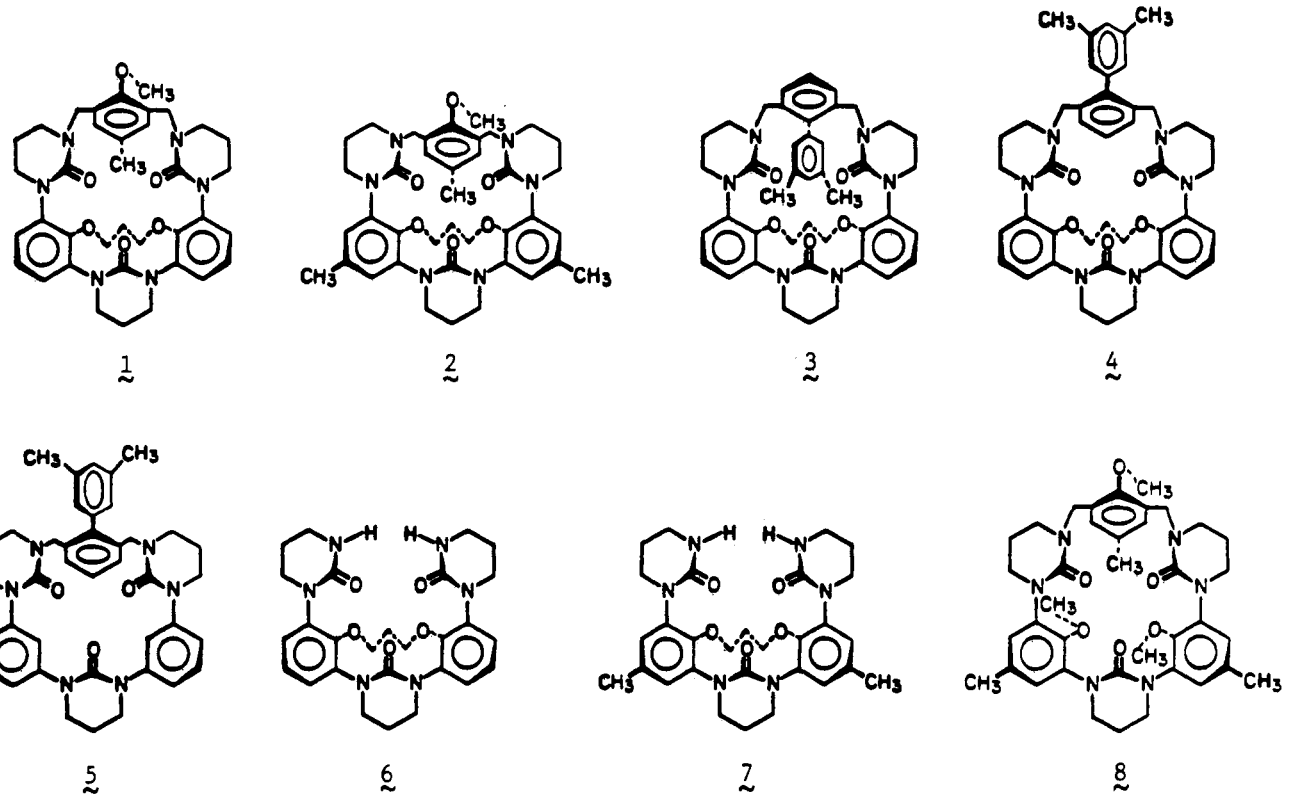
Chart I



single-flask reaction, crude **9** was converted in turn to its acid chloride ($SOCl_2$) and its acid azide (NaN_3, H_2O, $(CH_3)_2CO$), which was thermally rearranged to its isocyanate, partial hydrolysis of which produced amine which condensed with isocyanate to give urea **10** (66% overall). This compound was bridged with trimethylene glycol ditosylate in a phase-transfer reaction to produce cyclic urea **11** (58%), demethylation of which (HBr, AcOH) gave bisphenol **12** (88%). The dimethyl analogue of **12**, compound **14**, was prepared (80%) by nitrating **13**[5] with HNO_3–$CHCl_3$.

Nitrophenols **12** and **14** were converted with $CH_2(CH_2Br)_2$–K_2CO_3 to cycles **15** (73%) and **16** (69%), respectively. Reduction of the nitro to the amine groups (Sn–HCl) provided **17** (80%) and **18** (77%). These diamines reacted readily with $Cl(CH_2)_3$-NCO[9] to give trisurea compounds, **19** (96%) and **20** (91%), ring closures of which with KOH–THF in phase-transfer reactions ($PhCH_2NEt_3Br$) provided **6** (60%) and **7** (50%), respectively.

The synthesis of substituted xylyl dibromide, **25**, needed to complete the syntheses of hosts **3** and **4**, is outlined in Chart II. The two oxazolino groups of **21** (available from an earlier study)[10] activate the aryl fluoride toward nucleophilic aromatic substitution. Treatment of **21** with 3,5-dimethylphenylmagnesium bromide gave **22**, which without characterization was alkylated and hydrolyzed to acid **23** in 86% overall yield. Reduction of **23** with BH_3·THF gave diol **24** (94%). Treatment of **24** with HBr–$CHCl_3$ produced dibromide **25** (97%).

Chart III summarizes the ring-closing reactions used to obtain hemispherands **1–5**. Generally the disodium salts of thoroughly dried trisurea compounds **6**, **7**, or **27**[11] were formed with NaH in dry THF and mixed under moderate dilution conditions with dry solutions of dibromides **25** or **26**[12] in the same solvent. Compounds **6**, **7**, and **27** form very stable hydrates that can be freed of water only by prolonged heating under high vacuum at 140 °C or by adding them to distilling benzene. The reactions

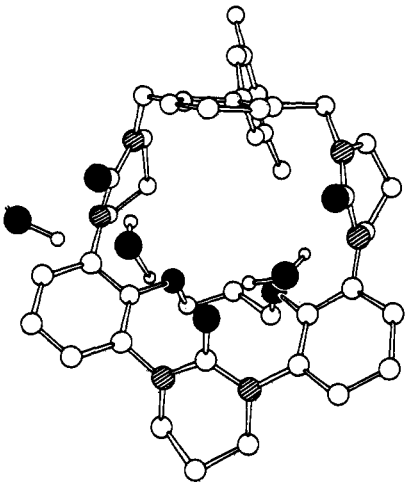


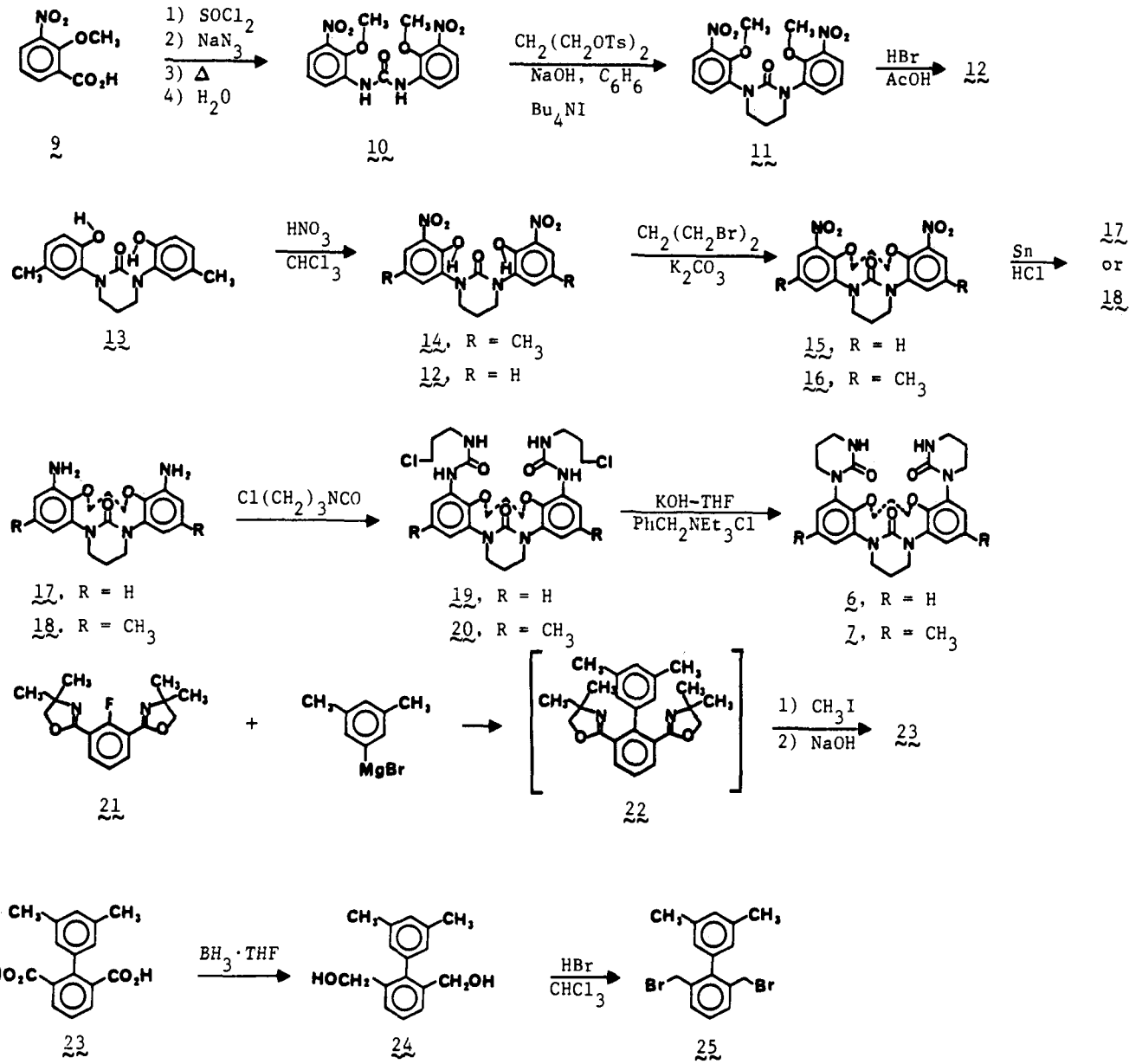
Figure 1. Crystal structure of molecule **3a** in crystal structure of **3**. Two water molecules bridge the three carbonyl groups, and two others bridge the guest waters of adjacent unit cells (oxygens are solid black, and nitrogens are shaded).

of **6** and **7** with **26** afforded **1** (47%) and **2** (20%), respectively. The cyclization of **6** with **25** gave, after gel permeation chromatographic separation, a one-to-one mixture (^1H NMR) of hosts **3** and **4** in 80–90% yield. They provided base line separation on a semipreparative reverse-phase HPLC column as their sodium bromide complexes with CH_3OH–H_2O–NaBr as the mobile phase, the more strongly binding isomer **3** moving faster than **4**. The similar ring closure of trisurea compound **27**[11] with dibromide **25** gave macrocycle **5** (50%).

Crystal and Solution Structure. The crystal structure data for **3–6** and a detailed crystallographic discussion are reported elsewhere.[3b] Here we discuss the general features of the crystal structures that relate to the design and behavior of the compounds as hosts. We also report the crystal structure of complex **2**·$(CH_3)_3CNH_3^+$. Attempts to obtain crystals of hemispherands **1** and **2** suitable for X-ray analysis failed. Their ^1H NMR spectra in $CDCl_3$ suggested them to be mixtures of equilibrating con-

(9) Siefken, W. *Justis Liebigs Ann. Chem.* **1949**, *562*, 75–136.
(10) We warmly thank M. P. deGrandpre, who first carried out and explored the chemistry of **21**.
(11) Nolte, R. J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1984**, *106*, 1416–1420.
(12) (a) Taylor, R.; Kennard, O. *Acc. Chem. Res.* **1984**, *17*, 320–326. (b) Murray-Rust, P.; Glusker, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 1018–1025.

Chart II



formers which, when complexed, became a nonequilibrating mixture of hemispheraplexes. In C_6D_6, 2·NaBr appeared to exist in a single conformation, that drawn for **2** in Chart I (NOE experiments).

The crystal structure of **3** contains two molecules per unit cell that are very similar to one another but differ in two important respects (Figures 1 and 2). In both structures three cyclic urea carbonyl groups are anti to the $OCH_2CH_2CH_2O$ bridge and to the dimethylphenyl group attached to the 1,3-xylyl bridge. The protons of the methylene parts of this latter bridge point away from the cavity in both structures. In structure **3a**, the unshared electron pairs of all five oxygens converge on the cavity, which is filled with two water molecules, each of which is hydrogen bonded to two carbonyl groups of the pseudometa cyclic urea units. Thus the centrally located carbonyl group is hydrogen bonded to two different waters. Each bound water molecule is hydrogen bonded by additional water molecules to like water molecules in adjacent unit cells. This provides 3 mol of water to each molecule of **3a** per unit cell. The symmetry of **3a** is compatible with the symmetry of the ^1H NMR signals of the substance in $CDCl_3$.

In structure **3b** of the same unit cell, the unshared electron pairs of four of the five oxygens converge on the cavity, but those of the fifth (one of the two $ArOCH_2$ oxygens) diverge from the cavity. As a result, one of the hydrogens of the attached CH_2 group partially fills the cavity. One water molecule is hydrogen bonded to the central carbonyl and to that flanking carbonyl

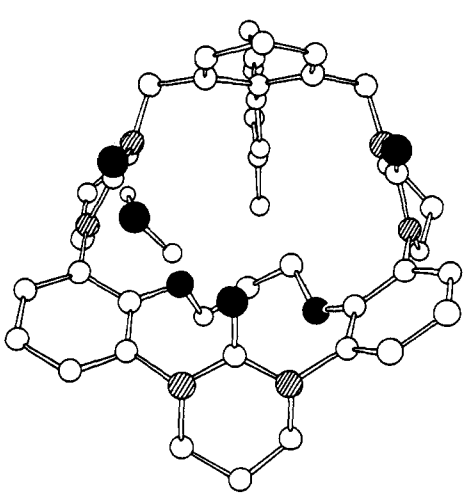
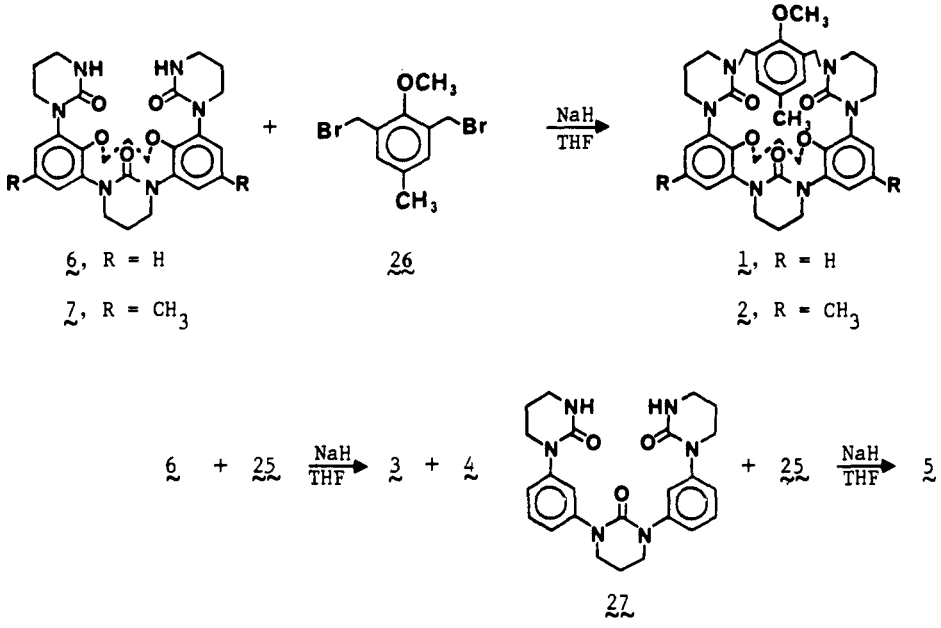


Figure 2. Crystal structure of molecule **3b** in crystal structure of **3**. One water molecule bridges two of the three carbonyl groups (oxygens are solid black, and nitrogens are shaded).

Chart III



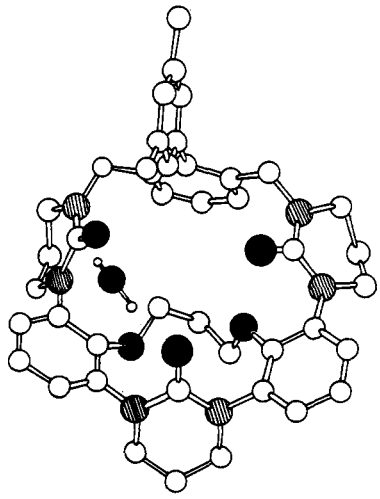


Figure 3. Crystal structure of **4**. One water molecule bridges two of the three carbonyl groups (oxygens are solid black, and nitrogens are shaded).

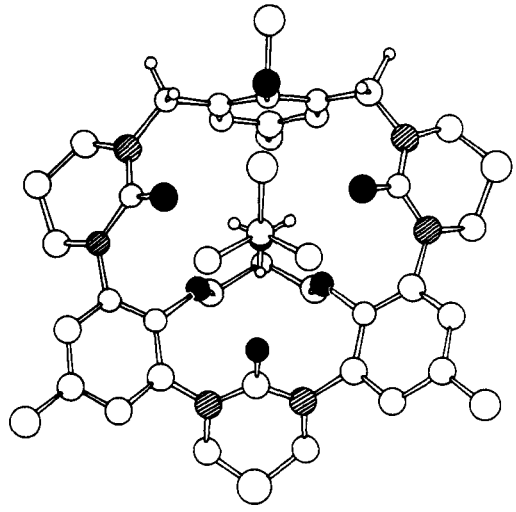


Figure 4. Crystal structure of **2**·$(CH_3)_3CNH_3^+$ with three NH···O=C sites (oxygens are solid black, and nitrogens are shaded).

proximate to the inward-turned CH_2 hydrogen. The resulting dissymmetry of **3b** is not compatible with the symmetry of the ^1H NMR signals of **3** dissolved in $CDCl_3$. We conclude that **3** in solution more closely conforms to crystal structure **3a** than to **3b**.

In the crystal structure of diastereomer **4** shown in Figure 3, the three carbonyl groups are anti to the $OCH_2CH_2CH_2O$ bridge and syn to the dimethylphenyl group attached to the 1,3-xylyl bridge. The protons of the methylene parts of this latter bridge point away from the cavity. The unshared electron pairs of four of the five oxygens converge on the cavity, but those of the fifth (one of the two $ArOCH_2$ oxygens) diverge from the cavity. Thus, one of the protons of the attached CH_2 group partially fills the cavity, as in **3b**. Also, as in **3b**, the two carbonyl groups flanking this ArO oxygen are hydrogen bonded to the two hydrogens of a water molecule located above the inward-turned CH_2 hydrogen. The resulting dissymmetry of **4** is compatible with the dissymmetry of the ^1H NMR signals of the compound in $CDCl_3$ solution. We conclude that **4** in solution also probably contains an inward-turned methylene proton. One methyl of the dimethylphenyl group attached to the 1,3-xylyl bridge is held over part of the opening to the cavity in **4**.

Figure 4 contains the crystal structure of the complex **2**·$(CH_3)_3CNH_3^+$. The complex is held together by three NH···O=C hydrogen bonds in a tripod arrangement, as anticipated by CPK molecular model examination. The C–N bond is essentially normal (88.3°) to the plane defined by the three carbonyl oxygens, and the CH_3–C–N–H dihedral angles are 62°, as anticipated. The three NH···O bond lengths are all about 2.75 Å. The OCH_2C-H_2CH_2O bridge is anti to the CH_3O group of the *m*-xylyl which completes the macrocycle. The angle of intersection of the plane of the *m*-xylyl unit and the best plane of the macroring is 84°. The crystal structure of **2**·$(CH_3)_3CNH_3^+$ closely resembles that of **8**·$(CH_3)_3CNH_3^+$, whose host (**8**) is more conformationally mobile than **2**.[5] The conformation of the rigidifying OCH_2C-H_2CH_2O bridge in **2**·$(CH_3)_3CNH_3^+$ resembles that observed in molecule **3a** in crystal structure **3**. The central methylene in both structures is oriented toward the *m*-xylyl unit. The results of NOE experiments with **2**·Na^+ in C_6D_6 indicate this same orientation in solution.

Figure 5 represents the crystal structure of macrocycle **5**. The compound is unsolvated and contains a mirror plane occupied by the dimethylphenyl and the central carbonyl groups. Unlike the crystal structures of **3a**, **3b**, and **4**, that of **5** orients the carbonyl group of the centrally located cyclic urea anti to the carbonyls of the other two units. In such an arrangement, the dipoles of the carbonyls partially cancel one another. The central carbonyl group is syn to the dimethylphenyl group as in **4**, but the flanking carbonyls are anti to the dimethylphenyl unlike the arrangement

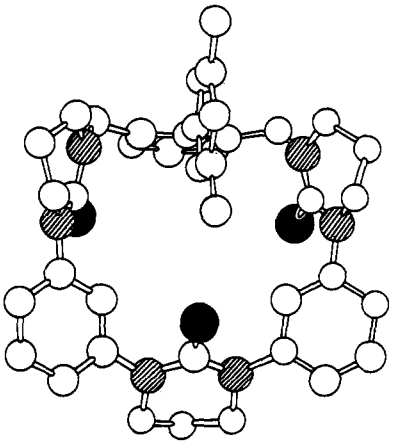


Figure 5. Crystal structure of **5** (oxygens are solid black, and nitrogens are shaded).

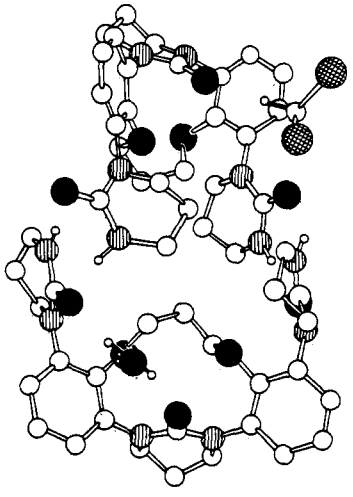
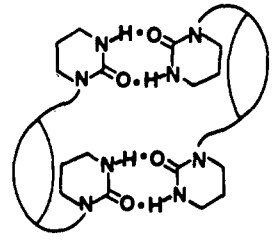


Figure 6. Crystal structure of **6**, with two molecules hydrogen bonded to one another at four NH···O=C sites in each unit cell. One CH_2Cl_2 bridges the two carbonyls of one molecule of **6**, and one CH_2Cl_2 bridges the two carbonyls of the other molecule of **6** (oxygens are solid black, nitrogens are shaded, and chlorines are cross-hatched).

in **4**. The methylene hydrogens of the 1,3-xylyl bridge diverge from the cavity, as in **3a**, **3b**, and **4**. The protons in the ^1H NMR spectrum of a solution of **5** in $CDCl_3$ have all been assigned.

Figure 6 shows that each of the two cyclic urea ends of two molecules of **6** are cyclically hydrogen bonded to one another to form a macrocycle in the unit cell of the crystal structure of the substance. The macrocycle is represented schematically in **28** and contains a hydrogen-bonding arrangement not unlike that found between complementary base pairs in RNA. The macrocycle of Figure 6 contains two pockets whose openings face upward. One is occupied by a water molecule whose hydrogens are spacially and electronically complementary to the carbonyl groups of two pseudometa urea units. Beneath this hydrogen-bonded water molecule is located one hydrogen that converges on the pocket, forcing the oxygen's unshared electrons of the $ArOCH_2$ group into a divergent conformation. A similar arrangement of parts was encountered in **3b** and **4**. The second pocket in the unit cell is occupied by a CH_2Cl_2 molecule whose two hydrogens are complementary to and span the carbonyl groups of two other pseudometa urea units. Again, one hydrogen of the $ArOCH_2$ group converges on the cavity beneath the bound CH_2Cl_2 molecule, and its oxygen's unshared electrons diverge from the cavity.

In the unit cells of the crystal structures of **3**, **4**, and **6** are found five different molecules containing the 12-membered ring composed of one cyclic urea, two aryls, and the $OCH_2CH_2CH_2O$ bridge. Of the five, four contain conformation **29b** and one (that of **3a**) contains conformation **29a**. Molecular models (CPK) of neither **29a** nor **29b** appear sterically strained. The dominance of **29b** in the five structures may reflect more cancellation of the dipoles of the proximate carbon oxygen bonds in that conformation than is observed in **29a**, in which the dipoles are more aligned with one another. Of the two arrangements, **29a** appears to offer much stronger cation binding potential, since the orbitals of the unshared electron pairs converge more on the cavity than in those of **29b**.



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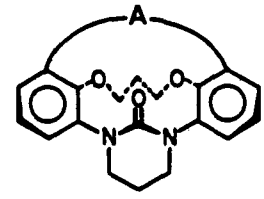
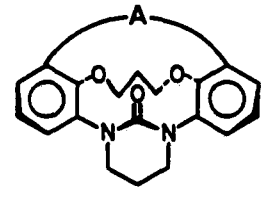


29a



29b

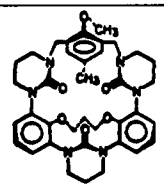
Molecular model examination of hosts containing this molecular module suggests that the fewer and more compressed are the atoms of bridge A in **29a** and **29b**, the more likely **29a** is to be the dominant conformer. For example, molecular models of diastereomer **3** provide an A bridge somewhat more compressed than the A bridge in diastereomer **4**, the effect being to elongate the A bridge in **4** compared to that in **3**. This explains why conformation **29a** is encountered in the crystal structure of **3** but not in that of **4**. It also suggests that **3** is better preorganized for binding than is **4**.

Statistical analysis of much crystallographic and neutron diffraction data indicates that there is a distinct preference for C=O···H—N hydrogen bonds to form in, or near to, the directions of the sp^2 lone pairs on carbonyl oxygens.[12] The locations of the hydrogens in the crystal structures involving **2**–**6** provide interesting information regarding the kind of hybridization of the orbitals on the carbonyl oxygens of the cyclic urea units. Complex **2**·$(CH_3)_3CNH_3^+$ has a crystallographic mirror plane containing the C=O···H—N—C atoms involving the cyclic urea unit at 6 o'clock in Figure 4. This O···H bond length is 1.9 Å, the C=O···H bond angle is 133°, and the O···H—N bond angle is 167°. The planes defined by the C=O···H hydrogen bonds at 2 and 10 o'clock intersect the planes of their respective NC(O)N urea atoms at angles of 76°. These O···H bond lengths are both 2.0 Å, the C=O···H bond angles each being 145° and the O···H—N bond angles each being 174°. These locations of the NH_3^+ hydrogens suggest that the hybridization at oxygen might be close to sp^3 with high negative charge density on oxygen.

In contrast, some of the hydrogens of the bound water molecules are close to lying in the same plane as that defined by the four urea atoms, suggesting close to sp^2 hybridization at oxygen of the C=O groups. In other cases, the hydrogens occupy positions about halfway between what would be expected for sp^2 and sp^3 hybridization at carbonyl oxygen. The average of 18 O···H—N bond angles found in the H_2O complexes of **3**–**6** is 163°. Host **2** complexes all of the alkali metal ions with high binding free energies (see next section). Molecular models of these complexes suggest that they possess structures incompatible with sp^2 hybridization at oxygen. These facts taken in sum suggest the cyclic urea oxygens are *soft ligands* with high geometric tolerance for binding. Possibly the hybridization at oxygen is flexible and responds to the demands of bound guests.

Correlation of Binding Power of Hosts with Structure. The free energies for hosts **1**–**4** and **7** binding Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and $(CH_3)_3CNH_3^+$ picrates are reported in

Table I. Free Energies of Binding ($-\Delta G°$, kcal mol^{-1}) and Association Constants (K_a, M^{-1}) of Picrate Salts at 25 °C in $CDCl_3$ Saturated with D_2O



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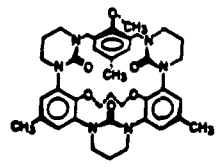

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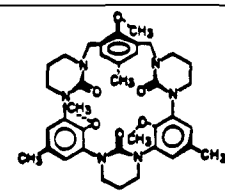

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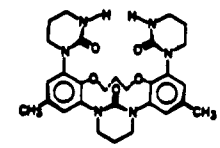
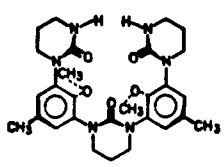
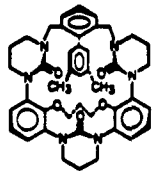


7

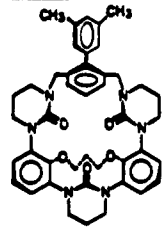
guest anion	$-\Delta G°$	K_a	$-\Delta G°$	K_a	$-\Delta G°$	K_a	$-\Delta G°$	K_a
Li	12.4	1.2×10^9	16.3	6.7×10^{11}	12.1	7.3×10^8	7.3	2.2×10^5
Na	12.7	2.0×10^9	16.0	5.2×10^{11}	15.4	1.9×10^{11}	7.6	3.7×10^5
K	12.3	1.0×10^9	16.4	1.0×10^{12}	15.6	2.7×10^{11}	7.7	4.4×10^5
Rb	12.0	6.1×10^8	15.7	3.1×10^{11}	14.2	2.5×10^{10}	7.4	2.6×10^5
Cs	11.7	3.7×10^8	15.8	3.7×10^{11}	13.1	3.9×10^9	7.3	2.2×10^5
NH_4	12.0	6.1×10^8	15.7	3.1×10^{11}	14.4	3.5×10^{10}	7.6	3.7×10^5
CH_3NH_3	11.2	1.6×10^8	14.9	8.2×10^{10}	14.4	3.5×10^{10}	7.3	2.2×10^5
t-$BuNH_3$	9.8	1.5×10^7	14.3	3.0×10^{10}	13.2	4.6×10^9	7.7	4.4×10^5
$-(\Delta G°)_{av}$	11.9		15.6		14.1		7.5	



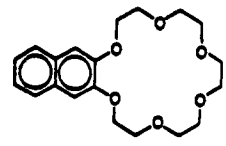
30



3



4



31

guest anion	$-\Delta G°$	K_a	$-\Delta G°$	K_a	$-\Delta G°$	K_a	$-\Delta G°$	K_a
Li			13.6	9.1×10^9	12.1	7.3×10^8	5.9	2.1×10^4
Na	6.6	6.8×10^4	16.7	1.7×10^{12}	13.7	1.1×10^{10}	8.3	1.2×10^6
K	6.9	1.1×10^5	15.7	3.1×10^{11}	13.9	1.5×10^{10}	10.8	8.1×10^7
Rb			14.8	6.9×10^{10}	11.8	4.4×10^8	9.6	1.1×10^7
Cs			14.5	4.2×10^{10}	10.5	4.9×10^7	8.3	1.2×10^6
NH_4	6.9	1.1×10^5	15.2	1.4×10^{11}	12.6	1.7×10^9	9.5	9.1×10^6
CH_3NH_3			14.0	1.8×10^{10}	11.8	4.4×10^8	7.5	3.1×10^5
t-$BuNH_3$			12.6	1.7×10^9	10.6	5.8×10^7	6.9	1.1×10^5
$-(\Delta G°)_{av}$	6.8		14.6		12.1		8.4	

Table I. Included for comparison are those for hosts **8**,[5] **30**,[5] and **31**.[13] The $-\Delta G°$ and K_a values were determined by extracting D_2O solutions of the picrate salts with $CDCl_3$ both in the absence and presence of the lipophilic hosts at 25 °C and measuring the amounts of picrate in each layer at equilibrium.[14,15]

The value of $-(\Delta G°)_{av}$ (kcal mol^{-1}) for a given host binding the eight different guests provides a general index of the binding abilities of the hosts of Table I. Arrangement of the hosts in decreasing order of values of this parameter provides the following order: **2** (15.6) > **3** (14.6) > **8** (14.1) > **4** (12.1) ~**1** (11.9) > **31** (8.4) > **7** (7.5) > **30** (6.8). This order correlates with what is known about the degree of preorganization of the hosts for binding. Of those hosts whose crystal structures are established, **3** > **4** > **7** in their preorganization for binding. The three poorest binders, corand **31**, hemipodand **7**, and podand **30**, possess many degrees of freedom and probably exist in solution in many poor binding conformations.

The differences between the eight hosts would probably be greater were the $-(\Delta G°)_{av}$ values determined in the gas phase. Molecular models suggest, and the crystal structures support, the idea that for the cyclic urea systems, the better preorganized the hosts are for binding the eight guests, the better preorganized they are for binding specific molecules of water, which must be largely displaced during complexation. The crystal structure **3a**, the most conformationally preorganized of the systems, contains 3 mol of bound water, more than is found in any of the other crystal structures. Like spherand **I**, which is preorganized both conformationally and to inhibit solvation of its binding sites,[16] **3** appears in molecular models and in its crystal structure to maximally inhibit solvation on one of the faces of its 18-membered ring. Unlike **I**, **3** maximally exposes its oxygens to binding guests and to solvation on the other face. In diastereomeric host **4**, the anti arrangement of the $CH_2CH_2CH_2$ bridge and of the dimethylphenyl group somewhat sterically inhibits solvation, guest binding, and contact ion pairing. We conclude that in the trisurea systems, it will be difficult to preorganize the support structure for binding specific guests without also preorganizing the system for solvation by small molecules such as water. This conclusion accounts for the fact that **I** binds Li^+ and Na^+ picrates with $-\Delta G°$ values of >23 and 19.2 kcal mol^{-1}, whereas **3** binds these same ions with the lower values of 13.6 and 16.7 kcal mol^{-1}, respectively.

Hosts **1** and **2** differ only by the presence in **2** and absence in **1** of two methyl groups para to the aryl oxygens. The $-\Delta(\Delta G°)_{av}$ value for **2** exceeds that for **1** by 3.7 kcal mol^{-1} (15.6 vs. 11.9 kcal mol^{-1}). We interpret this remarkably large difference as being due to additive steric and electronic effects. Molecular models of **2** show that the methyl groups protrude upward from the rim of an oxygen-lined nest in such a way as to limit the number of

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solvent molecules that can contact the oxygens. Not only do these methyl groups sterically inhibit solvation, they also lower the local dielectric constant of the binding sites. The methyl groups are electron releasing and thus slightly enhance the contributions of the aryloxy units to the binding potential of the hosts. Notice that these methyl groups are absent in **3** as well as in **1**. Were these methyl groups present in **3**, we would expeect its $-(\Delta G°)_{av}$ value to be much higher.

Hosts **2** and **8** differ only in the presence in **2** of a $CH_2CH_2CH_2$ bridge, which has been substituted for the two CH_3 groups of **8**. We expected from CPK model examination that **2** would be better preorganized for binding than **8**. This expectation was borne out. The $-(\Delta G°)_{av}$ value of **2** (15.6 kcal mol^{-1}) exceeds that of **8** (14.1 kcal mol^{-1}) by 1.5 kcal mol^{-1}. For every one of the eight guests, the binding power of the more preorganized host (**2**) exceeded that of the less preorganized host (**8**).

The importance of host preorganization is most strikingly illustrated through a comparison of the $-(\Delta G°)_{av}$ values of **2**, **7**, and **30** (15.6, 7.5, and 6.8 kcal mol^{-1}, respectively). The binding sites of these three compounds are essentially the same but differ in their states of preorganization for binding. Host **2** is preorganized by two bridges, **7** by one, and **30** by none. The difference in $-(\Delta G°)_{av}$ for **2** and **30** of 8.8 kcal mol^{-1} translates into a difference in average K_a values of $\sim 10^6$.

The ion selectivity of the trisurea family of hosts is remarkably low. Their macrorings are all 18-membered, and their $-\Delta G°$ values reach a maximum with either Na^+ or K^+ ions, the difference usually being within experimental error. The maximum guest selectivity is exhibited by **3**, the most rigidly preorganized of the cycles. The largest $\Delta(-\Delta G°)$ values are observed for **3** binding Na^+ vs. Li^+ (3.1 kcal mol^{-1}) and **3** binding NH_4^+ vs. $(CH_3)_3CNH_3^+$ (2.6 kcal mol^{-1}). These differences are small compared with those of other families of hemispherands[17] and cryptaspherands.[18]

One of the major objectives of this study was to determine if trisurea hemispherands could be prepared which exhibited strong binding characteristics and whose molecular modules would not ring-invert at ordinary temperatures. Compounds **3** and **4** represent such systems. Substitution of one of the aryloxy rings but not the other in either compound leads to a chiral system. If additional binding sites and steric barriers are incorporated, it might be possible to realize high chiral recognition in complexation of amino acids and their derivatives. We are examining this possibility.

In exploratory experiments carried out in $CDCl_3$ at 25 °C, 5 mol of $(CH_3)_3C—O—N=O$ were added to 1 mol of **3**, which caused the same kind of 200-MHz ^1H NMR changes for the $ArCH_2$ signals as were observed when **3** was mixed with aryldiazonium salts.[19] This experiment strongly suggests the formation of a one-to-one complex, held together by compensating dipole–dipole interactions between host and guest.

Experimental Section

General. Unless otherwise specified, all ^1H NMR spectra were obtained on a 200-MHz spectrometer in $CDCl_3$, and all mass spectra were taken at 70 eV. Solvent compositions are by volume. Unless indicated otherwise, $MgSO_4$ was used as a drying agent.

1,3-Bis(2-methoxy-3-nitrophenyl)urea (10). To 30 g (0.152 mol) of 2-methoxy-3-nitrobenzoic acid[6-8] in 125 mL of C_6H_6 was added 122.3 g (1.028 mol) of $SOCl_2$. The mixture was heated at reflux for 2.5 h, the benzene and excess $SOCl_2$ were distilled, and the residual oil was dried overnight *in vacuo*, giving a crystalline mass. This crude acid chloride was dissolved in 150 mL of acetone, cooled in an ice bath, and treated dropwise with a cold solution of 11.5 g NaN_3 (0.177 mol) in 35 mL of H_2O. [CAUTION! The acyl azide product may be explosive and should be treated with extreme care and appropriate blast protection.] After the mixture was stirred for 20 min at 0 °C, a solid was present. The mixture was transferred to a separatory funnel, diluted with 600 mL of ice-cold water, and extracted once with 200 mL and twice with 100 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ for 1 h at 0 °C and then suction filtered through fresh $MgSO_4$. Rotary evaporation of the filtrate at below room temperature afforded a pale-tan solid. This crude acyl azide was immediately dissolved and suspended in 100 mL of toluene. The flask was fitted with a large-volume reflux condenser (to accommodate foam). Behind a blast shield, the mixture was cautiously heated with a heating mantle to produce a yellow solution. When gas evolution became vigorous (much foaming!), the heating mantle was quickly removed. (Note: Ice should be kept available to moderate the reaction should it become too vigorous.) Once the violent reaction subsided (several minutes), the heating mantle was replaced, and the mixture was slowly heated to reflux. Much pale solid was present (the desired symmetrical urea–acyl azide was not dry). Very little further gas evolution was observed. After 1 h, the mixture was cooled, and 1.25 mL of H_2O (0.069 mol) was added. The gradually thickening suspension was stirred for 2 days, filtered, and washed with 10 mL of toluene and then with three 20-mL portions of pentane. The product was air-dried to give a white powder, 12.23 g (44%). The filtrate was treated with 0.1 mL of H_2O each day for the next 4 days, then filtered, washed with 10 mL of toluene and three 20-mL portions of pentane, and air-dried to give an additional 6.023 g; the total yield of **10** was 18.25 g (66%). A small sample was recrystallized from boiling benzene (0.1 g, 150 mL), to give glistening ivory-colored needles: mp 233–234 °C; IR (KBr) 3350 and 3265 (m, N*H*), 1660 (s, C=O), 1535 (vs, NO_2), 1355 (s, NO_2) cm^{-1}; ^1H NMR (acetone-d_6) δ 3.91 (s, 6 H, OCH_3), 7.32 (t, 2 H, J = 8.2 Hz, ArH), 7.53 (d of d, 2 H, J = 8.2, 1.5 Hz, ArH), 8.64 (d of d, 2 H, J = 3.2, 1.5 Hz, ArH), 8.89 (br s, 2 H, NH); mass spectrum (70 eV, 200 °C), m/z (relative intensity) 362 (M^+, 4), 194 ($ArNCO^+$, 70), 168 ($ArNH_2^+$, 100); mass spectrum (16 eV, 200 °C), m/z (relative intensity) 362 (M^+, 15), 194 ($ArNCO^+$, 59), 168 ($ArNH_2^+$, 100). Anal. Calcd for $C_{15}H_{14}N_4O_7$: C, 49.73; H, 3.90; N, 15.46. Found: C, 49.77; H, 4.03; N, 15.37.

1,3-Bis(2-methoxy-3-nitrophenyl)tetrahydro-2-pyrimidinone (11). To a stirred mixture of 30.0 g (0.083 mol) of **10** in 1830 mL of C_6H_6 under N_2 was added a cooled solution of 100.5 g of NaOH (2.51 mol) in 228 mL of H_2O, followed by 39.9 g of 1,3-propanediol ditosylate (0.104 mol) and 1.95 g of $Bu_4N^+I^-$ (0.0053 mol). The reaction mixture was flushed with N_2 and kept under a blanket of N_2 throughout the reaction; the flask was wrapped in Al foil to exclude light. The stirred mixture was heated to 46 °C in a water bath. The reaction was followed by TLC (silica, 1:1 petroleum ether–EtOAc, **10** R_f 0.58, **11** R_f 0.09). After 96 h, some starting material remained. An additional 7.5 g of ditosylate (0.020 mol) was added, and the mixture was stirred 48 h at 46 °C. A final 1.0 g of ditosylate (0.0026 mol) was added, and the mixture was stirred for 12 h and then cooled to 25 °C. The layers were allowed to separate, and the benzene layer was decanted through a pad of Celite on a sintered glass funnel. The aqueous layer was washed thoroughly with benzene. The combined benzene layers were washed with H_2O, dried, and concentrated to an oil, which was dissolved in 100 mL of CH_2Cl_2 and added to 400 mL of Et_2O. The solid that separated was collected to provide 5.4 g (16%) of **11**. The original dark aqueous phase was filtered through Celite, and the Celite pad was then extracted well with CH_2Cl_2. This CH_2Cl_2 solution was washed with H_2O, dried, and evaporated to give 13.8 g of product (41.4%), total yield 19.2 g (58%). (On a 10.0-g scale, a 65% yield was obtained; on a 1.0-g scale, the yield was 74%.) A sample was recrystallized from 1:1 benzene–cyclohexane, giving white needles: mp 233–235 °C; IR (KBr) 1640 (s, C=O), 1520 (vs, NO_2), 1355 (s, NO_2) cm^{-1}; ^1H NMR (acetone-d_6) δ 2.40 (quintet, 2 H, J = 5 Hz, $CH_2CH_2CH_2$), 3.84 (t, 4 H, J = 5 Hz, $NCH_2CH_2CH_2N$), 4.00 (s, 6 H, OCH_3), 7.22 (t, 2 H, J = 8.2 Hz, ArH), 7.7 (d of d, 2 H, J = 8.2, 2.3 Hz, ArH), 7.8 (d of d, 2 H, J = 8.2, 2.3 Hz, ArH); mass spectrum (280 °C), m/z (relative intensity) 402 (M^+, 0.5), 371 (100). Anal. Calcd for $C_{18}H_{18}N_4O_7$: C, 53.73; H, 4.51; N, 13.92. Found: C, 53.76; H, 4.52; N, 13.89.

1,3-Bis(2-hydroxy-3-nitrophenyl)tetrahydro-2-pyrimidinone (12). A suspension of 10.0 g (0.025 mol) of **11** in 80 mL of glacial AcOH was flushed with N_2, heated until it became homogeneous, and then diluted with 400 mL of 48% HBr in H_2O. The mixture was heated to reflux during 1 h, and after 30 min at reflux, the reaction was complete by TLC (silica, 2:1, CH_2Cl_2–EtOAc, **11** R_f 0.48, **12** R_f 0.36). The solution was cooled under N_2 and shaken with 2500 mL of H_2O. The mixture was extracted with six 300-mL portions of CH_2Cl_2, and the combined organic layers were washed 3 times with H_2O, dried, and concentrated to give 9.7 g of orange solid. The material was dissolved in 100 mL of CH_2Cl_2 and layered with 250 mL of Et_2O. Bright-yellow needles of **12** separated in several crops to give 8.17 g (88%): mp 185–186 °C dec; IR (KBr) 3250 (m, 1 H, ArOH), 1642 (m, C=O), 1540 (s, NC_2), 1350 (m, NO_2)

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(21) We recently have been successful at separating **3** and **4** by affinity chromatography on a reverse-phase silica HPLC column functionalized with aminopropyl groups with 1% NH_4Br in CH_3OH as the mobile phase. On this column, the poorer binder (**4**) eluted first.

cm^{-1}; ^1H NMR δ 2.37 (quintet, 2 H, J = 5.8 Hz, $CH_2CH_2CH_2$), 3.80 (t, 4 H, J = 5.8 Hz, $CH_2CH_2CH_2$), 6.78 (t, 2 H, J = 8.5 Hz, ArH), 7.65 (d of d, 2 H, J = 8.5, 1.7 Hz, ArH), 8.06 (d of d, 2 H, J = 8.5, 1.7 Hz, ArH), 10.92 (s, 2 H, OH); mass spectrum (70 eV, 190 °C), m/z (relative intensity) 374 (M^+, 47), 167 (100); mass spectrum (16 ev, 190 °C), m/z (relative intensity) 374 (M^+, 100), 167 (61). Anal. Calcd for $C_{16}H_{14}N_4O_7$: C, 51.34; H, 3.77; N, 14.97. Found: C, 51.40; H, 3.72; N, 14.80.

1,3-Bis(2-hydroxy-3-nitro-5-methylphenyl)tetrahydro-2-pyrimidinone (14). A stirred mixture of 52.4 g of **13**[5] (0.168 mol) and 1.1 L of $CHCl_3$ was cooled to −15 °C in a wet ice–methanol bath. Concentrated nitric acid (70%, 35.2 mL, 0.588 mol) was added portionwise over 10 min. The reaction mixture began to darken after 15 min. After 90 min, water (200 mL) was added and the mixture was allowed to warm to 25 °C. The $CHCl_3$ layer was washed with 200 mL of H_2O. The combined H_2O layers were extracted with 100 mL of $CHCl_3$. The combined $CHCl_3$ layers were dried and evaporated to leave a dark-orange solid. This solid was triturated with 400 mL of CH_2Cl_2, leaving 47.3 g of yellow–orange powder. The 400 mL of CH_2Cl_2 was treated with 2.5 L of Et_2O and allowed to stand for 6 h. The precipitate (5.7 g) was combined with the triturated solid to give a total yield of 54.0 g of pure **14** (80%): mp >220 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 2.20–2.50 (m, 2 H, NCH_2CH_2), 2.32 (s, 6 H, $ArCH_3$), 3.82 (m, 4 H, NCH_2CH_2), 7.59 (d, J = 2 Hz, 2 H, ArH), 7.95 (d, J = 2 Hz, 2 H, ArH), 10.9 (s, 2 H, OH); mass spectrum (280 °C), m/z (relative intensity) 402 (M^+). Anal. Calcd for $C_{18}H_{18}N_4O_7$: C, 53.73; H, 4.51. Found: C, 53.70; H, 4.52.

7,8,16,17-Tetrahydro-4,10-dinitro-15*H*-14,18-methano-6*H*,14*H*-dibenzo[*b*,*i*][1,11,4,8]dioxadiazacyclotetradecan-19-one (15). Procedure A. A suspension of 8.076 g of **12** (21.6 mmol), 400 mL of pure DMF, and 40.4 g of powdered anhydrous K_2CO_3 (292 mmol) was heated at 115 °C for 35 min, giving an orange–red solution. While the temperature was maintained at 115 °C, 8.1 mL of 1,3-dibromopropane (16.1 g, 79.8 mmol) was added by syringe over a 50-min period. The mixture was stirred at 115 °C for 2 h after the addition was complete and then allowed to cool for 12 h. The DMF was evaporated in vacuo at 65 °C, and the residue was stirred with 500 mL of CH_2Cl_2, filtered, and washed with 250 mL of CH_2Cl_2. The residue was then dissolved in 500 mL of H_2O and extracted with 200 mL of CH_2Cl_2. The combined organic phases were washed 3 times with 500 mL of H_2O, dried, and concentrated, giving 8.1 g of a pale-yellow solid. The crude product was dissolved in 150 mL of CH_2Cl_2 and layered with 325 mL of Et_2O. The combined crops that separated were collected to give 6.56 g (73%) of **15**: mp 267–269 °C (wets at 250 °C); IR (KBr) 1650 (s, C=O), 1520 (vs, NO_2), 1350 (s, NO_2) cm^{-1}; ^1H NMR δ 2.2–2.6 (m, 4 H, $CH_2CH_2CH_2$), 3.7–3.9 (m, 4 H, $NCH_2CH_2CH_2N$), 4.2–4.3 (m, 2 H, OCH_2), 4.4–4.5 (m, 2 H, OCH_2), 7.21 (t, 2 H, J = 8.0 Hz, ArH para to O), 7.50 (d of d, 2 H, J = 8.0, 1.7 Hz, ArH ortho to urea), 7.75 (d of d, 2 H, J = 8.0, 1.7 Hz, ArH ortho to NO_2); mass spectrum (70 eV, 250 °C), m/z (relative intensity) 414 (M^+, 8), 161 (100). Anal. Calcd for $C_{19}H_{18}N_4O_7$: C, 55.07; H, 4.38; N, 13.52. Found: C, 55.08; H, 4.23; N, 13.51.

7,8,16,17-Tetrahydro-2,12-dimethyl-4,10-dinitro-15*H*-14,18-methano-6*H*,14*H*-dibenzo[*b*,*i*][1,11,4,8]dioxadiazacyclotetradecan-19-one (16). Procedure A, when applied to 41.64 g of diphenol **14** and 21.81 g of 1,3-dibromopropane, gave 31.78 g (69%) of **16**: mp 305 °C dec; ^1H NMR (60 MHz) δ 2.00–2.20 (m, 4 H, NCH_2CH_2 and OCH_2CH_2), 2.36 (s, 6 H, $ArCH_3$), 3.60–4.00 (m, 4 H, NCH_2CH_2), 4.00–4.50 (m, 4 H, OCH_2CH_2), 7.40 (d, J = 2 Hz, 2 H, ArH), 7.64 (d, J = 2 Hz, 2 H, ArH); mass spectrum (220 °C), m/z (relative intensity) 442 (M^+). Anal. Calcd for $C_{21}H_{22}N_4O_7$: C, 57.01; H, 5.01; N, 12.66. Found: C, 57.14; H, 4.98; N, 12.59.

7,8,16,17-Tetrahydro-4,10-diamino-15*H*-14,18-methano-6*H*,14*H*-dibenzo[*b*,*i*][1,11,4,8]dioxadiazacyclotetradecan-19-one (17). Procedure B. To a mixture of 5.926 g of **15** (14.3 mmol), 17.7 g of granular tin metal (167 mmol, 30 mesh), and 64 mL of ethanol was added with stirring a solution of 15.6 mL of concentrated HCl in 43 mL of H_2O. The suspension was heated at reflux for 1 h, and the resulting hot solution was poured into 400 mL of H_2O. Saturated aqueous $NaHCO_3$ solution (150–200 mL) was slowly added to bring the pH to ca. 7. The suspension was filtered, and the residue was washed with H_2O, then ethanol, and finally Et_2O, giving a pale-yellow powder (**17** contaminated with tin salts). This material was extracted for 14 days with CH_2Cl_2 in a Soxhlet extractor. Evaporation of the CH_2Cl_2 afforded **17**, 4.08 g (80%), as a white powder. Recrystallization of a small sample from CH_2Cl_2/Et_2O afforded a microcrystalline product: mp 256–259 °C dec; IR (KBr) 3460 (m), 3400 (m), 3340 (s), 3300 (m), 3220 (m), 3200 (m, NH_2), 1620 (s, C=C) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.0–2.4 (m, 4 H, $CH_2CH_2CH_2$), 3.50–3.65 (m, 4 H, NCH_2), 3.75–3.90 (m, 2 H, OCH_2), 4.3–4.45 (m, 2 H, OCH_2), 4.87 (br s, 4 H, NH_2), 6.42 (d of d, 2 H, J = 8.0, 2.2 Hz, ArH), 6.58 (d of d, 2 H, J = 8.0, 2.2 Hz, ArH), 6.78 (t, 2 H, J = 8.0 Hz, ArH para to O); mass spectrum (250 °C), m/z (relative intensity) 354 (M^+, 100). Anal. Calcd for $C_{19}H_{22}N_4O_3$: C, 64.39; H, 6.26; N, 15.81. Found: C, 61.85; H, 6.40; N, 14.56 (calcd for $C_{19}H_{22}N_4O_3 \cdot H_2O$: C, 61.28; H, 6.50; N, 15.04).

7,8,16,17-Tetrahydro-2,12-dimethyl-4,10-diamino-15*H*-14,18-methano-6*H*,14*H*-dibenzo[*b*,*i*][1,11,4,8]dioxadiazacyclotetradecan-19-one (18). Application of procedure B to 15 g of **16** provided 10 g (77%) of **18**: mp 250–280 °C dec; ^1H NMR δ 2.00–2.40 (m, 4 H, NCH_2CH_2 and OCH_2CH_2), 2.18 (s, 6 H, $ArCH_3$), 3.50–3.90 (m, 8 H, NCH_2CH_2 and NH_2), 3.90–4.40 (m, 4 H, OCH_2CH_2), 6.45 (s, 4 H, ArH); mass spectrum (220 °C), m/z (relative intensity) 382 (M^+). Anal. Calcd for $C_{21}H_{26}N_4O_3$: C, 65.95; H, 6.85. Found: C, 65.71; H, 6.91.

***N*,*N*′-(7,8,16,17-Tetrahydro-19-oxo-15*H*-14,18-methano-6*H*-dibenzo[*b*,*i*][1,11,4,8]dioxadiazacyclotetradecane-4,10-diyl)bis[*N*′(3-chloropropyl)urea] (19). Procedure C.** To a stirred suspension of 3.69 g of diamine **17** (10.4 mmol) and 355 mL of dry CH_2Cl_2 was added 3.6 mL of 3-chloropropyl isocyanate[9] (4.1 g, 34.4 mmol). The mixture was stirred under N_2 for 72 h, at which point TLC (silica, 4:1 CH_2Cl_2–CH_3OH) showed only a single new spot (**17** R_f 0.53, **19** R_f 0.71). The slurry was reduced in volume to 25 mL on a rotary evaporator, and 400 mL of Et_2O was added, precipitating much solid. The product was mashed thoroughly on a vacuum filter, and washed well with Et_2O to give **19** as a white powder: 5.932 g (96%); mp 239–245 °C dec; IR (KBr) 3320 (ms, br, N—H), 1660 (s, C=O), 1630 (s, C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.90 (quintet, 4 H, $NHCH_2CH_2CH_2Cl$, J = 6.7 Hz), 2.0–2.4 (m, 4 H, $NCH_2CH_2CH_2N$ + $OCH_2CH_2CH_2O$), 3.25 (t, 4 H, J = 6.7 Hz, CH_2Cl), 3.6–3.7 (m, 4 H, NCH_2), 3.69 (t, 4 H, $NHCH_2$-CH_2CH_2Cl, J = 6.7 Hz), 3.9–4.0 (m, 2 H, OCH_2), 4.3–4.4 (m, 2 H, OCH_2), 6.8 (d of d, 2 H, J = 7.3, 1.6 Hz, ArH), 7.0 (br t, 4 H, J = 7.3 Hz, ArH + NH), 7.88 (br s, 2 H, NH) 8.0 (d of d, 2 H, J = 7.3, 1.6 Hz, ArH); mass spectrum (300 °C), m/z (relative intensity) 520 (M^+ − 2HCl, 4), 437 (45), 163 (100). Anal. Calcd for $C_{27}H_{34}Cl_2N_6O_5$: C, 54.64; H, 5.77; N, 14.16. Found: C, 54.69; H, 5.70; N, 13.99.

***N*,*N*′-(7,8,16,17-Tetrahydro-2,12-dimethyl-19-oxo-15*H*-14,18-methano-6*H*,14*H*-dibenzo[*b*,*i*][1,11,4,8]dioxadiazacyclotetradecane-4,10-diyl)bis[*N*′-(3-chloropropyl)urea] (20).** Application of procedure C to 11.2 g of **18** and 10.1 g of 3-chloropropyl isocyanate[9] gave 16.44 g (91%) of **20**: mp 200–210 °C dec; ^1H NMR (Me_2SO-d_6) δ 1.80–2.40 (m, 2 H, OCH_2CH_2, NCH_2CH_2, and $ClCH_2CH_2$), 2.21 (s, 6 H, $ArCH_3$), 3.10–3.30 (m, 4 H, $ClCH_2CH_2$), 3.50–3.80 (m, 8 H, NCH_2CH_2), 3.85–4.40 (m, 4 H, OCH_2CH_2), 6.60 (br s, 2 H, ArH), 6.96 (br t, 2 H, $NHCH_2$), 7.79 (s, 2 H, ArNH), 7.85 (br s, 2 H, ArH); mass spectrum (230 °C), m/z (relative intensity) 548 (M^+ − 72, loss of 2 HCl, no M^+ ion could be detected). Anal. Calcd for $C_{29}H_{38}Cl_2N_6O_5$: C, 56.04; H, 6.16. Found: C, 55.92; H, 6.11.

7,8,16,17-Tetrahydro-4,10-bis(tetrahydro-2-oxo-1(2*H*)-pyrimidinyl)-15*H*-14,18-methano-6*H*,14*H*-dibenzo[*b*,*i*][1,11,4,8]dioxadiazacyclotetradecan-19-one (6). Procedure D. A suspension of 5.932 g of **19** (9.99 mmol), 1500 mL of THF, 0.300 g of benzyltriethylammonium bromide (1.10 mmol) and 2.97 g of 95% powdered KOH (45.0 mmol) was stirred at 25 °C for 8 days, with ca. 0.25 mL of H_2O being added each day. At the end of this period, the suspended solid settled quickly when the stirring was halted. When the reaction is incomplete, the suspension settles slowly. The mixture was filtered under vacuum through a medium-sintered glass funnel, and the solid was washed with THF and Et_2O and air-dried. This solid was then washed through the filter with CH_2Cl_2. The resulting solution was evaporated to give a glass. This material was dissolved in 350 mL of CH_2Cl_2, and the solution was washed with two 100-mL portions of dilute aqueous HCl. The combined aqueous washes were extracted with six 75-mL portions of CH_2Cl_2. The combined organic layers were evaporated to dryness on a rotary evaporator. The residue was dried by azeotropic removal of H_2O with absolute EtOH on a rotary evaporator, and the solvent was removed. The resulting glass was dissolved in CH_2Cl_2, and **6** was precipitated with Et_2O, 3.10 g (60%), which appears as a single spot to TLC (silica, 4:1 CH_2Cl_2–MeOH; **19** R_f 0.40, **6** R_f 0.23): mp 230 °C dec; IR (KBr) 3400 (br, NH), 1645 (s, C=O), 1495 (s), 1445 (s), 1310 (ms) cm^{-1}; ^1H NMR δ 1.9–2.5 (br m, 8 H, $CH_2CH_2CH_2$), 3.3–4.5 (br m, 16 H, NCH_2 + OCH_2), 5.6 (br s, 2 H, NH), 7.1–7.3 (br m, 6 H, ArH); mass spectrum (270 °C), m/z (relative intensity) 521 (30), 520 (M^+, 100), 463 (33), 462 (38), 246 (34). Anal. Calcd for $C_{27}H_{32}N_6O_5$: C, 62.29; H, 6.20; N, 16.14. Found: C, 56.86; H, 5.97; N, 14.36 [calcd for $C_{27}H_{32}N_6O_6 \cdot H_2O \cdot 0.5CH_2Cl_2$: C, 56.84; H, 6.07; N, 14.46 (this sample had been dried at 140 °C under vacuum for ca. 96 h!)].

7,8,16,17-Tetrahydro-2,12-dimethyl-4,10-bis(tetrahydro-2-oxo-1-(2*H*)-pyrimidinyl)-15*H*-14,18-methano-6*H*,14*H*-dibenzo[*b*,*i*]-[1,11,4,8]dioxadiazacyclotetradecan-19-one (7). Application of procedure D to 5.67 g of **20** gave 2.5 g (50%) of **7**: mp 260–270 °C dec; ^1H NMR (55 °C) δ 1.80–2.50 (m, 8 H, NCH_2CH_2 and OCH_2CH_2), 2.26 (s, 6 H, $ArCH_3$), 3.30–3.90 (m, 12 H, NCH_2CH_2), 4.00–4.40 (m, 4 H,

OCH_2CH_2), 5.15 (br s, 2 H, NH), 6.91–6.96 (m, 4 H, ArH); mass spectrum (210 °C), m/z (relative intensity) 548 (M^+). Anal. Calcd for $C_{29}H_{36}N_6O_5 \cdot 0.5H_2O$: C, 62.46; H, 6.69. Found: C, 62.75; H, 6.68. Many unsuccessful attempts were made to obtain a satisfactory analysis for a water-free sample of **7**.

The complex, **7**·Na picrate, was formed by adding equivalent amounts of **7** and Na picrate in CH_2Cl_2 and precipitating the product by adding Et_2O: ^1H NMR δ 1.80–2.40 (m, 8 H, NCH_2CH_2 and OCH_2CH_2), 2.24 (s, 6 H, $ArCH_3$), 2.95–4.05 (m, 16 H, NCH_2CH_2 and OCH_2CH_2), 6.25 (br s, 2 H, NH), 6.80 (s, 2 H, ArH), 6.91 (s, 2 H, ArH), 8.78 (s, 2 H, ArH).

The t-$BuNH_3^+SCN^-$ complex was prepared by mixing 1 equiv of **7** and guest in CH_2Cl_2 and precipitating with Et_2O: ^1H NMR δ 0.98 (s, 9 H, $(CH_3)_3CNH_3^+$), 2.00–2.40 (m, 8 H, NCH_2CH_2 and OCH_2CH_2), 2.29 (s, 6 H, $ArCH_3$), 3.40–3.80 (m, 12 H, NCH_2CH_2), 3.80–4.60 (m, 4 H, OCH_2CH_2), 5.4 (br s, 2 H, NH), 6.92 (s, 2 H, ArH), 6.96 (s, 2 H, ArH). The resonance for the NH_3^+ protons was not located. Anal. Calcd for $C_{29}H_{36}N_6O_5 \cdot C_5H_{12}N_2S$: C, 59.98; H, 7.11; N, 16.46. Found: C, 59.70; H, 6.96; N, 16.24.

2,2′-(2-Fluoro-1,3-phenylene)bis[4,5-dihydro-4,4-dimethyl-2-oxazoline] (21).[10] A mixture of 47.1 g (256 mmol) of 2-fluoroisophthalic acid,[19] 1 mL of dry DMF, 250 mL of dry benzene, and 76 mL (1.06 mol) of thionyl chloride was refluxed for 5 h to give a clear solution. The solvent was evaporated under vacuum to give the bisacid chloride, which was recrystallized from hexane to provide 54.6 g (97%) of 2-fluoroisophthaloyl dichloride: mp 62.5–69 °C; mass spectrum, m/z 200 (M^+). Anal. Calcd for $C_8H_3Cl_2FO_2$: C, 43.48; H, 1.37; Cl, 32.11. Found: C, 43.55; H, 1.50; Cl, 31.97.

To 28.11 g (315 mmol) of 2-amino-2-methyl-1-propanol in 30 mL of CH_2Cl_2 stirred at 0 °C was added 17.4 g (78.7 mmol) of 2-fluoroisophthaloyl dichloride as a solid over 30 min. The thick mass was then stirred 15 min at room temperature, collected, washed well with distilled water, and dried over P_2O_5 under vacuum to provide N,N'-bis(2-hydroxy-1,1-dimethylethyl)-2-fluoro-1,3-benzenedicarboxamide as a white solid (20.7 g, 81%): mp 168–171 °C. An analytical sample was recrystallized from water to give the bisamide as white flakes. Anal. Calcd for $C_{16}H_{23}FN_2O_4$: C, 58.88; H, 7.10; N, 8.58. Found: C, 58.83; H, 7.05; N, 8.64.

This bisamide was converted to the bisoxazoline **21** as follows. Three identical reactions were conducted separately. To a stirred suspension of 10.0 g (0.031 mol) of the bisamide in 180 mL of dry CH_2Cl_2 cooled in an ice bath was added 1.5 mL of dry DMF followed by 15.8 mL (0.217 mol) of thionyl chloride (all at once). The clear solution was stirred at 0 °C for 45 min and then warmed to 25 °C. The resulting suspension was stirred for 2 days and then poured cautiously into a solution of 50 g of NaOH in 500 mL of water. After mixing well, this mixture was extracted with one 250-mL and two 150-mL portions of CH_2Cl_2. The combined organic layers were washed with 250 mL of water and dried. The combined solutions from the three reactions were concentrated to an oil, which was mixed with 50 mL of Et_2O (not all material dissolved). This mixture was suction filtered through 75 mL (dry volume) of medium-pressure grade silica gel in a 150-mL medium-sintered glass funnel. The pad was washed with 1250 mL of Et_2O to elute all mobile products. The filtrate was concentrated to an oil which crystallized to give 24.8 g (93%) of **21** (TLC, silica, Et_2O, R_f 0.31). An analytical sample was prepared by crystallization from CH_2Cl_2–hexane: mp 61–64 °C; ^1H NMR δ 1.39 (s, 12 H, CH_3), 4.10 (s, 4 H, CH_2), 7.20 (t, 1 H, ArH_5, J = 7.7 Hz), 7.94 (d of d, 2 H, $ArH_{4,6}$, J = 7.7 Hz, J_{H-F} = 6.5 Hz); mass spectrum, m/z (relative intensity) 290 (M^+). Anal. Calcd for $C_{16}H_{19}FN_2O_2$: C, 66.19; H, 6.60; N, 9.65; F, 6.54. Found: C, 66.14; H, 6.70; N, 9.60; F, 6.46.

3′,5′-Dimethyl-1,1′-biphenyl-2,6-dicarboxylic Acid (23). The Grignard reagent from 20.0 g of 5-bromo-1,3-xylene (0.108 mol) and 5.0 g of Mg (0.206 mol) was formed in 100 mL of THF. The mixture was stirred until the vigorous reaction had subsided and the temperature had returned to ca. 25 °C (2.5 h). Fluorobis(oxazoline) **21** (10.0 g, 0.0344 mol) was dissolved in 100 mL of dry THF under N_2, and the Grignard reagent was added via syringe. The mixture was heated at reflux for 3.5 h, cooled, and quenched with 100 mL of H_2O. The mixture was diluted with 300 mL of H_2O and extracted with 250 mL of Et_2O and three 125-mL portions of the same solvent. The combined organic layers were washed with three 125-mL portions of H_2O, dried, and concentrated to an oil. Nitromethane (250 mL) and 50 mL of CH_3I (ca. 114 g, 0.803 mol) were added, and the mixture was heated at reflux for 16 h. Solvent was removed on a rotary evaporator, and a solution of 55 g of NaOH (1.38 mol) in 300 mL of H_2O was added. The suspension was heated at reflux for 24 h, cooled, and extracted with three 250-mL portions of Et_2O. The aqueous phase was carefully acidified with concentrated aqueous HCl, cooled, and filtered, and the solid was washed well with H_2O. This material was then extracted repeatedly with Et_2O until no more dissolved. The combined Et_2O extracts were washed with two 200-mL portions of H_2O, filtered through $MgSO_4$, and concentrated, affording bisacid **23**: 7.99 g (86%); mp 243–244 °C; IR (KBr) 1695 (s) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.26 (s, 6 H, $ArCH_3$), 6.80 (s, 2 H, ArH), 6.95 (s, 1 H, ArH), 7.49 (t, 1 H, J = 7.6 Hz, ArH), 7.71 (d, 2 H, J = 7.6 Hz, ArH); mass spectrum (240 °C), m/z (relative intensity) 271 (17), 270 (M^+, 100), 237 (11), 206 (15), 179 (12), 178 (13), 165 (16), 152 (10). Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.92; H, 5.12.

2,6-Bis(hydroxymethyl)-3′,5′-dimethyl-1,1′-biphenyl (24). Diacid **23** (7.99 g, 29.6 mmol) was dissolved in 500 mL of dry THF under N_2 and treated with 118.2 mL of 1 M BH_3·THF (118.2 mmol). The cloudy white solution was heated at reflux for 4 h, cooled, and carefully quenched with 1 L of H_2O (foaming at first!). The mixture was extracted with three 250-mL portions of Et_2O, and the combined organic layers were washed with two 200-mL portions of saturated aqueous $NaHCO_3$ and 250 mL of H_2O, dried, and concentrated to an oil, which crystallized on standing. Residual solvent was removed in vacuo, affording **24** as a white, crystalline solid, 6.76 g (94%). An analytical sample was prepared by recrystallization from cyclohexane–benzene: mp 133–135 °C; IR (KBr) 3300–3150 (s, br, OH), 1050 (vs) cm^{-1}; ^1H NMR δ 1.43 (br s, 2 H, OH), 2.34 (s, 6 H, $ArCH_3$), 4.41 (s, 4 H, $ArCH_2O$), 6.82 (s, 2 H, ArH), 7.02 (s, 1 H, ArH), 7.4–7.5 (m, 3 H, ArH); mass spectrum (220 °C), m/z (relative intensity) 242 (M^+, 3), 224 (100), 209 (88), 206 (67), 193 (50), 181 (75), 165 (71). Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.24; H, 7.55.

2,6-Bis(bromomethyl)-3′,5′-dimethyl-1,1′-biphenyl (25). Diol **24** (6.76 g, 27.9 mmol) was dissolved in 500 mL of $CHCl_3$, and HBr gas was bubbled through the solution until saturated. The cloudy solution was stirred for 15 h, at which point TLC analysis (silica, CH_2Cl_2) showed a single spot ($R_f \sim 1.0$). The solution was washed with 500 mL of dilute aqueous $NaHCO_3$ and 500 mL of H_2O, dried, and concentrated to an oil. This was dissolved in CH_2Cl_2 and filtered through a 1- × 5-in. column of silica gel slurried in CH_2Cl_2, **25** eluting with CH_2Cl_2 at the solvent front in ca. 60 mL. Concentration of the solution afforded a colorless oil which slowly crystallized when allowed to stand 1 week at −20 °C or when seeded with an authentic sample of **25**: mp 61.6–62.2 °C; IR (neat) 1600 (ms), 1460 (ms), 1415 (ms), 1215 (s), 850 (ms), 760 (s), 710 (ms) cm^{-1}; ^1H NMR δ 2.37 (s, 6 H, $ArCH_3$), 4.22 (s, 4 H, $ArCH_2Br$), 6.95 (br s, 2 H, ArH), 7.05 (br s, 1 H, ArH), 7.29–7.48 (m, 3 H, ArH); mass spectrum (150 °C), m/z (relative intensity) 370 [M^+ ($^{81}Br)_2$, 5], 368 [M^+ ($^{79}Br^{81}Br$), 10], 366 (M^+ ($^{79}Br)_2$, 5], 207 (100). Anal. Calcd for $C_{16}H_{16}Br_2$: C, 52.20; H, 4.38. Found: C, 52.35; H, 4.39.

38-(3,5-Dimethylphenyl)-7,8,19,20,28,29,35,36-octahydro-6*H*,10*H*,16*H*,18*H*,32*H*,34*H*-59:17,21-dimethano-11,15-metheno-1,2,5-[1′,3′]pyrimidino-5*H*,27*H*-dibenzo[*b*,*u*][1,23,4,8,16,20]dioxatetraazacyclohexacosine-32,37,39-trione (3 and 4). Procedure E. Sodium hydride (0.775 g, 50% dispersion in oil, 16.1 mmol) in a N_2-flushed 1-L three-necked flask with a reflux condenser was washed with two 10-mL portions of dry THF to remove oil. Dry THF (1 L) and 1.0 g of **6** (1.92 mmol; dried 24 h under high vacuum at 110 °C before use) were added, and the mixture was heated at reflux until no undissolved **6** remained (ca. 6 h). The solution was cooled to −78 °C, and a solution of 0.716 g of dibromide **25** (1.94 mmol) dissolved in 20 mL of dry THF was added all at once. The resulting mixture was stirred for 2 h at −78 °C and allowed to warm to 25 °C. After being stirred at 25 °C for 24 h, the mixture was heated at reflux for 2 h, then cooled, and quenched with 8 mL of H_2O. Solvent was removed on a rotary evaporator, and the residue was dissolved in 150 mL of CH_2Cl_2 and washed with 100 mL of H_2O containing 10 mL of 2 N HCl. The aqueous phase was extracted with three 125-mL portions of CH_2Cl_2, and the combined organic layers were washed with four 125-mL portions of deionized H_2O, concentrated, and dried in vacuo. The residue (1.534 g) was gel chromatographed (100-Å Styragel, 24-ft column, CH_2Cl_2 as mobile phase) in eight equal portions (TLC, silica, 4:1 CH_2Cl_2–CH_3OH, **3** and **4** R_f 0.38), affording 1.10 g of pale-yellow foam, a mixture of **3** and **4** (79%). The reaction on one-quarter of this scale afforded an 89% yield of the diastereomers. This product was dissolved in CH_2Cl_2 and separated in six equal injections, on a 20- × 25-mm reversed phase (bonded C18) silica HPLC column, with 75% CH_3OH–25% H_2O–1% NaBr as the mobile phase. The fractions were concentrated to dryness under vacuum. The residues were dissolved in mixtures of CH_2Cl_2 and deionized H_2O, and the CH_2Cl_2 layers were washed with deionized H_2O until the hosts had decomplexed. Isomer **3** eluted first to give 0.459 g (33%) of glass-like blocks (crystallized from CH_2Cl_2–Et_2O). Isomer **4** eluted second, 0.442 g (32%), as clumps (crystallized from CH_2Cl_2–Et_2O).[18] Isomer **3**: mp >360 °C dec; IR (KBr) 1640 (vs, C=O), 1490 (s), 1470 (s), 1450 (s), 1430 (s), 1300 (s), 1225 (ms), 1200 (ms), 748 (ms) cm^{-1}; ^1H NMR δ 1.75 (m, 1 H, $CH_2CH_2CH_2$), 1.9–2.5 (m, 6 H, $CH_2CH_2CH_2$), 2.36 (s, 3 H, $ArCH_3$),

2.49 (s, 3 H, $ArCH_3$), 2.9 (m, 3 H, $CH_2CH_2CH_2$ + NCH_2), 3.4–3.9 (m, 14 H, $ArCH_2N$ + NCH_2 + OCH_2), 4.4 (br pseudo-t, 2 H, OCH_2), 4.54 (d, 2 H, J = 14 Hz, $^1/_2$ of AB, $ArCH_2N$), 6.77 (br s, 1 H, ArH), 6.95–7.20 (m, 9 H, ArH), 7.61 (d, 2 H, ArH); mass spectrum (70 eV, 290 °C), m/z (relative intensity) 727 (24), 726 (M^+, 58), 207 (100); mass spectrum (16 eV, 270 °C), m/z (relative intensity) 727 (51), 726 (M^+, 100). Anal. Calcd for $C_{43}H_{46}N_6O_5$: C, 71.05; H, 6.38; N, 11.56. Found: C, 71.24; H, 6.49; N, 11.53 (dried 72 h at 140 °C under high vacuum). Isomer 4: mp >300 °C dec; IR (KBr) 1635 (vs, C=O), 1495 (vs), 1450 (s), 1435 (s), 1300 (s), 1215 (s, br) cm^{-1} [nearly superimposable on isomer **3** (small differences in 900-1000 cm^{-1} region)]; ^1H NMR δ 1.6–7.7 (m, all H's except CH_3), notable features at δ 2.28 (s, 3 H, $ArCH_3$), 2.30 (s, 3 H, $ArCH_3$), 5.10–5.22 (m, 2 H), 5.80 (m, 2 H), 7.67 (br s, 2 H); mass spectrum (70 eV, 320 °C), m/z 727 (23), 726 (M^+, 46), 207 (100); mass spectrum (16 eV, 320 °C), m/z 727 (49), 726 (M^+, 100). Anal. Calcd for $C_{43}H_{46}N_6O_5$: C, 71.05; H, 6.38; N, 11.56. Found: C, 71.17; H, 6.34; N, 11.51 (dried 72 h at 140 °C under high vacuum).

7,8,19,20,28,29,35,36-Octahydro-38-methoxy-13-methyl-6*H*,10*H*,16*H*,18*H*,32*H*,34*H*-59:17,21-dimethano-11,15-metheno-1,2,5-[1′,3′]pyrimidino-5*H*,27*H*-dibenzo[*b*,*u*][1,23,4,8,16,20]dioxatetrazacyclohexacosine-32,37,39-trione (1). Procedure E was applied to 0.388 g of 50% NaH dispersion (8.08 mmol) in 500 mL of THF, 0.500 g (0.960 mmol) of **6** (dried as before), and 0.300 g of 2,6-bis(bromomethyl)-4-methylanisole[13] (**26**, 0.974 mmol). Gel chromatography of the product in four portions afforded 0.351 g (55%) of crude product, which was dissolved in CH_2Cl_2 and precipitated with Et_2O to give **1**, 300 mg (47%). A sample was purified for analysis and binding studies by preparative TLC (silica, 4:1 CH_2Cl_2–CH_3OH, R_f 0.39). The silica was extracted thoroughly with 1:1 CH_2Cl_2–CH_3OH, and the solid obtained was dissolved in CH_2Cl_2. The solution was washed 5 times with deionized water to remove salts and concentrated, and the product was recrystallized by diffusion of a layer of Et_2O into a CH_2Cl_2 solution of **1** in a test tube to give small white crystals: mp >360 °C dec; IR (KBr) 1640 (s, C=O), 1500 (s), 1475 (s), 1445 (s), 1210 (ms, br) cm^{-1}; ^1H NMR (broad and largely featureless) δ 1.4 (m), 1.8–2.5 (m, with $ArCH_3$ singlets at 2.30, 2.37), 3.2–4.7 (m), 5.6 (broad hump), 6.8–7.2 (m, ArH). **1**·NaBr complex (D_2O-saturated $CDCl_3$); ^1H NMR δ 1.4 (m), 0.14 (m), 2.0–2.6 (m containing $ArCH_3$ singlets at 2.31, 2.43), 3.2–4.7 (m, with $ArOCH_3$ singlet at 3.70), 5.26 (d, J = 15.4 Hz), 5.42 (d, J = 14.6 Hz) (~2:1 ratio, half of an AB), 6.8–7.2 (m, ArH). These spectra suggest **1** exists as rapidly interconverting conformations, two of which become locked in **1**·NaBr. **1**: mass spectrum (70 eV, 330 °C), m/z (relative intensity) 666 (M^+, 15), 520 (21), 44 (100); (16 eV, 330 °C), m/z (relative intensity) 666 (M^+, 39), 58 (100). Anal. Calcd for $C_{37}H_{42}N_6O_6$: C, 66.65; H, 6.35; N, 12.60. Found: C, 66.56; H, 6.47; N, 12.75 (dried 96 h at 140 °C under high vacuum).

7,8,19,20,28,29,35,36-Octahydro-38-methoxy-3,13,23-trimethyl-6*H*,10*H*,16*H*,18*H*,32*H*,34*H*-59:17,21-dimethano-11,15-metheno-1,2,5-[1′,3′]pyrimidino-5*H*,27*H*-dibenzo[*b*,*u*][1,23,4,8,16,20]dioxatetraazacyclohexacosine-32,37,39-trione (2). Procedure E was applied to 0.7 g (1.3 mmol) of **7** (dried under high vacuum for 24 h at 140 °C), 1.5 g (31 mmol) of NaH (oil free) in 500 mL of THF, and 0.42 g of dibromide **26**[13] in 15 mL of THF. The crude product in CH_2Cl_2 was shaken with a solution of 5 g of NaBr in H_2O, and the organic layer was evaporated to give crude **2**·NaBr. This material was chromatographed on 75 g of silica gel with 92:8 CH_2Cl_2–CH_3OH to give material that was further purified by precipitation from CH_2Cl_2 by addition of Et_2O. The precipitated material was dissolved in CH_2Cl_2, and the solution was washed with four 100-mL portions of deionized H_2O: ^1H NMR, 2.40 (m, 8 H, NCH_2CH_2 and OCH_2CH_2), 2.26 (s, 9 H, $ArCH_3$), 3.30–4.20 (m, 21 H, NCH_2CH_2, OCH_2CH_2, $ArOCH_3$, and $ArCH_2N$), 5.85 ($^1/_2$ AB, J = 14 Hz, 2 H, $ArCH_2N$), 6.91 (s, 2 H, ArH), 6.95 (s, 2 H, ArH), 7.00 (s, 2 H, ArH); mass spectrum (70 eV, 260 °C), m/z (relative intensity) 694 (M^+). Anal. Calcd for $C_{39}H_{46}N_6O_6·H_2O$: C, 65.71; H, 6.50. Found: C, 65.85; H, 6.84. After drying under high vacuum at 140 °C for 24 h we found the following. Anal. Calcd for $C_{39}H_{46}N_6O_6$: C, 67.42; 6.67. Found: C, 66.96; H, 6.64. ^1H NMR of **2**·NaBr: δ 2.00–2.40 (m, 8 H, NCH_2CH_2 and OCH_2CH_2), 2.27 (s, 6 H, $ArCH_3$), 2.37 (s, 3 H, $ArCH_3$), 3.50–4.10 (m, 16 H, NCH_2CH_2 and OCH_2CH_2), 3.67 (s, 3 H, $ArOCH_3$), 3.50 and 5.20 (AB, J = 15 Hz, 4 H, $ArCH_2N$), 6.80 (s, 2 H, ArH), 6.88 (s, 2 H, ArH), 7.08 (s, 2 H, ArH). A 500-MHz ^1H NMR spectrum of **1**·NaBr in C_6D_6 was taken and analyzed, complete with a variety of NOE experiments. Conclusions are that the complex exists predominantly in one conformation in which the three carbonyl groups and the 2-methoxyl of the 1,3-xylyl unit are syn to one another and the $CH_2CH_2CH_2$ bridge is in a fixed conformation, probably the one that thrusts a central proton into the face of the bridging anisyl unit (a chemical shift difference of more than 1 ppm is observed between the geminal $CH_2CH_2CH_2$ protons).

34-(3,5-Dimethylphenyl)-1,7,11,17,21,29-hexaazaheptacyclo[27.3.1.1^{2,6}.1^{7,11}.1^{12,16}.1^{17,21}.1^{23,27}]octatriaconta-2,4,6(38),12,14,16(36),23,25,27(34)-nonaene-33,35,37-trione (5). Procedure E was applied to 0.45 g of NaH dispersion (50% in oil, 9.38 mmol), 0.500 g (1.12 mmol) of trisurea system **27**[11] in 400 mL of THF, and 0.415 g (1.13 mmol) of dibromide **25** in 5 mL of THF. The reaction mixture was never heated but was allowed to stir for 63 h at 25 °C. The crude product was chromatographed in three portions on a 24-ft Styragel column with CH_2Cl_2 as the mobile phase to give 360 mg (49%) of **5** (TLC, silica, 4:1 CH_2Cl_2–CH_3OH, R_f 0.48). A solution of this material in CH_2Cl_2 was layered with Et_2O to give **5** as large, clear prisms: mp 345–353 °C dec; IR (KBr) 1640 (vs, C=O), 1590 (s), 1480 (vs), 1420 (vs), 1385 (ms), 1300 (vs), 1195 (s), 770 (ms), 740 (ms) cm^{-1}; ^1H NMR δ 1.67–1.80 and 2.04–2.18 (m, 6 H, $CH_2CH_2CH_2$), 2.24–2.37 (m, 2 H, NCH_2), 2.36 (s, 3 H, $ArCH_3$), 2.37 (s, 3 H, $ArCH_3$), 2.95–3.07 (m, 2 H, NCH_2), 3.36–3.50 (m, 2 H, NCH_2), 3.54–3.70 (m, 4 H, NCH_2), 3.8–3.9 (m, 2 H, NCH_2), 3.88 (d, 2 H, J = 14.1 Hz, $^1/_2$ of AB, $ArCH_2N$), 4.32 (d, 2 H, J = 14.1 Hz, $^1/_2$ of AB, $ArCH_2N$), 6.71–7.55 (m, 14 H, ArH); mass spectrum (270 °C), m/z (relative intensity) 655 (43), 654 (M^+, 100), 207 (67), 206 (77). Anal. Calcd for $C_{40}H_{42}N_6O_3$: C, 73.37; H, 6.46; N, 12.83. Found: C, 73.24; H, 6.55; N, 12.75.

Determination of Association Constants and Free Energies of Complexation. The technique has been described in detail.[14,15] The $-\Delta G°$ and K_a values of Table I are the average of two determinations, the maximum difference in $-\Delta G°$ values being 0.5 kcal mol^{-1}. The initial host and guest concentrations for **1–4** were 0.001 M and for **7** and **30** were 0.015 M.

Crystal Structure Data for Complex 2·$(CH_3)_3CNH_3^+SCN$. This complex crystallizes in the tetragonal system $I4/m$. Unit-cell dimensions are a = 21.146 (4) Å, c = 19.3225 (3) Å, V = 8656 Å^3, and Z = 8. The host and the guest each have a mirror plane relating two half molecules. The crystal was examined on a modified Picker Facs-1 diffractometer, Mo Kα radiation, at 128 K. The structure was determined by direct methods. R is currently 0.13. Full details will be published elsewhere.