factors were those given by Cromer and Mann[53] and by Stewart et al.[54] for non-hydrogen and hydrogen atoms, respectively. Real and imaginary anomalous dispersion corrections to the atomic scattering factors were included.[55] In the last cycle of least-squares refinement the maximum parameter shift was less than 0.32 of a standard deviation. The final R values[56] are listed in Table III. Final difference Fourier maps showed the residual electron density (e Å^3) for each structure as indicated in Table III.

(53) Cromer, D. T.; Mann, J. B. *Acta Crystallogr., Sect. A* **1968**, *A24*, 321.
(54) Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175.
(55) "International Tables for X-Ray Crystallography", 3rd ed.; Kynoch Press: Birmingham, United Kingdom, 1968; Vol. III, Table 3.3.2C, pp 2115–2116.
(56) $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$; $R_2 = [\sum w(|F_o| - |F_c|)^2/\sum w(F_o)^2]^{1/2}$, $w = 1/\sigma(F_o)^2$.

Acknowledgment. We thank the U.S. Army Research Office for the support of this work through Grant No. DAAG 2982-K-0045, and G. L. Lang for the Mössbauer data. The Mössbauer work was supported by the National Institutes of Health through Grant No. HL-16860. We also thank R. A. Nissan and J. L. Desorcie for obtaining the NMR data.

Registry No. 1, 940-71-6; **2**, 83437-98-3; **3**, 83447-76-1; 4, 2950-45-0; **5**, 90866-55-0; **6**, 90866-56-1; **7**, 90866-57-2; $Na_2Fe_2(CO)_8$, 64913-30-0; $Na_2Fe(CO)_4$, 14878-31-0; $Fe(CO)_5$, 13463-40-6; $Fe_2(CO)_9$, 15321-51-4; $Ru_3(CO)_{12}$, 15243-33-1; Fe, 7439-89-6; Ru, 7440-18-8.

Supplementary Material Available: Listing of thermal parameters, root mean square displacements, and observed and calculated structure factors for compounds **2**, **3**, and **7** (51 pages). Ordering information is given on any current masthead page.

Host–Guest Complexation. 30. Quinquaryl and Bis(urea) Binders[1]

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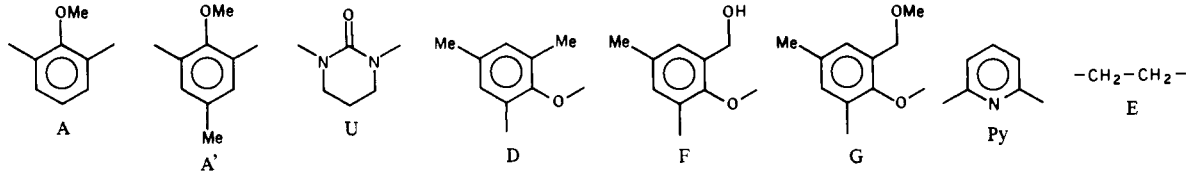
Contribution from the Department of Chemistry of the University of California at Los Angeles, Los Angeles, California 90024. *Received January 10, 1984*

Abstract: Six new types of macrocycles and one open-chain analogue are described, along with their conformational behavior and binding free energies toward alkali metal, ammonium, and alkylammonium picrates. The cycles are 20-membered and are composed by attaching aryloxy, cyclic urea, pyridyl, ethylene, methylene, and oxygen units to one another. The structures and points of attachment of all but the latter two units are drawn and are symbolized by capital letters. The structures of



the hosts and the synthetic intermediates are indicated by line formulas consisting of sequences of letters which represent the sequences of units bonded to one another in the hosts. The key intermediate in the synthesis of A′(A′DE)$_2$O (**5**) and A′(A′DCH$_2$)$_2$Py (**6**) was bis(phenol) A′(A′DH)$_2$ (**18**). Ring closure of this compound with O(CH$_2$CH$_2$OTs)$_2$ and base gave A′(A′DE)$_2$O (**5**, 49%) and with BrCH$_2$PyCH$_2$Br and base gave A′(A′OCH$_2$)$_2$Py (**6**, 11%). Treatment of the second key intermediate, bis(phenol) A(UDH)$_2$ (**32**), with O(CH$_2$CH$_2$OTs)$_2$ and base gave A(UDE)$_2$O (**7**, 56%) and with BrCH$_2$PyCH$_2$Br and base gave A(UDCH$_2$)$_2$Py (**8**, 29%). A mixture of the third key intermediate, bis(hydroxymethylphenol) A(UFH)$_2$ (**33**), with BrCH$_2$PyCH$_2$Br and base gave bis(hydroxymethylene) compound A(UFCH$_2$)$_2$Py (**9**, 47%), methylation of which produced A(UGCH$_2$)$_2$Py (**10**, 82%). Methylation of A(UFH)$_2$ (**33**) directly gave open-chain reference compound A(UFMe)$_2$ (**11**, 38%). Spectral experiments (^{1}H NMR and ^{13}C NMR) demonstrated that free cycles A(UDCH$_2$)$_2$Py (**8**), A(UFCH$_2$)$_2$Py (**9**), and A(UGCH$_2$)$_2$Py (**10**) exist in solution as two conformers, one that binds guests (binding or B′ conformer) and one that is nonbinding (N′ conformer). In solution, the two conformers equilibrate observably on the human and slowly on the ^{1}H NMR time scales. When treated with guest, each host gives a single complex formed instantaneously with B′ but over a period of hours with N′. Interestingly, A(UDCH$_2$)$_2$Py (**8**) crystallizes in the free state and as its NaClO$_4$ complex as its binding (B′) conformer, which is disfavored in CDCl$_3$ solution at equilibrium ([N′]/[B′] = 3 at 28 °C). In the absence of polar or ionic catalysts, the B′ conformer goes to the N′ conformer at 28 °C with $\Delta G^{\ddagger} \sim 22$ kcal mol^{-1}. In contrast, A(UFCH$_2$)$_2$Py (**9**) crystallizes as its nonbinding (N′) conformer, which also predominates in the free state in CDCl$_3$–DCON(CD$_3$)$_2$ solution ([N′]/[B′] = 2.2 at 28 °C). Molecular models and NMR spectral comparisons suggest that the N′ conformations of A(UDCH$_2$)$_2$Py (**8**), A(UFCH$_2$)$_2$Py (**9**), and A(UGCH$_2$)$_2$Py (**10**) either have their single methyl groups or their two methylene groups turned inward to fill their cavities. The binding free energies ($-\Delta G°$) at 25 °C in CDCl$_3$ saturated with D$_2$O were determined by the extraction technique for hosts **5–11** binding the picrate salts of Li$^+$, Na$^+$, K$^+$, Rb$^+$, Cs$^+$, NH$_4^+$, CH$_3$NH$_3^+$, and t-BuNH$_3^+$. Maximum binding by the six cycles of the guests was observed for Na$^+$ or K$^+$ ions, with $-\Delta G°$ values in the 13.3–10.0 kcal mol^{-1} range. Quinquaryl systems, A′(A′DE)$_2$O (**5**) and A′(A′DCH$_2$)$_2$Py (**6**), were stronger binders of all ions (except t-BuNH$_3^+$) than the cyclic urea-containing hosts **7–10**, a fact attributed to the higher degree of preorganization for binding of the former compounds. All cycles showed high values for complexing CH$_3$NH$_3^+$, which ranged from 11.3 kcal mol^{-1} for A′(A′DCH$_2$)$_2$Py (**6**) to 9.0 kcal mol^{-1} for A′(A′DE)$_2$O (**5**) and A(UDCH$_2$)$_2$Py (**8**). The highest structural recognition of host toward guest was observed with A′(A′DCH$_2$)$_2$Py (**6**) binding CH$_3$NH$_3^+$ 5.3 kcal mol^{-1} better than t-BuNH$_3^+$ (factor of 8000 difference in association constants). The same host favored binding Na$^+$ over Li$^+$ by 4.7 kcal mol^{-1} (factor of 3000). Of the six cyclic hosts, this one showed the highest binding and greatest discrimination among ions. Molecular model comparisons of **5–11** show A′(A′DCH$_2$)$_2$Py (**6**) to be the most rigidly preorganized for binding. The structure and discrimination in binding of this system nicely illustrate the principles of complementarity and preorganization in complexation. Flexible open-chain model host A(UFCH$_3$)$_2$ (**11**) showed peak binding for Cs$^+$ at $-\Delta G° = 6.5$ kcal mol^{-1}. It also bound ions K$^+$ and larger with values that ranged from 5.8 to 6.2 kcal mol^{-1}. The terminal hydroxyl groups probably hydrogen bond one another in its complexes.

Earlier papers demonstrated that appropriate combinations of p-methylanisyl, cyclic urea, methylene, methyleneoxy, and ethyleneoxy units to form 18-membered to 21-membered ring macrocycles resulted in hosts that were both stronger and more

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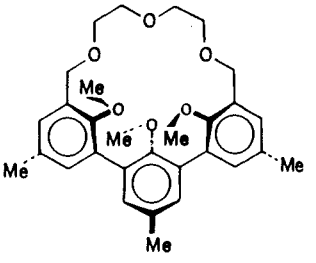
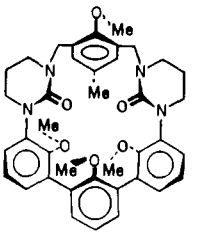
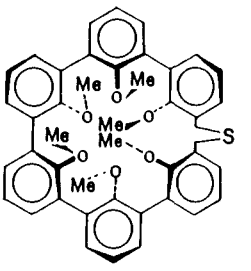
Chart I



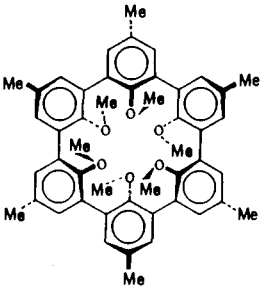
1, $A'(A'CH_2OE)_2O$



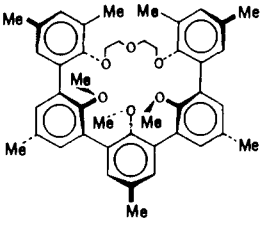
2, $A(AUCH_2)_2A'$



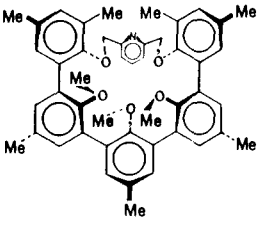
3, $(A)_6(CH_2)_2S$



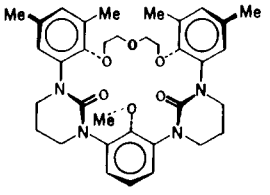
4, $A'(A'A')_2A'$



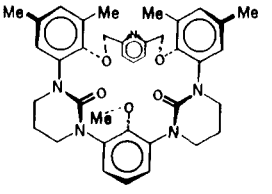
5, $A'(A'DE)_2O$



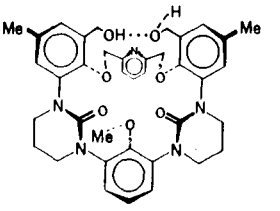
6, $A'(A'DCH_2)_2Py$



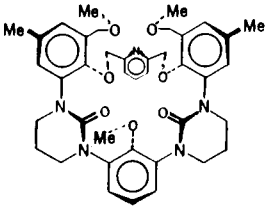
7, $A(UDE)_2O$



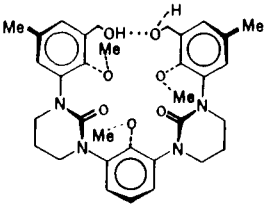
8, $A(UDCH_2)_2Py$



9, $A(UFCH_2)_2Py$



10, $A(UGCH_2)_2Py$



11, $A(UFCH_3)_2$

discriminating binders of alkali metal, ammonium, and alkylammonium ions than the chorands, which are composed entirely of ethyleneoxy and catechol units. Hosts $A'(A'CH_2OE)_2O$ (**1**),[2] $A(AUCH_2)_2A'$ (**2**),[3] and $(A)_6(CH_2)_2S$ (**3**)[4] are examples of hemispherands, at least half of whose structures are self-organizing for binding during synthesis rather than by the guest during the complexing act. Host $A'(A'A')_2A'$ (**4**) exemplifies a spherand whose structure is fully self-organized for complexation during synthesis.[5-7] The structures of these and the new hosts are indicated in line formulas by sequences of letters, each representing the units used to compose the hosts or their synthetic intermediates (see end of abstract).

Here, we report the syntheses and the conformational and binding behavior of six new 20-membered ring systems and one open-chain model compound. These hosts were designed and investigated for several purposes: to extend our survey of the relationship between structure and binding,[8] to further explore the utility for molecular design of the principles of complementarity and preorganization, to produce a system that combines a complexing and orienting site with a potentially chemically reactive site for the study of the catalytic effects of complexation. The

(1) We thank the U.S. Public Health Service for Grant GM 12640, which supported this research.

(2) (a) Koenig, K. E.; Lein, G. M.; Stuckler, P.; Kaneda, T.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3553–3566. (b) Cram, D. J.; Dicker, I. B.; Lein, G. M.; Knobler, C. B.; Trueblood, K. N. *Ibid.* **1982**, *104*, 6827–6828.

(3) Cram, D. J.; Dicker, I. B.; Knobler, C. B.; Trueblood, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 6828–6830.

(4) Cram, D. J.; deGrandpre, M. P.; Knobler, C. B.; Trueblood, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 3286–3292.

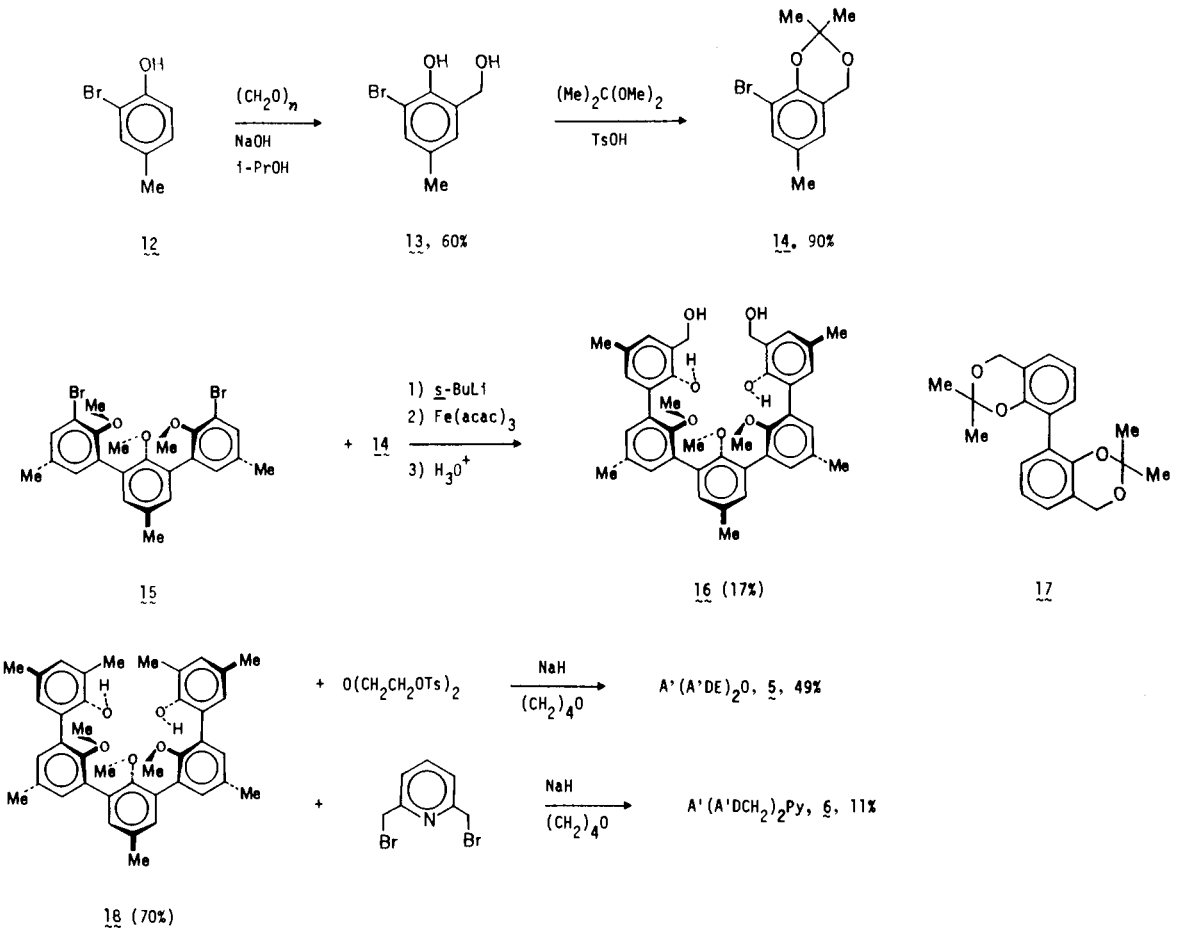
(5) Cram, D. J.; Kaneda, T.; Helgeson, R. C.; Lein, G. M. *J. Am. Chem. Soc.*, **1979**, *101*, 6752–6754.

(6) Cram, D. J.; Lein, G. M.; Kaneda, T.; Helgeson, R. C.; Knobler, C. B.; Maverick, E.; Trueblood, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 6228–6232.

(7) Trueblood, K. N.; Knobler, C. B.; Maverick, E.; Helgeson, R. C.; Brown, S. B.; Cram, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 5594–5596.

(8) Cram, D. J.; Trueblood, K. N. *Top. Curr. Chem.* **1981**, *78*, 43–106.

Scheme I



target compounds possess structures **5–11**. Of these, A′(A′DE)$_2$O (**5**) and A′(A′DE)$_2$Py (**6**) in CPK molecular models are well over half self-organized for binding due to the enforced conformations of the three OCH_3 groups supported by the framework of the A′–A′–A′ sequence. Cycles **7–10** have in common the sequence U–A–U, which models indicate orients their three oxygens in the same staggered conformation of the A′–A′–A′ assembly but which allows the methyl of the A′ unit to orient either into or away from the cavity. Cycle A(UFCH$_2$)$_2$Py (**9**) and its open-chain model A(UFCH$_3$)$_2$ (**11**) possess CH_2OH groups. In models of their complexes with $^+H_3NCHRCO_2C_6H_4NO_2$-*p* guests, the CH_2OH group of the host is proximate to the CO_2 group of the guest. Results of kinetic studies of host–guest transacylations involving **9** and **11** are reported in a companion paper.[9]

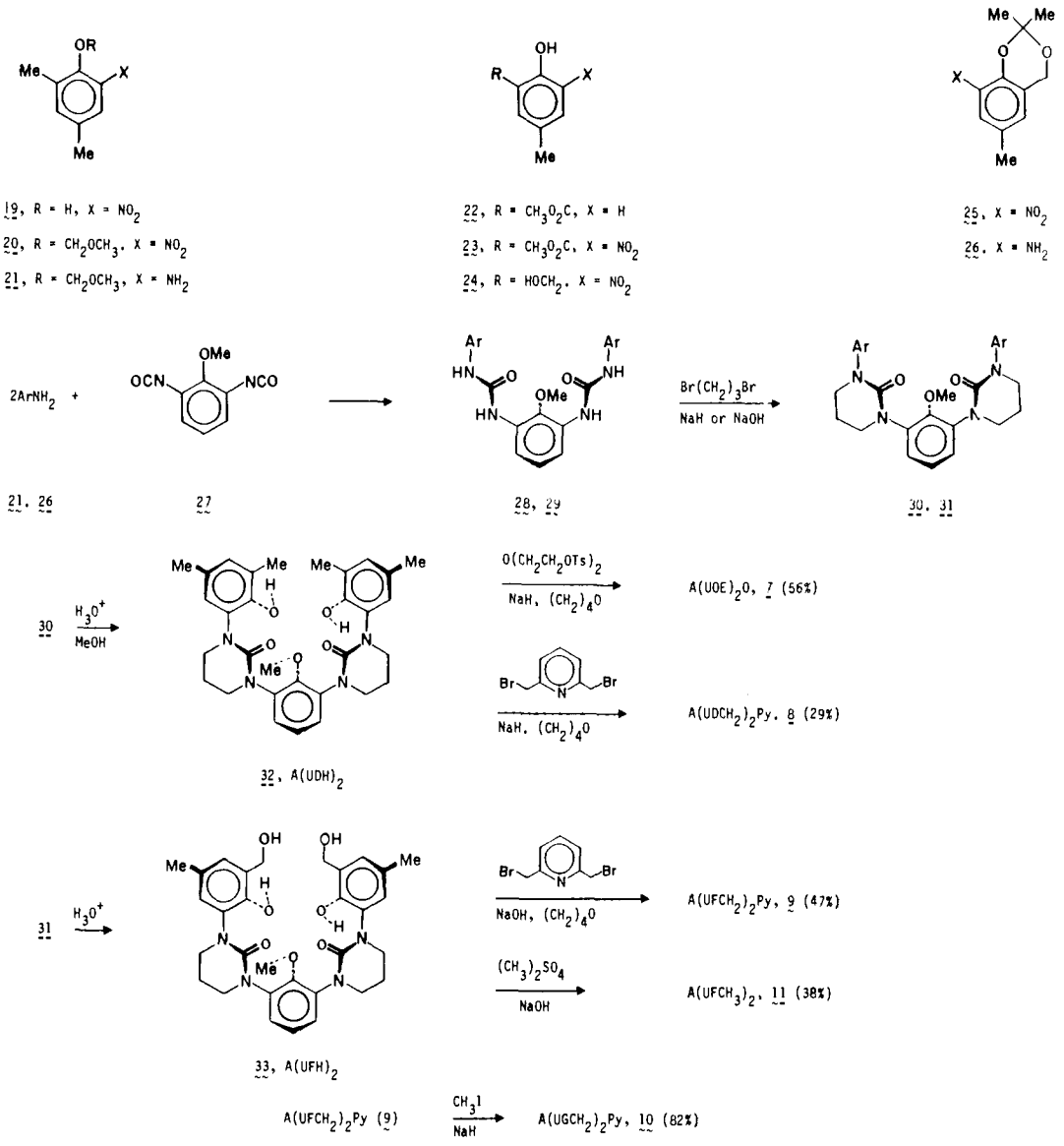
Results and Discussion

Syntheses. The synthesis of quinquaryl hosts A′(A′DE)$_2$O (**5**) and A′(A′DCH$_2$)$_2$Py (**6**) involved bis(phenol) A′(A′DH)$_2$ (**18**) as the key intermediate, whose synthesis from commercially available **12** is outlined. Hydroxymethylation of **12** under controlled conditions gave **13**[10] (60%), which was converted to its acetonide, **14** (90%). Cross-coupling of **14** and **15**[5] was accomplished in a maximum of 17% yield by lithiating (*s*-BuLi) 1 mol of **15** and 15 mol of **14** and oxidizing the mixture with Fe(acac)$_3$ in (CH$_2$)$_4$O.[5] Although many oxidants and conditions were tried, homocoupling of 2 mol of **14** to produce **17** was favored over the desired statistical cross-coupling leading to **16**. Removal of the protecting acetonide groups of the coupled product gave **16**, whose benzyl hydroxyl groups were hydrogenolyzed (H_2–Pd) to give **18** (70%). When a mixture of **18** and either diethylene glycol ditosylate or 2,6-bis(bromomethyl)pyridine[11] was added under high-dilution conditions to NaH–(CH$_2$)$_4$O, macrocycles A′(A′DE)$_2$O (**5**, 49%) and A′(A′DCH$_2$)$_2$Py (**6**, 11%) were produced, respectively. Both hosts were isolated and purified as their NaBr complexes. Attempts to carry out similar ring closures with tetraol **16** led to inseparable mixtures.

The syntheses of the hosts containing the cyclic urea units involved either A(UDH)$_2$ (**32**) or A(UFH)$_2$ (**33**) as key intermediates, whose preparations are outlined. Methoxymethylation of 2,4-dimethyl-6-nitrophenol (**19**)[12] with $BrCH_2OCH_3$ and base gave the O-protected product **20**, reduction of which with H_2–Pt gave amine **21**[13a] in 95% overall yield. The methyl ester (**22**) of commercially available 2-hydroxy-5-methylbenzoic acid was nitrated as a suspension in aqueous nitric acid to give **23** (85%), which precipitated, inhibiting further unwanted reactions. Reduction of **23** with (CH$_2$)$_4$O·BH_3 gave diol **24** (82%), whose two hydroxyl groups were protected as an acetonide by treatment of **24** with (CH$_3$)$_2$C(OCH$_3$)$_2$–TsOH–C_6H_6 to produce **25** (91%). Reduction of **25** with H_2–Pt gave amine **26** (98%) without hydrogenolysis of the benzyloxy group. The two substituted anilines with their hydroxyls protected (**21** and **26**) were each added to the isocyanate groups of 1,3-diisocyanato-2-methoxybenzene (**27**)[13b] to form bis(urea) compounds **28** (91%) and **29** (92%), respectively. These substances were doubly annulated with Br(CH$_2$)$_3$Br, **28** producing **30** (47%) with NaH as base and **29** giving **31** (37%) under phase-transfer conditions. The main side reactions were allylations. The hydroxyl groups of **30** and **31** were de-

(9) Cram, D. J.; Katz, H. E.; Dicker, I. *J. Am. Chem. Soc.* following paper in this issue.
(10) Hayes, B. T.; Hunter, R. F. *J. Appl. Chem.* **1958**, *8*, 743–748. These authors monobrominated *p*-cresol and hydroxymethylated the product with formalin and NaOH to give **13**.
(11) Newcomb, M.; Timko, J. M.; Walba, D. M.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6392–6398.
(12) Hodgkinson, W. R.; Limpach, L. *J. Chem. Soc.* **1893**, 104–110.
(13) (a) Taub, B.; Hino, J. B. *J. Org. Chem.* **1961**, 5238–5239. (b) Crandall, E. W.; Harris, L. *Org. Prep. Proced.* **1969**, *1*, 147–156.

Scheme II



protected with acid to give $A(UDH)_2$ (**32**, 85%) and $A(UFH)_2$ (**33**, 60%), respectively.

Hosts **7–11**, which contain cyclic urea units, were prepared from $A(UDH)_2$ (**32**) or $A(UFH)_2$ (**33**) as follows. Under high-dilution conditions, a solution of **32** and $O(CH_2CH_2OTs)_2$ in $(CH_2)_4O$ was added to a mixture of NaH–$(CH_2)_4O$ to produce $A(UDE)_2O$ (**7**, 56%), which crystallized directly. Similarly, **32** and $BrCH_2PyCH_2Br$ gave $A(UDCH_2)_2Py$ (**8**, 29%), which was purified through crystallization of its $NaClO_4$ complex. Reaction of $A(UFH)_2$ (**33**) with $BrCH_2PyCH_2Br$ in NaOH–wet $(CH_2)_4O$ gave $A(UFCH_2)_2Py$ (**9**, 47%) which crystallized directly and showed very limited solubility in CH_2Cl_2, $CHCl_3$, or CH_3CN but was readily soluble in CH_3OH or $HCON(CH_3)_2$. The phenolic hydroxyl groups of $A(UFH)_2$ (**33**) were selectively methylated with $(CH_3)_2SO_4$–NaOH–H_2O to form open-chain host $A(UFCH_3)_2$ (**11**, 38%). Methylation of the two hydroxymethyl groups of $A(UFCH_2)_2Py$ (**9**) with CH_3I–NaH gave $A(UGCH_2)_2Py$ (**10**, 82%).

Structures of Hosts and Complexes. Unfortunately, we failed in attempts to obtain crystals suitable for crystal structure determinations of hosts **5–11** and their complexes. However, 200-MHz ^1H NMR spectral comparisons of the free and complexed systems provided indications of their conformational structures when coupled with CPK molecular model examinations and analogies with systems whose crystal structures are known. Crystal structures of $A'(A'A')_2A'$ (**4**),[6] $A'(A'CH_2OE)_2O$ (**1**),[8] and $(A)_6(CH_2)_2S$ (**3**)[4] all show an alternate up-down-up arrangement of their methoxy oxygens. Their attached methyl groups are oriented away from the cavity with the exception of the two methyls of the $A–CH_2–S–CH_2–A$ units of $(A)_6(CH_2)_2S$ (**3**), which turn inward and fill the cavity of this 21-membered ring system. The cavity of $A'(A'CH_2OE)_2O$ (**1**) is filled with two methylenes and that of $A'(A'A')_2A'$ is empty.

In CPK molecular models of **5–10**, the five aryl oxygens or the three aryl oxygens and two urea oxygens appear to possess the enforced alternate up-down-up arrangement. However, continuation of this alternating pattern to include the CH_2OCH_2 oxygen of the EOE bridge or the nitrogen of the CH_2PyCH_2 bridge leads to structures whose cavities have collapsed due to enforced elongation of the A′–A′–A′, U–A–U, EOE, or CH_2PyCH_2 assemblies that span the two D, F, or G units. This enforcement is due to the bulk of the respective CH_3, CH_2OH, or CH_2OCH_3 groups attached ortho to the oxygens of these three units. This elongated conformation is referred to as the nonbinding or N conformation, and it resembles the crystal structure observed for uncomplexed $A'(A'CH_2OE)_2O$ (**1**).[8] The only conformation that generates a spherical cavity lined with electron pairs is that found in the structures formulated for **5–10**, which for each host is referred to as a binding or B conformation. In the B conformation, the aryloxy or urea oxygens possess the alternating up-down-up arrangement, but the sixth oxygen or nitrogen of the EOE or CH_2PyCH_2 bridge is syn to the oxygen located at 6 o'clock in the

drawings, rather than anti, as in the N conformation. Thus in the binding conformations (B) of **5–10**, four oxygens lie in a plane perpendicular to a mirror plane and the other two heteroatoms lie close to one another in the mirror plane. To pass from conformation N to conformation B, the only rotational barrier of consequence involves a 180° rotation around each Ar–O bond of the D, F, or G units. Such a movement involves the methylene of the $ArOCH_2$ group passing the ortho CH_3, CH_2OH, or CH_2OCH_3 group of the respective D, F, or G units. In the four systems containing the CH_2PyCH_2 bridge, this rotational barrier appears large enough to be potentially observable at room temperature with ^1H NMR spectral probes. The two systems containing the EOE bridge are much more flexible, and the N → B barrier appears in models to be lower, since the EOE bridge can elongate more than the CH_2PyCH_2 bridge.

The NMR spectra of **5–10** and their complexes are consistent with the above conformational analysis. The ^1H NMR spectra of **5–10** point to their structures possessing a mirror plane or structures that rapidly interconvert to provide averaged structures with a mirror plane. In the spectra of $A'(A'DCH_2)_2Py$ (**6**), $A(UDCH_2)_2Py$ (**8**), $A(UFCH_2)_2Py$ (**9**), and $A(UGCH_2)_2Py$ (**10**) taken at 28 °C, the CH_2 protons are diastereotopic. Therefore, the ring inversions of the aryloxy groups are slow on the ^1H NMR time scale. The spectra of $A'(A'DE)_2O$ (**5**) and $A'(UDCH_2)_2Py$ (**8**) were too complex to interpret, but model examination suggests the same thing is true in these hosts as well.

Spectral studies of $A(UDCH_2)_2Py$ (**8**) in $CDCl_3$ at 28 °C show the compound exists in two interconverting conformations, one of which is binding (B′) and the other one is not (N′). Crystalline $A(UDCH_2)_2Py$ (**8**) dissolved in $CDCl_3$ gave the spectrum of B′, which over a 2.5-h period produced N′ and B′ in the ratio [N′]/[B′] = 3.0 by ^1H NMR and 3.3 by ^{13}C NMR. The $\Delta G^{\ddagger}$ for N′ → B′ was found to be 22 kcal mol^{-1} by kinetic measurements. Addition to the equilibrium mixture in $CDCl_3$ of excess sodium picrate dissolved in $(CD_3)_2SO$ gave an immediate spectrum indicating the presence of N′ and B′·Na^+ in the ratio [N′]/[B′·Na^+] = 2.0. After 30 min, only B′·Na^+ was detected. Saturation with D_2O of the $CDCl_3$ solution of an equilibrium mixture of uncomplexed N′ and B′ at 28 °C lowered the [N′]/[B′] ratio at equilibrium from 3.0 to 2.4, probably because D_2O acts as guest for B′. Addition of an excess of $A'(A'A')_2A'$ (**4**) in $CDCl_3$ to a solution of $A(UDCH_2)_2Py$·$NaClO_4$ in $CDCl_3$ saturated with D_2O initially produced only B′ (by transfer of Na^+ to **4**), which slowly went to the equilibrium mixture of B′ and N′.

Conformer N′ detected by NMR probably has the structure N predicted with molecular models and B′ probably has structure B. It is possible that B′ is a rapidly equilibrating mixture of conformers, B and B modified by turning the methyl of its central methoxyl group inward to fill the cavity. In models such a reorganization appears to lead to a somewhat strained structure, but one that possesses the thermodynamic advantage of having no intramolecular cavity.[14] Interestingly, **8** crystallizes in its B′ form, which is less stable in solution than its N′ form.

Diol host $A(UFCH_2)_2Py$ (**9**) in 90% $CDCl_3$–10% CD_3OD (by volume) provided a ^1H NMR spectrum the equivalent of a single conformer. In $(CD_3)_2SO$ solution, two conformers were observed which were nearly equally present at 100 °C but their signals showed no sign of coalescing. The two different kinds of CH_2 protons of each conformer remained diastereotopic at this temperature. In 90% $CDCl_3$–10% $DCON(CD_3)_2$ solution 20 min after its preparation from crystalline **9** at 28 °C, two conformers were visible, with [N′]/[B′] ~ 5.5. After 31 h, the conformers had equilibrated to give [N′]/[B′] = 2.2. Upon addition of 1 equiv of $CH_3CH(CO_2C_6H_4NO_2\text{-}p)NH_3ClO_4$ dissolved in the same medium, all the ^1H NMR signals of B′ immediately disappeared and those of complex appeared. Over the next 3 h the signals of N′ slowly disappeared to produce those of the complex. We conclude that conformation N′ has structure N and that B′ has structure B, or one in which its methyl group is turned inward to fill the cavity. Unlike $A(UDCH_2)_2Py$ (**8**), which crystallized in its B′ form, $A(UFCH_2)_2Py$ (**9**) crystallized in its N′ form.

Only one conformation (or a rapidly equilibrating equivalent) was detectable in the ^1H NMR spectra in $CDCl_3$ at 28 °C of $A'(A'DE)_2O$ (**5**), $A'(A'DCH_2)_2Py$ (**6**), and $A(UDCH_2)_2Py$ (**7**). The EOE bridges in **5** and **6** appear flexible enough not to greatly inhibit rotations about the Ar–O bonds of the D units. Thus conformations B′ and N′ probably average at a rate fast enough on the ^1H NMR time scale to provide simple spectra. This equilibration between binding and nonbinding conformers then must be fast enough so that complexation appears to be instantaneous on the human time scale, which is observed. Molecular model examination of $A'(A'DCH_2)_2Py$ (**6**) suggests that the rotations required for conversion of B to N should be even more inhibited than those observed for $A(UDCH_2)_2Py$ (**8**). Thus the spectrum observed for $A'(A'DCH_2)_2Py$ (**6**) is attributed to the compound both in solution and in the crystal having the B conformation, or B modified by turning the methyl of the methoxy group on the mirror plane inward to fill the cavity. In models the barrier to this rotation appears low. Turning the methyls of the other two methoxyl groups inward appears to introduce much more strain into the system. Thus of the six cyclic hosts, only $A'(A'DCH_2)_2Py$ (**6**) appears to exist in solution exclusively in the B form or in a conformation very close to the B form. Thus it is preorganized for complexation more than the other hosts. Its cavity is shaped like a cup of significant depth with a semicircular rim delineated by the two methyls of the two outer methoxyls and the aryl methyls of the bridge. The axis of the central O–CH_3 group is parallel to the pyridine ring, which places the O and N atoms close to one another, with the methyl group contacting the face of the pyridine ring.

The binding conformation of $A(UFCH_2)_2Py$ (**9**) in models is identical with that of $A(UDCH_2)_2Py$ (**8**) except for the O–H···OH bridge postulated for the former system. This bridge can be formed with no perturbation of the conformations of the macroring that generate the cavity. The hydroxyl group that donates a hydrogen bond to the oxygen of the second hydroxyl orients the unshared electron pairs of its oxygen so that they contact spheres inserted into the cavity of the model. The oxygen accepting the hydrogen bond can contact a sphere inserted into the cavity only by breaking the hydrogen bond. We were unable to construct any *nonbinding* conformations of $A(UFCH_2)_2Py$ (**9**) in which the two OH groups either hydrogen bonded one another or any other oxygens intramolecularly. Thus this intramolecular hydrogen bond should enhance the binding power of **9** rather than inhibit it as has been observed with some other synthetic hosts.[15]

Free Energies of Complexation. The association constants (K_a) and free energies of complexation ($-\Delta G°$ values) for hosts **5–11** binding the alkali metal and ammonium picrates were determined by the extraction method.[16] Solutions of Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and t-$BuNH_3^+$ picrates in D_2O were extracted with $CDCl_3$ in the absence and presence of host. The hosts and their complexes were essentially insoluble in the D_2O layer. The concentrations of host and guest were adjusted to use the more sensitive part of the scale. The K_a and $-\Delta G°$ values determined at 25 °C in $CDCl_3$ saturated with D_2O were calculated and are recorded in Table I.

Two complications arose with some of the cyclic urea hosts. (*1*) The relative insolubility of $A(UFCH_2)_2Py$ (**9**) in $CDCl_3$ limited the determinations of K_a and $-\Delta G°$ values to the better bound guests (Na^+, K^+, $CH_3NH_3^+$, and t-$BuNH_3^+$ picrates). (2) Since hosts $A(UDCH_2)_2Py$ (**8**), $A(UFCH_2)_2Py$ (**9**), and $A(UGCH_2)_2Py$ (**10**) in $CDCl_3$ are slowly interconverting mixtures of binding and nonbinding conformers (see last section), several hours of mixing of the two phases were required before equilibrium within and

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Table I. Association Constants (K_a) and Binding Free Energies ($-\Delta G°$) of Hosts for Picrate Salt Guests in $CDCl_3$ Saturated with D_2O at 25 °C[a]

host structure	guest cation	K_a, M^{-1}	$-\Delta G°$,[b] kcal mol^{-1}	host structure	guest cation	K_a, M^{-1}	$-\Delta G°$,[b] kcal mol^{-1}
$A'(A'DE)_2O$[c] (5)	Li[d]	1.0×10^6	8.2[e]	$A(UDCH_2)_2Py$[f] (8)	Li	2.9×10^5	7.4
	Na	3.6×10^8	11.7		Na[g]	1.7×10^7	9.8
	K	9.0×10^8	12.2		K	7.8×10^6	9.4
	Rb	1.1×10^8	10.9		Rb	1.4×10^6	8.4
	Cs	2.1×10^7	9.8		Cs	8.7×10^5	8.1
	NH_4	3.3×10^7	10.3		NH_4	4.7×10^6	9.1
	CH_3NH_3	4.3×10^6	9.0		CH_3NH_3[g]	4.0×10^6	9.0
	t-$BuNH_3$[d]	2.0×10^4	5.8		t-$BuNH_3$	5.0×10^5	7.8
$A'(A'DCH_2)_2Py$[c] (6)	Li	1.9×10^6	8.6	$A(UFCH_2)_2Py$[c,h] (9)	Li[i]		
	Na	6.3×10^9	13.3		Na	5.4×10^8	11.7
	K	1.2×10^9	12.4		K	1.9×10^8	11.3
	Rb	8.4×10^7	10.8		Rb[i]		
	Cs	8.0×10^7	10.8		Cs[i]		
	NH_4	7.0×10^7	10.7		NH_4[i]		
	CH_3NH_3	2.0×10^8	11.3		CH_3NH_3[j]	4.2×10^7	10.4
	t-$BuNH_3$	2.5×10^4	6.0		t-$BuNH_3$	8.4×10^6	9.4
$A(UDE)_2O$[f] (7)	Li[e]	7.8×10^4	6.7	$A(UGCH_2)_2Py$[k] (10)	Li[l]	1.1×10^6	8.1
	Na	2.2×10^7	10.0		Na[m]	7.5×10^7	10.7
	K	4.3×10^7	10.4		K	3.5×10^7	10.1
	Rb	1.3×10^7	9.7		Rb	9.0×10^6	9.4
	Cs	4.5×10^6	9.1		Cs	4.2×10^6	9.0
	NH_4	4.1×10^6	9.0		NH_4	9.2×10^6	9.5
	CH_3NH_3[c]	6.7×10^7	10.6		CH_3NH_3	1.9×10^7	9.8
	t-$BuNH_3$[c]	1.6×10^7	9.8		t-$BuNH_3$	2.8×10^6	8.6
				$A(UFMe)_2$[f] (11)	Li[n]		<6
					Na[n]		<6
					K[e]	1.8×10^4	5.8
					Rb[e]	2.5×10^4	6.0
					Cs[e]	5.4×10^4	6.5
					NH_4[e]	2.9×10^4	6.1
					CH_3NH_3	2.3×10^4	6.2
					t-$BuNH_3$	3.7×10^4	6.2

[a] Unless noted otherwise, the layers were mixed for 1 min. [b] Unless noted otherwise, these values are the averages of those calculated from absorbance of the aqueous and organic phases. Maximum differences between values based on each phase were 0.3 kcal mol^{-1}. The differences were usually less. [c] Initial concentrations of host and guest were 0.001 M unless otherwise indicated. [d] Initial concentrations of host and guest were 0.006 M. [e] Based on absorbance of only the organic phase since aqueous-phase measurements are nearly off scale. [f] Initial concentration of host and guest was 0.015 M. [g] Absorbance of two layers did not change when layers were mixed for 1 min and for 90 min. [h] layers equilibrated in 25 h. [i] Host was insufficiently soluble in $CDCl_3$ to make binding on scale for these ions. [j] After a 16-h equilibration of layers, a small amount of precipitated complex was removed and compensated for in the calculations. [k] Layers equilibrated in 24 h. [l] Layers equilibrated in 2 h. [m] Layers equilibrated in 14 h. [n] Below 6 kcal mol^{-1} limit of detection.

between phases was reached. The absence of change in the ^1H NMR spectra of the organic phases and (or) change of the picrate ion absorbance in the two phases were used as criteria of the establishment of equilibria.

The binding by $A(UGCH_2)_2Py$ (**10**) of piperidinium picrate was also determined by the same kind of extraction technique to give $K_a = 7.9 \times 10^{-4}$ M^{-1} and $-\Delta G° = 6.7$ kcal mol^{-1} (see Experimental Section).

Correlation of Binding with Structure. All of the cyclic hosts contain 20 atoms in their macrorings, which grossly appears to control the patterns of binding free energies as the metal ion guests are changed. All of these hosts bind maximally to either Na^+ or K^+ at the 10.0–10.3 kcal mol^{-1} level, with 0.9 kcal mol^{-1} (or less) structural recognition exhibited in differentiating between these two ions. Of the metal ions, Li^+ is always the poorest bound at the 6.1–8.1 kcal mol^{-1} level. The Rb^+ and Cs^+ ions are bound with values ranging from 8.1 to 10.9 kcal mol^{-1}, the former being the more complementary guest by a maximum of 1.1 kcal mol^{-1} and a minimum of zero. As has been observed with $(A)_6(CH_2)_2S$ (**3**) and its relatives,[4] Rb^+ and NH_4^+ are complexed with similar free energies, which never differ by more than 0.7 kcal mol^{-1} and are in the 9.0–10.9 kcal mol^{-1} range. Similarly, there is little difference in how these guests bind NH_4^+ and $CH_3NH_3^+$, all values being within the 9.0–11.3 kcal mol^{-1} range. The macrocycles containing the cyclic urea unit (U) favor binding $CH_3NH_3^+$ over t-$BuNH_3^+$ by a maximum of 1.2 kcal mol^{-1} within a range of 7.8–10.6 kcal mol^{-1}. However, very high structural recognition in complexation is observed when hosts $A'(A'DE)_2O$ (**5**) and $A'(A'DCH_2)_2Py$ (**6**) bind $CH_3NH_3^+$ and t-$BuNH_3^+$. The former binds $CH_3NH_3^+$ with 9.0 and t-$BuNH_3^+$ with only 5.8 kcal mol^{-1}, whereas the latter gives values of 11.3 and 6.0 kcal mol^{-1} for the corresponding guests. Thus $A'(A'DE)_2O$ has a cavity 3.2 and $A'(A'DCH_2)_2Py$ a cavity 5.3 kcal mol^{-1} more complementary to $CH_3NH_3^+$ than to t-$BuNH_3^+$. In other words, $A'(A'DE)_2O$ binds $CH_3NH_3^+$ better than t-$BuNH_3^+$ by a factor of ~200 and $A'(A'DCH_2)_2Py$ by the very substantial factor of 8000. The open-chain host $A(UFMe)_2$ (**11**) shows very little discrimination between guests, all measurable $-\Delta G°$ values falling between 5.8 and 6.5 kcal mol^{-1}.

The hosts provide the following order in their binding ability toward almost all of the guests except Li^+ and t-$BuNH_3^+$: $A'(A'DCH_2)_2Py$ (**6**) > $A'(A'DE)_2O$ (**5**) > $A(UFCH_2)_2Py$ (**9**) > $A(UDE)_2O$ (**7**) ≳ $A(UGCH_2)_2Py$ (**10**) > $A(UDCH_2)_2Py$ (**8**) >> $A(UFMe)_2$ (**11**). This order is readily interpretable in terms of the *principle of preorganization* (organization for binding during synthesis rather than during complexation).[6] Both CPK molecular model examination and ^1H NMR spectral analysis indicate that the two quinquaryl systems, $A'(A'DCH_2)_2Py$ (**6**) and $A'(A'DE)_2O$ (**5**), are more self-organizing for binding than the hosts containing the cyclic urea units. The three methyls of the three A′ units are probably oriented away from the cavity in the free host, which forces the unshared electron pairs of their attached oxygens into a binding position, as has been observed in the crystal structures of $A'(A'CH_2OE)_2O$ (**1**), $A_6(CH_2)_2S$ (**3**), and $A'(A'A')_2A'$ (**4**). The conformational rigidity of the CH_2PyCH_2 unit in $A'(A'DCH_2)_2Py$ (**6**), as compared to the flexibility of the EOE unit in $A'(A'DE)_2O$ (**5**), explains why the former is both a better binding and more discriminating host. Unlike the unshared

electrons of the EOE oxygen, the unshared electron pair of the nitrogen always must converge on the cavity. Thus at least five, and possibly all six, binding sites of A′(A′DCH$_2$)$_2$Py (**6**) appear to be preorganized for binding, as compared with three for A′-(A′DE)$_2$O (**5**).

Molecular models show clearly why A′(A′DCH$_2$)$_2$Py (**6**) is complementary to $CH_3NH_3^+$ ($-\Delta G° = 11.3$ kcal mol^{-1}) and noncomplementary to *t*-BuNH_3^+ ($-\Delta G° = 6.0$ kcal mol^{-1}). In the only reasonable model for A′(A′DCH$_2$)$_2$Py·$CH_3NH_3^+$, the pyridine and methoxyl oxygens of the outer A′ units beautifully provide a tripod receptor for the NH_3^+ group. The hydrogens of the CH_3N group of the guest contact the methyl hydrogens of the two D groups. Substitution of three methyls for the three hydrogens of the CH_3N group can be accomplished only by introducing considerable strain into the system.

The NMR spectra of the macrocycles containing two cyclic urea units and a pyridine unit indicate that well over half of the conformational population is nonbinding and equilibrates with the binding conformation much slower than complexation occurs. Although the pyridine nitrogen and cyclic urea oxygens are held by the macrocycle in binding conformations, the OCH_3 or OCH_2 oxygens are largely in nonbinding conformations. As importantly, the cyclic urea oxygens are much more highly exposed to hydrogen bonding by the water present in the $CDCl_3$ than are the anisyl groups. This water must be displaced during complexation. Thus, a heavy reorganizational burden is put on the guest during complexation of the urea hosts, which more than cancels the intrinsically stronger binding ability of urea over anisyl oxygens.[3] Even the extra binding oxygens found in A(UFCH$_2$)$_2$Py (**9**) and A-(UGCH$_2$)$_2$Py (**10**) do not go all the way in overcoming this reorganizational energy burden. Although open-chain compound A(UFCH$_3$)$_2$ (**11**) probably is partially organized for binding by its hydrogen-bonding ends, the conformational reorganizational burden is so heavy that its binding is barely on scale. Thus the degree of preorganization of these hosts for binding appears as the dominant factor in determining their binding free energies. Host A′(A′A′)$_2$A′ (**4**) represents the extreme example of preorganization, since its binding sites do not have to be desolvated or relocated during complexation.[6]

A comparison of the complexing by A(UGCH$_2$)$_2$Py (**10**) of $CH_3NH_3^+$ (9.8 kcal mol^{-1}) and of $(CH_2)_5NH_2^+$ (6.7 kcal mol^{-1}) provides an imperfect measure of the difference in energy of tripod vs. dipod binding. No strain is observable in the model of A-(UGCH$_2$)$_2$Py·$(CH_2)_5NH_2^+$ in which the two cyclic urea units are the binding sites. Interestingly, the dipod binding turns out to be about two-thirds that of the tripod binding.

Experimental Section

General. Solvents were fractionally distilled before use, Et_2O and tetrahydrofuran (THF) from sodium benzophenone ketyl, *t*-BuOH and CH_2Cl_2 from CaH_2, and C_6H_6 from $LiAlH_4$. Alkyllithium reagents were employed as dispersions in hydrocarbon solvents. Organic solutions obtained during isolation of products were dried with $MgSO_4$ unless otherwise indicated. Silica gel chromatography was performed with E. Merck silica gel, particle size 0.063–0.200 mm (gravity columns) or 0.040–0.063 mm (medium-pressure columns). The medium-pressure scrubber column was 250 × 25 mm inner diameter. Silica gel TLC was performed on E. Merck glass plates, 0.5 or 1.0 mm thick. Alumina for column chromatography was MCB, 80–325 mesh. Alumina TLC plates were E. Merck plastic sheets. Columns for GPC (high pressure) were 20 ft by 0.375 in. outer diameter, packed with either 100-Å Styragel (Waters) or SX-12 Bio Beads (Bio-Rad, 200–400 mesh). Elution of GPC columns was carried out with doubly distilled CH_2Cl_2. Melting points were recorded on a Thomas-Hoover apparatus and are uncorrected. Reported R_f values are approximate and are given mainly for comparisons of starting materials and the various products. All new compounds gave elemental analyses within 0.30% of theory. Analytic samples were dried at 140 °C whenever practical. Mass spectra were taken on an AE-1 model MS-9 double-focusing spectrometer interfaced by Kratos Co. to a Data General Nova 3. Data were obtained at 16 eV unless otherwise indicated and at the indicated probe temperature. Infrared spectra were obtained on a Perkin-Elmer Model 297 instrument in the indicated media. Peak positions are in reciprocal centimeters. Nuclear magnetic resonance spectra were recorded on a 200-MHz Bruker WP-200 spectrometer. Chemical shifts are reported in parts per million downfield from internal $(CH_3)_4Si$. Coupling constants (J values) are given in hertz. Positional assignments of coupled protons were confirmed by homonuclear decoupling.

8-Bromo-2,2,6-trimethyl-4*H*-1,3-benzodioxin (14). A solution of 2-bromo-4-methylphenol (56 g, 0.30 mol) and paraformaldehyde (96 g = 3.2 mol "HCHO") in 600 mL of 2-propanol and 160 mL of water was purged with N_2. Potassium hydroxide (53 g, 85%, 0.72 mol) was added, and the mixture was stirred under N_2 at 60–70 °C for 6 h. The reaction was quenched by the addition of 180 g of $NaHCO_3$ and by cooling to room temperature. The 2-propanol was evaporated at reduced pressure. The residue was dissolved in 500 mL of H_2O and extracted with four portions of 200 mL of EtOAc. The combined organic layers were washed with brine, dilute hydrochloric acid, and more brine. The organic layer was dried, filtered, and concentrated to a syrup. This syrup was dissolved in 200 mL of CH_2Cl_2 and applied to a column of 600 g of silica gel. Nonpolar material was eluted with 3 L of CH_2Cl_2, and 2-bromo-**6**-(hydroxymethyl)-4-methylphenol (**13**) was eluted with 1.5 L of 20% Et_2O/80% CH_2Cl_2 (v/v) to give 39 g (60%) as a syrup, which was immediately converted to its acetonide, **14**. To a solution of **13** (38.4 g, 0.177 mol) in 400 mL of benzene were added 2,2-dimethoxypropane (18.4 g, 0.177 mol) and 100 mg of *p*-toluenesulfonic acid monohydrate. The solution was stirred and heated 17 h just below its boiling point (60–70 °C). The methanol–benzene azeotrope was distilled (head temperature, 60 °C), and TLC analysis of the mixture at this point showed the reaction to be about 80% complete. Additional 2,2-dimethoxypropane (3.0 g) were added, and the solution was heated at 60–80 °C for 1 h to complete the reaction (TLC). The solution was washed with two 100-mL portions of 1% aqueous NaOH and 100 mL of brine, dried, filtered, and concentrated to give 40.8 g (90%) of **14** as an oil of adequate purity for further reaction. Analytically pure material was isolated by chromatography of 28 g on 200 g of silica gel with 1200 mL of 50% CH_2Cl_2/50% petroleum ether as the mobile phase to produce 24 g of **14** as a colorless oil, which crystallized on standing: mp 40–41 °C, bp 105 °C (2 mm); ^{1}H NMR ($CDCl_3$) δ 1.56 (s, CH_3)$_2$C, 6 H), 2.24 (s, $ArCH_3$, 3 H), 4.78 (s, CH_2, 2H), 6.71 (Ar H, 1 H), 7.22 (Ar H, 1 H); MS (150 °C) M$^+$ 256; R_f 0.7 (10% Et_2O–90% CH_2Cl_2, v/v, silica gel). Anal. Calcd for $C_{11}H_{13}BrO_2$: C, H.

8,8-Bis(2,2-dimethyl-4*H*-1,3-benzodioxin) (17). A solution of 2-bromo-6-(hydroxymethyl)-4-methylphenol acetonide **14** (1.5 g, 5.8 mmol) in 12 mL of THF was stirred at −78 °C under N_2. Secondary butyllithium (5.4 mL of 1.25 M dispersion, 6.7 mmol) was added. After 5 min, the cold organolithium solution was added to a solution of Fe(acac)$_3$ (2.47 g, 6.98 mmol) in 45 mL of benzene which was being stirred and heated at reflux under N_2. After 30 min of additional heating, during which time a thick orange precipitate formed, the mixture was allowed to cool. The solution was diluted with ether and washed portionwise with a total of 180 mL of 2 N HCl solution and then 50 mL of saturated aqueous $NaHCO_3$. The solution was dried, filtered, and concentrated. The resulting oil was chromatographed on a SX-12 GPC column. The major fraction, retention volume, 110 mL, was chromatographed on a medium-pressure silica gel scrubber column with CH_2Cl_2 as the mobile phase. The material that eluted at 50–120 mL yielded 580 mg (56%) of product as a light foam. The center cut from the silica column was crystallized as white rectangular prisms from pentane: mp 120–122 °C; ^{1}H NMR ($CDCl_3$) δ 1.48 (s, $(CH_3)_2$C, 12 H), 2.28 (s, $ArCH_3$, 6 H), 4.85 (s, CH_2, 4 H), 6.74 (m, Ar H, 2 H), 6.90 (m, Ar H, 2 H); R_f 0.3 (CH_2Cl_2, silica gel). Anal. Calcd for $C_{22}H_{26}O_4$: C, H.

2,2′′′′-Dihydroxy-5,5′,5′′,5′′′,5′′′′-pentamethyl-2′,2′′,2′′′-trimethoxy-1,1′:3′,1′′:3′′,1′′′:3′′′,1′′′′-quinquephenyl-3,3′′′′-dimethanol (16). A solution of **15**[5] (514 mg, 0.99 mmol) and acetonide **14** (3.8 g, 14.8 mmol) in 35 mL of THF was stirred at −78 °C under N_2. Secondary butyllithium (1.49 mL of 1.3 M dispersion, 19.3 mmol) was added by syringe. After 6 min, the organolithium solution at −78 °C was added to a solution of Fe(acac)$_3$ (7.1 g, 20.1 mmol) in 130 mL of THF at reflux. Heating was continued for 2.25 h as a thick orange precipitate formed. The mixture was diluted with 150 mL of Et_2O, and the iron salts were removed by repeated washing with 2 N HCl solution (700 mL total) followed by 2 × 75 mL of brine. The organic solution was dried, filtered, and concentrated. Gel permeation chromatography of the resulting oil on SX-12 gave a high molecular weight (>400) fraction of 670 mg of 80-mL retention volume. This material was deprotected in a stirred solution of 5 mL of $CHCl_3$, 15 mL of MeOH, 1.5 mL of H_2O, and 0.3 mL of concentrated hydrochloric acid. After 5 h, $NaHCO_3$ was added until the pH of the solution was approximately 7, and then the organic solvents were evaporated. Brine (70 mL) was added, and the mixture was extracted with two 50-mL portions of CH_2Cl_2. The combined organic layers were dried, filtered, and concentrated to give 640 mg of foam. This material was chromatographed on a medium-pressure silica gel scrubber column, and product was eluted with 100 mL of CH_2Cl_2, 120 mL of 15%

EtOAc/85% CH_2Cl_2 (v/v), and then 300 mL of 20% EtOAc/80% CH_2Cl_2 (v/v). Concentration of the 20% EtOAc eluant to a yellow foam or glass gave 110 mg (17%) of the desired tetraol, **16**. An analytical sample was prepared as a glass by preparative TLC, R_f 0.3 (20% EtOAc/80% CH_2Cl_2, v/v, silica gel); ^1H NMR ($CDCl_3$) δ 2.35 (s, $ArCH_3$, 6 H), 2.41 (s, $ArCH_3$, 9 H), 3.21 (s, OCH_3, 3 H), 3.36 (s, OCH_3, 6 H), 4.75 (s, CH_2, 4 H), 7.1–7.3 (m, Ar H, 10 H); MS (200 °C) M^+ – 18, 616 (100%). Anal. Calcd for $C_{40}H_{42}O_7$: C, H. The major product of this reaction was dimer **17**.

2,2′′′′-Dihydroxy-3,3′′′′,5,5′,5′′,5′′′,5′′′′-heptamethyl-2′,2′′,2′′′-trimethoxy-1,1′:3′,1′′:3′′,1′′′:3′′′,1′′′′-quinquephenyl (18). Pentaaryl tetraol **16** (180 mg, 0.28 mmol) was shaken in 40 mL of EtOAc with 200 mg of $PdCl_2$ for 5 days under 3 atm of H_2. The solution was filtered through Celite and the solid washed with EtOH. The combined filtrates were concentrated, the residue was dissolved in CH_2Cl_2, and the solution was filtered through 7 g of silica gel. Concentration of the column eluant gave 120 mg (70%) of **18** as a white glass: ^1H NMR ($CDCl_3$) δ 2.287 (s, Ar CH_3, 6 H), 2.320 (s, Ar CH_3, 6 H), 2.386 (s, Ar CH_3, 3 H), 2.396 (s, Ar CH_3, 6 H), 3.262 (s, OCH_3, 3 H), 3.369 (s, OCH_3, 6 H), 7.00 (s, Ar H, 2 H), 7.03 (s, Ar H, 2 H), 7.08 (s, OH, 2 H), 7.17 (m, Ar H, 6 H); MS (200 °C), m/z (M^+) 602; R_f 0.6 (CH_2Cl_2, silica gel). Anal. Calcd for $C_{40}H_{42}O_5$: C, H.

1,3,7,12,17,21,23-Heptamethyl-34,35,36-trimethoxy-31*H*-5,9:10,14:15,19-trimetheno-26,30-nitrilo-9*H*,25*H*-dibenzo[*j*,*a*][1,9]dioxacyclooctacosine (6). A solution of pentaaryl diol **18** (96 mg, 0.159 mmol) and 2,6-bis(bromomethyl)pyridine[11] (42 mg, 0.159 mmol) in 120 mL of THF was stirred under N_2. Sodium hydride (20 mg of a 50% dispersion in oil, 0.42 mmol) was added and pulverized with a glass rod, and then the mixture was heated at reflux for 18 h. The reaction was quenched with dilute aqueous $NaHCO_3$ and the THF evaporated at reduced pressure. The residue was dissolved in CH_2Cl_2 and this solution was washed twice with H_2O, dried, filtered, concentrated, and passed through the 100-Å GPC column. The monomeric fraction (retention volume of 220 mL) was stirred for 1 h in $CHCl_3$ with saturated aqueous NaBr and then recovered from the $CHCl_3$ layer by evaporation. Crystallization of the residue from toluene gave 14 mg (11%) of cycle **6** as its NaBr complex, which was a white solid: mp > 200 °C dec; ^1H NMR ($CDCl_3$) δ 2.286 (s, OCH_3, 3 H), 2.342 (s, Ar CH_3, 6 H), 2.367 (s, Ar CH_3, 6 H), 2.434 (s, Ar CH_3, 9 H), 3.21 (s, OCH_3, 6 H), 4.63, 4.66 (q, A_2B_2, J = 14 Hz, CH_2, 4 H), 6.89 (d, J = 8 Hz, 3,5-Py H, 2 H), 7.0–7.25 (m, Ar H, 10 H), 7.56 (t, J = 8 Hz, 4-Py H, 1 H).

This complex was dissolved in 1 mL of $CDCl_3$ and vortexed with 2 × 3 mL of deionized H_2O, and the organic layer was concentrated to a clear glass which was free cycle **6**: MS (230 °C), m/z (M^+) 705 (79%), 674 (100%); ^1H NMR ($CDCl_3$) δ 2.317 (s, Ar CH_3, 6 H), 2.323 (s, Ar CH_3, 6 H), 2.35 (s, Ar CH_3, 9 H), 2.50 (s, OCH_3, 3 H), 3.26 (s, OCH_3, 6 H), 4.93, 5.23 (q, A_2B_2, J = 14 Hz, CH_2, 4 H), 6.9–7.2 (m, Ar H, 10 H), 7.30 (d, J = 8 Hz, 3,5-Py H, 2 H), 7.51 (t, J = 8 Hz, 4-Pyr H, 1 H). Anal. Calcd for $C_{47}H_{47}NO_5$: C, H; high-resolution MS, m/z calcd for $C_{47}H_{47}NO_5$ 705.3454, found 705.3502.

1,3,7,12,17,21,23-Heptamethyl-25,26,28,29-tetrahydro-31,32,33-trimethoxy-5,9:10,14:15,19-trimetheno-9*H*-dibenzo[*h*,*y*][1,4,7]trioxacyclohexacosine (5). A mixture of pentaaryl diol **18** (110 mg, 0.182 mmol), diethylene glycol ditosylate (78 mg, 0.183 mmol), NaH (26 mg of 50% dispersion, 0.54 mmol), and 150 mL of THF was heated for 4 days at reflux under N_2. The THF was evaporated and the residue was dissolved in 80 mL of CH_2Cl_2. This solution was washed twice with 2 × 50 mL of H_2O, using solid $MgSO_4$ as necessary to clear emulsions. The organic layer was dried, filtered, and concentrated. The resulting oil was stirred with 10 mL of $CHCl_3$ and 3 mL of saturated aqueous NaBr for 45 min. The organic layer was dried, filtered, concentrated to a solid, and crystallized from CH_2Cl_2–toluene to yield after drying at 100 °C under vacuum 77 mg (49%) of **5**·NaBr·$C_6H_5CH_3$ as white crystals: mp > 250 °C dec; ^1H NMR ($CDCl_3$) δ 2.301 (s, Ar CH_3, 6 H), 2.354 (s, $C_6H_5CH_3$, 3 H), 2.432 (s, Ar CH_3, 9 H), 2.545 (s, Ar CH_3, 6 H), 3.103 (s, OCH_3, 3 H), 3.194 (s, Ar CH_3, 6 H), 3.36 (d, J = 10 Hz, OCH, 2 H), 3.55 (d, J = 9 H, OCH, 2 H), 3.8–4.0 (m, OCH_2, 4 H), 6.91 (s, Ar H, 2 H), 7.05 (s, Ar H, 2 H), 7.2 (m, Ar H (including $C_6H_5CH_3$), 9 H), 7.30 (s, Ar H, 2 H). Anal. Calcd for $C_{44}H_{48}O_6$·NaBr·$C_6H_5CH_3$: C, H, Br.

A portion (35 mg) of the NaBr complex was dissolved in 5 mL of CH_2Cl_2 and vortexed 3 times with 14 mL of deionized water. The organic layer was concentrated to 24 mg (88%) of free cycle **5** as a glass: ^1H NMR ($CDCl_3$) δ 2.289 (s, Ar CH_3, 6 H), 2.303 (s, Ar CH_3, 6 H), 2.345 (s, Ar CH_3, 6 H), 2.386 (s, Ar CH_3, 3 H), 3.187 (s, OCH_3, 6 H), 3.216 (s, OCH_3, 3 H), 3.5–4.1 (m, OCH_2CH_2, 8 H), 6.89 (m, Ar H, 2 H), 6.96 (d, J = 2 Hz, Ar H_3, 4 H), 7.08 (d, J = 2 Hz, Ar H, 2 H), 7.15 (s, Ar H, 2 H); MS (230 °C), m/z (M^+) 672. Anal. Calcd for $C_{44}H_{48}O_6$: C, H.

Methyl 2-Hydroxy-5-methyl-3-nitrobenzoate (23). Methyl 2-hydroxy-5-methylbenzoate (**22**) (35 g, 0.21 mol) (prepared by HCl-catalyzed esterification of 2-hydroxy-5-methylbenzoic acid) was mechanically stirred as an emulsion with 350 mL of H_2O with cooling in an ice bath. Nitric acid (350 mL of 70%) was added, and stirring was continued 23 h as the ice bath slowly warmed to room temperature. A light yellow powder separated and was washed with water and petroleum ether to give **23**, 38 g (85%): mp 142–144 °C; ^1H NMR ($CDCl_3$) δ 2.37 (s, Ar CH_3, 3 H), 4.01 (s, OCH_3, 3 H), 7.97 (s, Ar H, 2 H), 11.8 (s, OH, 1 H). Anal. Calcd for $C_9H_9NO_5$: C, H, N.

2-Hydroxy-5-methyl-3-nitrobenzenemethanol (24). Methyl 2-hydroxy-5-methyl-3-nitrobenzoate (**23**) (34 g, 0.16 mol) was dissolved in 1200 mL of THF under N_2. Borane–THF complex (0.325 mol) was added with stirring. When the evolution of H_2 had ceased, the solution was heated at reflux for 3 h. The mixture was then cooled and slowly quenched with H_2O. The THF was evaporated at reduced pressure. The residue was dissolved in 400 mL of ether and 400 mL of dilute hydrochloric acid. The ether layer was washed with 100 mL of dilute hydrochloric acid, and the combined aqueous layers were extracted with 200 mL of ether. The combined ether layers were washed with water, dried, filtered, concentrated, and crystallized from EtOH to yield 21.8 g (82%) of **24** as yellow needles: mp 93–96 °C; ^1H NMR ($CDCl_3$ δ 2.28 (br s, OH, 1 H), 2.35 (s, Ar CH_3, 3 H), 4.78 (s, CH_2, 2 H), 7.51 (s, Ar H, 1 H), 7.85 (s, Ar H, 1 H), 10.83 (s, Ar OH, 1 H). Anal. Calcd for $C_8H_9NO_4$: C, H, N.

8-Nitro-2,2,6-trimethyl-4*H*-1,3-benzodioxin (25). A solution of 2-(hydroxymethyl)-4-methyl-6-nitrophenol (**24**) (13.5 g, 0.074 mol) and 2,2-dimethoxypropane (15.4 g, 0.15 mol) in 250 mL of benzene was stirred at 60 °C under N_2. Tosylic acid monohydrate (250 mg) was added. After 16 h, solvent was distilled until the head temperature reached 75 °C. After cooling the solution to 65 °C, 15 g of additional dimethoxypropane was added, followed after 30 min by 200 mL of benzene. Solvent was distilled slowly for 3 h, leaving 300 mL of solution. Solid NaOMe was added, following by a 1% aqueous solution of NaOH. The organic layer was separated, washed thoroughly with 1% NaOH in water, dried, filtered, concentrated, and chromatographed on 300 g of alumina. A nonpolar impurity was eluted with 200 mL of 33% CH_2Cl_2/67% petroleum ether followed by the product, which was eluted with 500 mL of CH_2Cl_2. The yield of **25** was 14.9 g (91% as a yellow solid): mp 60–63 °C; ^1H NMR ($CDCl_3$) δ 1.58 (s, $(CH_3)_2C$, 6 H), 2.31 (s, Ar CH_3, 3 H), 4.86 (s, CH_2, 2 H), 7.03 (s, Ar H, 1 H), 7.59 (s, Ar H, 1 H); R_f 0.7 (CH_2Cl_2, alumina). Anal. Calcd for $C_{11}H_{13}NO_4$: C, H, N.

8-Amino-2,2,6-trimethyl-4*H*-1,3-benzodioxin (26). A solution of nitro acetonide **25** (2.0 g, 9.0 mmol) in 100 mL of EtOAc was shaken with 100 mg of PtO_2 under 3 atm of H_2 for 2.7 h. Filtration of the solution through Celite and concentration of the filtrate gave 1.7 g (98%) of amine **26** as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.52 (s, $(CH_3)_2C$, 6 H), 2.17 (s, Ar CH_3, 3 H), 3.6 (br s, NH_2, 2 H), 4.74 (s, CH_2, 2 H), 6.18 (s, Ar H, 1 H), 6.39 (s, Ar H, 1 H). Anal. Calcd for $C_{11}H_{15}NO_2$: C, H, N.

When the hydrogenation was performed under more concentrated conditions, side reactions occurred.

***N*,*N*′′-(2-Methoxy-1,3-phenylene)bis[*N*′-[2-(methoxymethoxy)-3,5-dimethylphenyl]urea] (28).** Anisole 2,6-dicarboxazide was prepared by the reaction of the bis acid chloride of anisole-2,6-dicarboxylic acid with NaN_3 in H_2O–acetone at 5 °C. The bis carboxazide (8.5 g, 0.0345 mol) was dried under vacuum at room temperature and then dissolved in 300 mL of toluene, treated with $MgSO_4$, and filtered. This solution was heated 30 min at 80 °C under N_2, effecting rearrangement to the isocyanate **27**[13b] with the evolution of N_2 ($\nu_{N=N=N}$ of the azide = 2140 cm^{-1}, ν_{NCO} of the isocyanate = 2240 cm^{-1} in the IR). A solution of 3,5-dimethyl-2-(methoxymethoxy)aniline (**21**)[13a] (13.8 g, 0.0763 mol) in 60 mL of dry toluene was added. The mixture was stirred under N_2 and heated at 85 °C for 3 h. The solution was allowed to cool for 14 h. The precipitate which formed was collected and washed with toluene and petroleum ether to yield 17.4 g (91%) of **28**: mp 235–236 °C; ^1H NMR (Me_2SO-d_6) δ 2.22 (s, Ar CH_3, 6 H), 2.32 (s, Ar CH_3, 6 H), 3.52 (s, OCH_3, 6 H), 3.70 (s, Ar OCH_3, 3 H), 4.94 (s, CH_2, 4 H), 6.66 (s, Ar H, 2 H), 6.96 (t, J = 8.3 Hz, Ar H, 1 H), 7.74 (s, Ar H, 2 H), 7.75 (d, J = 8.3 Hz, Ar H, 2 H), 8.79 (s, NH, 2 H), 8.86 (s, NH, 2 H); IR (KBr) 3280 (s), 2900 (m), 1640 (s), 1600 (s), 1540 (s), 1480 (s), 1300 (m), 1210 (s), 1160 (m), 1070 (m), 960 (s). Anal. Calcd for $C_{29}H_{36}N_4O_7$: C, H, N.

***N*,*N*′′-(2-Methoxy-1,3-phenylene)bis[*N*′-(2,2,6-trimethyl-4*H*-1,3-benzodioxin-8-yl)urea] (29).** Anisole 2,6-dicarboxazide (5.4 g, 0.022 mol, rearranged to the bis(isocyanate)) and the aniline acetonide **26** (9.4 g, 0.049 mol) were submitted to reaction in toluene similarly to the preparation of **28**. The precipitated solids produced were ground to a powder before washing with toluene and petroleum ether to give 11.6 g (92%) of **29** as a white powder: mp 140 °C dec; ^1H NMR (Me_2SO-d_6) δ 1.54 (s, $(CH_3)_2C$, 12 H), 2.21 (s, Ar CH_3, 6 H), 3.73 (s, OCH_3, 3 H), 4.77 (s, CH_2, 4 H), 6.50 (s, Ar H, 2 H), 7.00 (t, J = 8.3 Hz, Ar H, 1 H), 7.75

(d, J = 8.3 Hz, Ar H, 2 H), 7.82 (s, Ar H, 2 H), 8.58 (s, NH, 2 H), 8.92 (s, NH, 2 H); IR (KBr) 3300 (s), 2900 (m), 1660 (s), 1600 (m), 1520 (s), 1470 (s), 1250 (s), 1190 (s), 1130 (s), 870 (m); R_f 0.6 (EtOAc, silica gel). Anal. Calcd. for $C_{31}H_{36}N_4O_7$: C, H, N.

1,1′-(2-Methoxy-1,3-phenylene)bis[tetrahydro-3-(2-(methoxymethoxy)-3,5-dimethylphenyl)-2(1*H*)-pyrimidinone] (30). Bis(urea) **28** (4.5 g, 8.1 mmol), 1,3-dibromopropane (17 mL, 34 g, 0.17 mol), and NaH (7.5 g of 50% dispersion, 0.16 mol) were stirred in 700 mL of THF at reflux under N_2. After 24 h, the excess NaH was cautiously destroyed with H_2O, and the THF was evaporated at reduced pressure. The residue was suspended in 200 mL of H_2O and extracted into 300 mL and two 50-mL portions of CH_2Cl_2. The combined c ganic layers were dried, filtered, concentrated, and chromatographed on 100 g of silica gel. The products were eluted with EtOAc under pressure from a nitrogen line. Fractions of 35 mL of eluant were collected, and **30** was found in fractions 13–42, 2.4 g (47%) as a white foam: ^{1}H NMR ($CDCl_3$) δ 2.24 (s, Ar CH_3, 6 H), 2.29 (s, Ar CH_3, 6 H), 2.2 (m, C–CH_2–C, 4 H), 3.60 (s, OCH_3, 6 H), 3.7 (m, NCH_2, 8 H), 3.91 (s, Ar OCH_3, 3 H), 5.05 (s, OCH_2, 4 H), 6.89 (s, Ar H, 2 H), 6.94 (s, Ar H, 2 H), 7.0–7.2 (m, Ar H, 3 H); IR (film on NaCl) 2940 (m), 1650 (s), 1490 (s), 1430 (s), 1300 (m), 1200 (m), 1160 (w), 1070 (w), 970 (m); R_f 0.1 (EtOAc, silica gel); MS (200 °C) M^+ 632 (6), 602 (9), 588 (12), 556 (100), 544 (21), 204 (11), 45 (34). Anal. Calcd for $C_{35}H_{44}N_4O_7$: C, H, N.

1,1′-(2-Methoxy-1,3-phenylene)bis[tetrahydro-3-(2,2,6-trimethyl-4*H*-1,3-benzodioxin-8-yl)-2(1*H*)-pyrimidinone] (31). The bis(urea) bis(acetonide) **29** (5.0 g, 8.7 mmol) and 1,3-dibromopropane (12 mL, 24 g, 0.12 mol) were dissolved in 200 mL of benzene. A solution of 60 g of NaOH in 60 mL of H_2O was added followed by 2 g of benzyltriethylammonium bromide dissolved in a small amount of H_2O. The mixture was stirred vigorously at 50 °C, and a dark color was observed, which became orange with time. After 20 h, the benzene layer was separated and the aqueous layer was extracted with 100 mL of ether containing a small amount of CH_2Cl_2. The organic layers were combined, dried, filtered, concentrated, and chromatographed on 60 g of silica gel with EtOAc as the mobile phase to yield 2.1 g (37%) of **31** as a colorless foam: ^{1}H NMR ($CDCl_3$) δ 1.52 (s, $(CH_3)_2C$, 12 H), 2.24 (s, Ar CH_3, 6 H), 2.2 (m, C–CH_2–C, 4 H), 3.6–3.8 (m, NCH_2, 8 H), 3.95 (s, OCH_3, 3 H), 4.80 (s, Ar CH_2, 4 H), 6.67 (s, Ar H, 2 H), 7.00 (s, Ar H, 2 H), 7.0 (m, Ar H, 1 H), 7.19 (d, J = 8 Hz, Ar H, 2 H); IR (film on NaCl) 2920 (m), 1650 (s), 1490 (s), 1430 (s), 1370 (m), 1300 (m), 1270 (w), 1250 (m), 1200 (s), 1130 (m), 1060 (w), 1000 (w), 950 (w), 870 (m), 800 (w), 740 (m); MS (240 °C), m/e (M^+ – 58) 598 (0.6), (M^+ – 116) 540 (3), 509 (9), 87 (7), 58 (83), 43 (100); R_f 0.15 (EtOAc, silica gel). Anal. Calcd for $C_{37}H_{44}N_4O_7$: C, H, N.

1,1′-(2-Methoxy-1,3-phenylene)bis[tetrahydro-3-[2-hydroxy-3,5-dimethylphenyl]-2(1*H*)-pyrimidinone] (32). The protected bis(urea) **30** (1.85 g, 2.9 mmol) was stirred in 200 mL of MeOH and 15 mL of concentrated HCl–H_2O. After 40 min, $NaHCO_3$ was added until the pH was 6–7 and the MeOH was evaporated. The residue was suspended in 200 mL of H_2O and extracted into 200-mL and 100-mL portions of CH_2Cl_2. The organic layer was dried, filtered, and concentrated. The concentrate was chromatographed on 50 g of silica gel with EtOAc as the mobile phase, and 20-mL fractions were collected. Product **32** (1.35 g, 85%) was obtained from fractions 4–11 as white foam: ^{1}H NMR ($CDCl_3$) δ 2.24 (s, Ar CH_3, 6 H), 2.26 (s, Ar CH_3, 6 H), 2.2 (m, C–CH_2–C, 4 H), 3.73 (m, NCH_2, 4 H), 3.92 (s, OCH_3, 3 H), 3.9 (m, NCH_2, 4 H), 6.84 (s, Ar H, 4 H), 7.1–7.3 (m, Ar H, 3 H); IR (film on NaCl) 2940 (w), 2700–3500 (br, OH), 1625 (s), 1540 (w), 1490 (s), 1440 (s), 1350 (w), 1300 (m), 1240 (m), 1200 (m), 1000 (w), 850 (w), 730 (w); MS (230 °C), m/z 544 (100), 513 (51), 392 (39), 366 (30), 222 (23), 204 (11); R_f 0.6 (EtOAc, silica gel). Anal. Calcd for $C_{31}H_{36}N_4O_5$: C, H, N.

1,1′-(2-Methoxy-1,3-phenylene)bis[tetrahydro-3-[2-hydroxy-3-(hydroxymethyl)-5-methylphenyl]-2(1*H*)-pyrimidinone] (33). The bis(acetonide) **31** (760 mg, 1.16 mmol) was dissolved in 150 mL of MeOH and stirred with 0.75 g of Dowex-50 sulfonic acid resin (washed profusely with concentrated $H_3O^+Cl^-$, H_2O, MeOH, and CH_2Cl_2) for 80 min. The reaction was followed by TLC (R_f of starting material 0.39, of diol 0.32, of tetraol **33** 0.25, 12% EtOH/88% EtOAc by volume, silica gel). Filtration and concentration of the mixture gave 570 mg (90%) of white foam, which was 90% pure tetraol, suitable for subsequent reactions. Chromatography of 760 mg of this foam on 25 g of silica gel with 180 mL of 5% EtOH/95% EtOAc (v/v) as the mobile phase gave a mixture containing some product. Subsequent elution with 220 mL of 10% EtOH/90% EtOAc (v/v) gave 450 mg of pure **33** as a foam: ^{1}H NMR δ 2.29 (s, Ar CH_3, 6 H), 2.3 (m, C–CH_2–C, 4 H), 2.75 (br s, OH, 2 H), 3.75 (m, NCH_2, 4 H), 3.92 (s, OCH_3, 3 H), 3.9 (m, C–CH_2–C, 4 H), 4.66 (s, Ar CH_2, 4 H), 6.93 (s, Ar H, 2 H), 6.96 (s, Ar H, 2 H), 7.2 (m, Ar H, 3 H), 8.43 (br s, Ar OH, 2 H); IR (film on NaCl) 3300 (br, OH), 2900 (m), 1620 (s), 1570 (m), 1480 (s), 1430 (s), 1300 (s), 1230 (m), 1210 (m), 1000 (m), 730 (m); MS (240 °C) (M^+ – 18) 558 (3), 544 (5), 527 (4), 513 (4), 219 (2), 177 (5), 163 (11), 59 (62), 58 (40), 45 (27), 43 (100). Anal. Calcd for $C_{31}H_{36}N_4O_7$: C, H, N.

7,8,17,18-Tetrahydro-35-methoxy-1,3,21,23-tetramethyl-16*H*,31*H*-5,9:15,19-dimethano-10,14-metheno-26,30-nitrilo-6*H*,25*H*-dibenzo[*b*,*s*][1,21,4,8,14,18]dioxatetraazacyclooctacosine-34,36-dione (8). A suspension of NaH (114 mg, 50% dispersion, 2.38 mmol) in 100 mL of THF was stirred at reflux unde N_2. A solution of bis(urea) diol **32** (430 mg, 0.789 mmol) and 2,6-bis(bromomethyl)pyridine (209 mg, 0.789 mmol) in 60 mL of THF was added over a 20-h period from a constant rate addition funnel. After an additional 10 h at reflux, H_2O was added and the THF evaporated. The residue was shaken with 125 mL of CH_2Cl_2 and 100 mL of H_2O. The organic layer was dried, filtered, and concentrated to a solid, which could not be redissolved in CH_2Cl_2. This complexed material was therefore shaken with 100 mL of CH_2Cl_2 and 100 mL of deionized water. The organic layer was twice washed with 100-mL portions of deionized water to effect decomplexation. Concentration of the organic layer left a residue which was redissolved in CH_2Cl_2 and put through a GPC column of 100-Å gel. The major peak, retention volume 180 mL, was precipitated with cyclohexane and petroleum ether to give 235 mg of crude product. This material was vortexed for 7 min with $CHCl_3$ and saturated aqueous $NaClO_4$. The layers were carefully separated, the organic layer was concentrated, and the product was crystallized from 20 mL of $CHCl_3$/20 mL cyclohexane (v/v) over a 2-day period at 25 °C to give 180 mg (29%) of **8**·$NaClO_4$ as colorless, granular crystals: ^{1}H NMR ($CDCl_3$) δ 2.149 (s, Ar CH_3, 6 H), 2.274 (s, Ar CH_3, 6 H), 2.4 (m, C–CH_2–C, 4 H), 3.184 (s, Ar OCH_3, 3 H), 3.7–4.1 (m, NCH_2, 8 H), 4.93, 5.44 (q, AB, J = 14.2 Hz, OCH_2, 4 H), 6.919 (s, Ar H, 4 H), 7.136 (s, Ar H, 3 H), 7.35 (d, J = 7.8 Hz, 3,5-Py H, 2 H), 7.86 (t, J = 7.8 Hz, 4-Py H, 1 H); IR (KBr) 2950 (m), 2870 (w), 1640 (vs), 1600 (sh), 1500 (vs), 1440 (s), 1330 (m), 1320 (m), 1220 (vs), 1100 (vs). Anal. Calcd for $C_{38}H_{41}ClN_5NaO_9$: C, H, Cl, N.

The free cycle was prepared by dissolving the complex in wet CH_2Cl_2 (2–5 mL) and vortexing 3 times with twice that volume of deionized water each time. Evaporation of the organic layer left a white crystalline solid, mp > 235 °C dec, which existed in solution as two slowly interconverting conformers (see future section for NMR analysis). The conformers were separable by TLC, R_f 0.07 and 0.7 (20% EtOH/80% EtOAc, silica gel) for the crystalline and noncrystalline conformers, respectively; IR (KBr) 2920 (m), 2860 (m), 1640 (s), 1580 (m), 1470 (s), 1430 (s), 1300 (m), 1200 (s), 1040 (m), 1000 (m), 790 (m), 750 (m); MS (240 °C), m/z (M^+) 647 (100), 616 (38). Anal. Calcd for $C_{38}H_{41}N_5O_5$, C, H, N.

7,8,17,18,25,26,28,29-Octahydro-32-methoxy-1,3,21,23-tetramethyl-16*H*-5,9:15,19-dimethano-10,14-metheno-6*H*-dibenzo[*h*,*y*][1,4,7,10,14,20,24]trioxatetraazacyclohexacosine-31,33-dione (7). Bis(urea) diol **32** (750 mg, 1.38 mmol) and diethylene glycol ditosylate (570 mg, 1.38 mmol) were stirred in 750 mL of THF under N_2. Sodium hydride (166 mg of 50% dispersion, 3.45 mmol) was added, and the mixture was heated 48 h at reflux. Water was added and the THF evaporated at reduced pressure. The residue was dissolved in 250 mL of CH_2Cl_2, and the solution was washed with 200 mL of pH 11 water and three 200-mL portions of neutral water, dried, filtered, and concentrated to 900 mg. Gel permeation chromatography (100-Å column) indicated almost exclusively monomeric material (retention vol 190 mL). The monomeric band was crystallized from ethyl acetate to give 510 mg (56%) of **7** (white crystals): mp > 300 °C dec; ^{1}H NMR ($CDCl_3$) δ 2.2 (m, C–CH_2–C, 4 H), 2.226 (s, Ar CH_3, 6 H), 2.247 (s, Ar CH_3, 6 H), 3.5–4.4 (m, NCH_2 and OCH_2, 16 H), 3.910 (s, OCH_3, 3 H), 6.8–7.2 (m, Ar H, 7 H). When a molar excess of *tert*-butylammonium picrate in $CDCl_3$ was added to this solution, the following spectrum was obtained: ^{1}H NMR δ 2.24 (s, Ar CH_3, 6 H), 2.26 (s, Ar CH_3, 6 H), 2.35 (m, C–CH_2–C, 4 H), 3.6–4.2 (m, NCH_2 and OCH_2, 14 H), 3.98 (s, OCH_3, 3 H), 4.68 (m, OCH_2, 2 H), 6.89 (d, Ar H, 4 H), 7.21 (t, Ar H, 3 H). Free **7** gave the following additional data: IR (KBr) 2920 (m), 2850 (m), 1650 (vs), 1580 (w), 1470 (s), 1430 (s), 1300 (m), 1200 (m), 1120 (m), 1010 (m), 850 (w), 790 (w), 750 (w), 680 (w); MS (240 °C), m/z (M^+) 614 (2), 583 (100), 571 (16), 526 (22). Anal. Calcd for $C_{35}H_{42}N_4O_6$: C, H, N.

7,8,17,18-Tetrahydro-1,23-bis(hydroxymethyl)-35-methoxy-3,21-dimethyl-16*H*,31*H*-5,9:15,19-dimethano-10,14-metheno-26,30-nitrilo-6*H*,25*H*-dibenzo[*b*,*s*][1,21,4,8,14,18]dioxatetraazacyclooctacosine-34,36-dione (9). The bis(urea)tetrol **33** (580 mg, 1.01 mmol) and 2,6-bis(bromomethyl)pyridine (267 mg, 1.01 mmol) were dissolved in 700 mL of THF and stirred under N_2. A solution of NaOH (81 mg, 2.02 mmol) in 15 mL of H_2O was added, and the mixture was heated 42 h at reflux. The THF was removed at reduced pressure. The residue was suspended in 200 mL of H_2O and extracted into 200 mL and then 50 mL of additional CH_2Cl_2. The combined organic layers were washed with 100 mL of H_2O, dried, filtered, and concentrated. The residue was

crystallized from methanol–acetonitrile by evaporating the methanol over 3 days at 25 °C. The first crop was 230 mg and the second crop 90 mg of white crystals, which were washed with acetonitrile and CH_2Cl_2 to give a total of 320 mg of **9** (47%): mp 270 °C; ^1H NMR (10% CD_3OD/90% $CDCl_3$) δ 2.2–2.4 (m, C–CH_2–C, 4 H), 2.336 (s, Ar CH_3, 6 H), 3.111 (s, OCH_3, 3 H), 3.6–4.0 (m, NCH_2, 8 H), 4.72, 4.89 (q, AB, J = 12.7 Hz, Ar CH_2, 4 H), 5.05, 5.28 (q, AB, J = 11.4 Hz, OCH_2Py, 4 H), 7.0–7.3 (m, Ar H, 7 H), 7.74 (d, J = 7 Hz, 3,5-Py H, 2 H), 7.90 (t, J = 7 Hz, 4-Py H, 1 H); IR (KBr) 3400 (s), 2900 (m), 1630 (s), 1480 (s), 1440 (s), 1300 (m), 1200 (s); MS (240 °C), m/z (M^+) 679 (12), 648 (25), 573 (35), 555 (10), 527 (13), 163 (13), 107 (100), 43 (11). Anal. Calcd for $C_{38}H_{41}N_5O_7$: C, H. N.

7,8,17,18-Tetrahydro-1,23-bis(methoxymethyl)-35-methoxy-3,21-dimethyl-16*H*,31*H*-5,9:15,19-dimethano-10,14-metheno-26,30-nitrilo-6*H*,25*H*-dibenzo[*b*,*s*][1,21,4,8,14,18]dioxatetraazacyclooctacosin-34,36-dione (10). A solution of cycle **9** (100 mg, 0.15 mmol) in 10 mL of dry DMF was stirred under N_2. Sodium hydride (42 mg of 50% dispersion, 0.9 mmol) and CH_3I (55 μL, 125 mg, 0.9 mmol) were added. After 16 h the DMF was removed under vacuum. The residue was dissolved in 100 mL of CH_2Cl_2 and washed with three portions of 50 mL of H_2O. The organic layer was dried, filtered, and concentrated to give 125 mg of white solid. This solid was reprecipitated from CH_2Cl_2/cyclohexane/petroleum ether by removal of the CH_2Cl_2 to give 85 mg (82%) of **10** as an amorphous white solid: ^1H NMR ($CDCl_3$) δ (major solution conformer) 2.1–2.3 (m, C–CH_2—C, 4 H), 2.306 (s, Ar CH_3, 6 H), 3.20 (s, Ar OCH_3, 3 H), 3.48 (s, OCH_3, 6 H), 3.6–4.0 (m, NCH_2, 8 H), 4.49, 4.73 (q, AB, J = 11 Hz, Ar CH_2O, 4 H), 5.02, 5.39 (q, AB, J = 11 Hz, OCH_2Py, 4 H), 7.0–7.3 (m, Ar H, 7 H), 7.68 (d, J = 8 Hz, 3,5-Py H, 2 H), 7.86 (t, J = 8 Hz, 4-Py H, 1 H); IR (film on NaCl) 2900 (s), 1650 (s), 1580 (m), 1480 (s), 1430 (s), 1200 (s), 900 (s), 750 (s); MS (240 °C), m/z (M^+) 707 (93), 692 (79), 676 (100), 660 (27), 632 (11), 601 (12), 312 (16), 107 (17). Anal. Calcd for $C_{40}H_{45}N_5O_7$: C, H, N.

1,1′-(2-Methoxy-1,3-phenylene)bis[tetrahydro-3-[2-methoxy-3-(hydroxymethyl)-5-methylphenyl]-2(1*H*)-pyrimidinone] (11). Bis(urea)tetraol **33** (100 mg, 0.173 mmol) was stirred in 25 mL of THF under N_2. Sodium hydroxide (14 mg, 0.35 mmol, dissolved in 0.5 mL of H_2O) and $(CH_3)_2SO_4$ (33 μL, 44 mg, 0.35 mmol) were added, and the solution was heated 1 h at 60 °C. The THF was evaporated under vacuum, and the residue was dissolved in 70 mL of CH_2Cl_2. The solution was washed with 40 mL of H_2O, dried, filtered, and concentrated. The residue was chromatographed on 4 g of alumina. Less polar material eluted with 50 mL of 1% CH_3OH/99% CH_2Cl_2 (v/v), followed by product, eluted with 10 mL of 3% CH_3OH/97% CH_2Cl_2 (v/v) to give **11** as a glass, 40 mg (38%): ^1H NMR ($CDCl_3$) δ 2.2–2.4 (m, C–CH_2–C, 4 H), 2.276 (s, Ar CH_3, 6 H), 2.7–2.8 (m, NCH_2, 8 H), 3.879 (s, OCH_3, 6 H), 3.904 (s, OCH_3, 3 H), 4.67 (br s, CH_2O, 4 H), 7.0–7.2 (m, Ar H, 7 H); IR (film on NaCl) 3400 (m), 2900 (m), 1630 (s), 1480 (s), 1440 (s), 1300 (m), 1200 (m), 1000 (w); MS (230 °C), m/z (M^+) 604 (1), 573 (100), 571 (31), 557 (20). Anal. Calcd for $C_{36}H_{40}N_4O_7$: C, H, N.

Conformational Reorganization of Host A(UDCH$_2$)$_2$Py (8). A sample of host **8** (crystallized by concentration of a solution of the substance in wet CH_2Cl_2, 2 mg) was dissolved in 0.50 mL of $CDCl_3$. The conversion of the cycle from its binding conformer (B′) to an equilibrium mixture of B′ and its nonbinding conformer (N′), in which the latter predominated, was monitored by integration of the OCH_3 signals of B′ and N′ in the ^1H NMR spectrum of the mixture. Eight points were taken over a 2.5-h period, in which the ratio of integrals (this ratio equals X of eq 1) at each time were calculated. The time associated with each spectrum was considered to be 1 min after the start of each 2-min acquisition of data. The probe temperature was 28 °C. The final equilibrium value of [N′]/[B′] = 3.0 agrees reasonably well with an independently calculated value of 3.3 derived from ^{13}C NMR spectral data.[17] The rate constant k for N′ going to B′ was calculated from the results through use of eq 1, in which X = [N′]/[B′] at time t and K is the equilibrium

$$\ln\left(\frac{K-X}{X+1}\right) = -k\left(1+\frac{1}{K}\right)t + \ln K + c \qquad (1)$$

constant. Since at time infinity X = [N′]/[B′] = K = 3.0, eq 1 reduces to eq 2. A plot of ln [(3 − X)/(X + 1)] vs. t gave a slope of 0.0369 min^{-1}

$$\ln\left(\frac{3-X}{X+1}\right) = -\tfrac{3}{4}kt + c' \qquad (2)$$

(correlation coefficient of 0.998), which with eq 2 gave $k = 4.6 \times 10^{-4}$ s^{-1}. From this rate constant was calculated $\Delta G^{\ddagger}$ = 22 kcal mol^{-1} activation energy for converting B′ to N′ at 28 °C.

(17) We thank Professor Thorlief Anthonsen for this determination, whose details will be published elsewhere.

To an equilibrium mixture of N′ and B′ in $CDCl_3$ at 28 °C was added a molar excess of sodium picrate dissolved in a minimum of $(CD_3)_2SO$, and the ^1H NMR spectrum was immediately recorded (the ratio of $CDCl_3$ to $(CD_3)_2SO$ was about 10:1 by volume). A mixture of only N′ and **8**·Na^+ in a 2:1 ratio was observed. After 0.5 h, only the spectrum of **8**·Na^+ was visible.

An equilibrium mixture of N′ and B′ at 28 °C in $CDCl_3$ with [N′]/[B′] = 3.0 was saturated with D_2O. Integrations of the new solution gave [N′]/[B′] = 2.4. Dissolution of a molar excess of A′(A′A′)$_2$A′ (4)[5] in a solution of **8**·$NaClO_4$ in $CDCl_3$ saturated with D_2O gave a solution whose ^1H NMR spectrum initially showed the presence of **8**·Na^+, free **8** in its B′ conformation, **4** and 4·Na^+. This spectrum slowly shifted to one in which B′ and N′ were present in equilibrium proportions, and **8**·Na^+ had gone to 4·Na^+.

Pertinent ^1H NMR spectral data are as follows: conformer A ($CDCl_3$) δ 2.3 (m, C–CH_2–C, 4 H), 2.27 (s, Ar CH_3, 6 H), 2.41 (s, Ar CH_3, 6 H), 3.19 (s, OCH_3, 3 H), 3.65 (m, NCH_2, 6 H), 3.9 (m, NCH_2, 2 H), 4.97, 5.29 (q, AB, J = 11.5 Hz, OCH_2, 4 H), 6.97 (s, Ar H, 4 H), 7.0 (m, Ar H, 1 H), 7.14 (m, Ar H, 2 H), 7.68 (d, J = 7 Hz, 3,5-Py H, 2 H), 7.84 (t, J = 7 Hz, 4-Py H, 1 H); conformer B ($CDCl_3$) δ 2.2 (m, C–CH_2–C, 4 H), 2.29 (s, Ar CH_3, 6 H), 2.35 (s, Ar CH_3, 6 H), 2.98 (s, OCH_3, 3 H), 3.6–4.0 (m, NCH_2, 8 H), 4.98, 5.21 (q, AB, J = 12 Hz, OCH_2, 4 H), 6.96 (s, Ar H, 4 H), 7.3 (m, Ar H, 3 H), 7.55 (d, J = 7.8 Hz, 3,5-Py H, 2 H), 7.7 (t, J = 7.8 Hz, 4-Py H, 1 H); free **8** ($CDCl_3$/$(CD_3)_2SO$, v/v) (partial list) δ 2.28 (s, Ar CH_3), 2.30 (s, Ar CH_3), 3.74 (s, OCH_3), 5.24 (collapsed AB, OCH_2), 6.96 (s, Ar H), 7.17 (s, Ar H), 7.57 (d, J = 7.8 Hz, 3,5-Py H); **8**·Na^+ picrate$^-$ complex ($CDCl_3$/$(CD_3)_2SO$, v/v) (partial list) δ 2.18 (s, Ar CH_3), 2.27 (s, Ar CH_3), 3.11 (s, OCH_3), 4.94, 5.29 (q, AB, J = 13.7 Hz, OCH_2), 6.92 (s, Ar H), 7.17 (s, Ar H), 7.24 (d, J = 7.3 Hz, 3,5-Py H).

L-Alanine 4-Nitrophenyl Ester Perchlorate. The *N*-(*tert*-butoxycarbonyl) derivative of L-alanine *p*-nitrophenyl ester (1.0 g, 3.2 mmol) obtained from Sigma was dissolved in 4 mL of EtOH. A slight deficiency of 7 N $HClO_4$ (0.41 mL, 2.9 mmol) was added with stirring. After 40 min the solution was slowly brought to 60 °C. Approximately 60 mL of benzene was added and the solvents were distilled until the heat temperature reached 80 °C. The remaining benzene was removed at reduced pressure, leaving a yellow semisolid. Digestion of the semisolid with hot $CHCl_3$ gave a white precipitate, which was collected and crystallized from 10 mL of warm EtOAc by slow addition of $CHCl_3$. The mixture was cooled to −20 °C to give 640 mg (64%) of product, mp 168–70 °C; ^1H NMR (60 MHz, 25% CD_3OD/75% $CDCl_3$) 1.78 (d, J = 7 Hz, CH_3, 3 H), 4.3 (q, J = 7 Hz, CH, 1 H), 4.4 (br s, NH_3, 3 H), 7.48 (d, half of AA′BB′, J = 9 Hz, Ar H, 2 H), 8.32 (d, half of AA′BB′, J = 9 Hz, Ar H, 2 H). Anal. Calcd for $C_9H_{11}ClN_2O_8$: C, H, Cl, N.

Conformational Reorganization of Host A(UFCH$_2$)$_2$Py (9). A solution of diol **9** (2 mg), $DCON(CD_3)_2$ (200 μL), buffer (0.02 M in diisopropylethylamine and in amine perchlorate prepared in $CDCl_3$, 200 μL), and $CDCl_3$ (1.8 mL) was prepared in a 2-mL volumetric flask. The 200-MHz NMR spectrum of this solution showed the diol to exist 80–90% as conformer N′ 20 min after the solution was prepared. After equilibration over 31 h, the percentage of a second conformer (B′) had increased to about 30% ([N′]/[B′] ≃ 2.2), as determined by integration of the OCH_3 signals. Upon addition of ≥1 equiv L-alanine *p*-nitrophenyl ester perchlorate as a 0.04 M solution in 10% $DCON(CD_3)_2$/90% $CDCl_3$ by volume, all NMR peaks assigned to conformer B′ immediately disappeared and new signals assigned to a complex were observed. Peaks assigned to conformer N′ persisted at first, but slowly disappeared.

When a similar experiment was performed with ester present from the start, conformer B′ was not observed. Instead, peaks due to conformer N′ diminished in intensity over 3 h as all of the diol present formed complex with the ester. After 31 h, new peaks in the region δ 4.4–5.6 were observed and were attributed to acylated **9**. Peaks due to *p*-nitrophenol were observed as well at δ 6.95 and 8.1. Pertinent ^1H NMR data are as follows: conformer N′ (partial listing) δ 2.30 (Ar CH_3), 3.21 (OCH_3), 4.79, 4.89 (q, A_2B_2, J = 12.7 Hz, Ar CH_2O), 5.03, 5.38 (q, A_2B_2, J = 11.2 Hz, Ar OCH_2Py), 7.71 (d, J = 7 Hz, 3,5-H of pyridine ring), 7.84 (t, J = 7 Hz, 4-H of Py); conformer B′ δ 2.32 (Ar CH_3), 3.06 (OCH_3), 4.80 (collapsed AB, Ar CH_2O), 5.01, 5.26 (q, A_2B_2, J = 14 Hz, Ar OCH_2Py), 7.57 (d, J = 8 Hz, 3,5-H of Py); complex δ 2.33 (Ar CH_3), 3.40 (Ar OCH_3), 4.61 (collapsed AB, Ar CH_2O), 8.28 (d, half of AA′BB′, J = 9 Hz, Ar H of *p*-nitrophenyl group) (remaining peaks obscured by buffer and solvent).

Two conformers of **9** were also observed in $(CD_3)_2SO$. Their ratio approached 1:1 when heated above 100 °C but did not show any sign of coalescence. All CH_2 protons remained diastereotopic.

Determination of Association Constants and Free Energies of Complexation. The standard method for determining K_a and $-\Delta G°$ values previously reported[16] was used for hosts **5**, **6**, **7**, and **11** binding Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and *t*-$BuNH_3^+$ picrates, where equil-

ibrations between phases and conformers were essentially instantaneous on the human time scale. With hosts **8**, **9**, and **10**, equilibration between conformers in the organic phase was observable on the human time scale, although equilibration of guest between phases was essentially instantaneous. With these hosts, the mixing times in tightly stoppered Pyrex tubes of the two phases was extended as needed to reach equilibrium between noncomplexed guest in the D_2O phase and complexed guest in the $CDCl_3$ phase. Those times are recorded in the footnotes of Table I.

Because of the insolubility of diol $A(UFCH_2)_2F$ (**9**) in $CDCl_3$, a 0.001 M solution of this diol was prepared by dissolving 4.0 mg of the substance in 0.20 mL of MeOH and 1 mL of $CDCl_3$. The methanol was washed out of this solution with 3 mL of deionized water, as shown by the absence of CH_3OH peaks in the ^1H NMR of the washed solution. The resulting $CDCl_3$ solution was used to determine the K_a and $-\Delta G°$ values.

The distribution constant, K_d, of piperidinium picrate between $CDCl_3$ and D_2O was determined by the same method used for determining the K_d values for the other salts.[16] The piperidinium picrate used was precipitated and recrystallized from ethanol and dried at 110 °C under high vacuum. Triplicate determinations of ϵ and K_d were performed: ϵ = 17300 ± 300 M^{-1} cm^{-1}; K_d = 8.0 ± 0.7 M^{-1} (90–95% confidence limits). The K_a for $A(UGCH_2)_2Py$ (**10**) complexing this salt was determined at initial concentrations of 0.015 M for host and guest. The phases were equilibrated for 24 h. The two phases gave $-\Delta G°$ values that agreed to within 0.2 kcal mol^{-1}.

Registry No. **3**, 83604-23-3; **3**·LiPic, 91129-27-0; **3**·*t*-$BuNH_3ClO_4$, 91129-28-1; **3**·$MeNH_3ClO_4$, 91129-29-2; **4**, 84011-90-5; **5**, 84011-89-2; **6**, 69605-90-9; **8**, 91084-78-5; **9**, 91084-76-3; **10**, 42062-54-4; **11**, 67350-30-5; **12**, 83604-28-8; **13**, 83604-29-9; **14**, 83604-30-2; **15**, 83604-32-4; **16**, 84011-91-6; **17**, 91129-24-7; **18**, 84011-94-9; **19**, 84011-95-0; **20**, 84011-98-3; **23**, 16069-36-6; **24**, 84027-48-5; **25**, 91129-26-9; 2-methoxy-3-nitro-5-methylaniline, 83604-27-7; 2-fluoroisophthaloyl dichloride, 91129-30-5; *N*,*N*′-bis(2-hydroxy-1,1-dimethylethyl)-2-fluoro-1,3-benzenedicarboxamide, 91129-31-6; L-alanine *p*-nitrophenyl ester perchlorate, 84011-92-7; β-alanine 4-nitrophenyl ester perchlorate, 91129-32-7; L-phenylalanine 4-nitrophenyl ester perchlorate, 91129-33-8; glycine 4-nitrophenyl ester perchlorate, 91129-34-9.

Host–Guest Complexation. 31. A Transacylase Partial Mimic[1]

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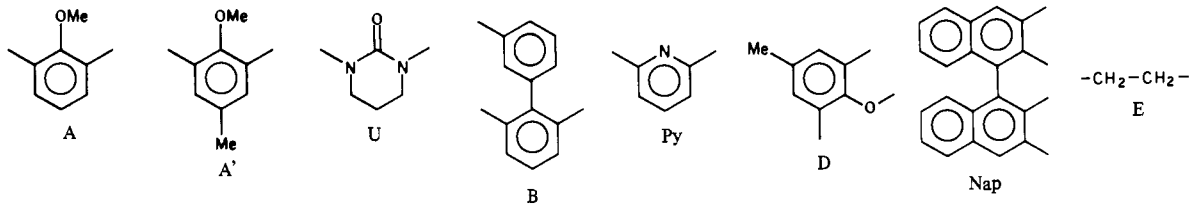
Abstract: The first two stages are reported of an incremental approach to the synthesis of hosts that mimic serine transacylases. The hosts are 20-membered macrocycles and are composed by attaching to one another aryloxy, cyclic urea, pyridyl, biphenyl, ethylene, methylene, and oxygen units. The structures and points of attachment of all but the latter two units are drawn and are symbolized by capital letters. The structures of the hosts and synthetic intermediates are indicated by line formulas consisting



of sequences of letters, which represent sequences of units bonded to one another in the host. In the first stage of our approach the compound $U(A'UCH_2)_2A'$ was designed and prepared and its binding properties toward Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and *t*-$BuNH_3^+$ picrates in $CDCl_3$ at 25 °C were determined. The free energies of binding ($-\Delta G°$ values) varied from a low of 12.1 to a high of 15.2 kcal mol^{-1}. A crystal structure of the complex $U(A'UCH_2)_2A'$·*t*-$BuNH_3ClO_4$ indicated the substance possessed the expected organization. The complex is held together by the three hydrogen bonds, $RN^+(H\cdots O{=}C)_3$, in which the carbonyl groups are parts of the three cyclic urea units (U). The high binding power of $U(A'UCH_2)_2A'$ is attributed to the presence of the three cyclic urea units and particularly to their high degree of preorganization. The key ring-closing reaction involved H–U–A′–U–A′–U–H reacting with $BrCH_2$–A′–CH_2Br in tetrahydrofuran–NaH to produce $U(A'UCH_2)_2A'$·NaBr (50%). In the second stage, host $U(A'UCH_2)_2BCH_2OH$ was designed and prepared by a similar reaction between H–U–A′–U–A′–U–H with $(BrCH_2)_2BCH_2OCH_3$ to produce $U(A'UCH_2)_2BCH_2OCH_3$ (36%), which was converted to $U(A'UCH_2)_2BCH_2OH$. This compound contains both a binding site complementary to RNH_3^+ guests and a nucleophilic hydroxyl group complementary to the guest carbonyl group in complexes such as $U(A'UCH_2)_2BCH_2OH{\cdot}CH_3CH(CO_2C_6H_4NO_2\text{-}p)NH_3ClO_4$. The $-\Delta G°$ values of $U(A'UCH_2)_2BCH_2OH$ binding the above picrate salt series in $CDCl_3$ at 25 °C varied from a low of 10.6 to a high of 15.4 kcal mol^{-1}. When the alanine complex of this nucleophilic host was dissolved in CH_2Cl_2–10% pyridine (by volume) at 25 °C, transacylation occurred to give $U(A'UCH_2)_2BCH_2O_2CCH(CH_3)NH_3ClO_4$. The kinetics of transacylation were followed in $CDCl_3$ buffered with R_3N–R_3NHClO_4 (R_3N is diisopropylethylamine). Pseudo-first-order (saturation) kinetics were observed under conditions where host concentration greatly exceeded that of guest. The reaction was first order in buffer ratio, and therefore the active nucleophile was O^-. Under the same reaction conditions, the noncomplexing model compound, H_2BCH_2OH, underwent no detectable reaction. Upper limits were placed on its rate of acylation. Comparisons of the bimolecular acylation rates by $CH_3CH(CO_2C_6H_4NO_2\text{-}p)NH_3ClO_4$ of $U(A'UCH_2)_2BCH_2OH$ and of H_2BCH_2OH were made to assess all the effects of complexing. The complexing system has a second-order rate constant for acylation that is $\approx 10^{11}$ times greater than the second-order rate constant of the noncomplexing system. Addition of $NaClO_4$ acted as a competitive inhibitor for acylation of $U(A'UCH_2)_2BCH_2OH$. The kinetics of acylation of two other possible hosts were examined, $A[UD(CH_2OH)CH_2]_2Py$ and $E(OEOEO)_2Nap(CH_2OH)_2$. Although rate accelerations were observed, the amine base (R_3N) appeared to deprotonate the RNH_3^+ group of the complexes competitively with deprotonating the CH_2OH groups. As a result, the rates were not first order in R_3N–RNH_3ClO_4 ratio. We have demonstrated that molecular design and syntheses of hosts highly preorganized to be complementary to guest reactants can through tailored complexation produce enormous rate acclerations in chemical reactions.

The structure and mechanism of action of the serine transacylases have been thoroughly enough studied to stimulate the design and synthesis of nonpeptide model catalysts. The active sites contain a complexing cavity, an acyl-accepting and -releasing

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