were reacted as described for the preparation of **3**, except that the reflux after addition of the base was continued for 9 h. The product (12.5 g, 81%) was first distilled at 160 °C (0.015 Torr) as a viscous yellowish oil and next crystallized from pentane to a white crystalline mixture of isomers, mp 45-56 °C: ^{1}H NMR (CCl_4) δ 7.36-7.02 (m, 14 H), 6.8 (br s, 2 H), 2.06 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 143.44, 141.7, 138.76, 137.73, 137.54, 137.38, 129.87, 129.73, 129.48, 129.33, 128.74, 128.28, 128.12, 127.96, 127.0, 126.9, 126.35, 126.4, 125.87 (aromatic carbons) 132.3, 131.8 (=C(CH_3)C_6H_5), 125.58 (HC=), 26.0, 17.2, 17.0 (CH_3); IR ($CHCl_3$) 3040 (m), 1680 (m), 1590 (m), 1480 (m), 1430 (s) cm^{-1}; MS, *m/e* (%) (EI) 310 (M, 30), 295 (M - CH_3, 8), 218 (M - $C_6H_5CH_3$, 11), 217 (M - C_6H_6 - CH_3, 13), 205 (M - C_6H_5 - C_2H_4, 59), 203 (M - C_2H_6 - C_6H_5, 20), 105 ($C_6H_5CHCH_3$, 100), 91 (C_7H_7, 44), 77 (C_6H_5, 24), 65 (C_5H_5, 8) (CI) 311 (M + 1, 29), 310 (M, 100), 105 (56). Anal. Calcd for $C_{24}H_{22}$: C, 92.86; H, 7.14. Found: C, 92.59; H, 6.86.

1,2-Bis(2,2-dibromo-3-methyl-3-phenylcyclopropyl)benzene (28). To a suspension of potassium *tert*-butoxide (2.89 g, 25.8 mmol) in dry pentane (150 mL) cooled to 0 °C under nitrogen was added **27** (2 g, 6.5 mmol). The mixture was cooled to -75 °C, and bromoform (6.53 g, 25.8 mmol) was added slowly with stirring. Stirring was continued for 24 h at ambient temperature, and after addition of ether-methylene chloride, the solution was washed with 100 mL of 1% HCl solution and water (4 × 100 mL). The organic phase was dried ($MgSO_4$) and treated with active charcoal. Evaporation of the solvent afforded 3.3 g of a brown and very viscous liquid. On addition of a little ether white crystals separated, which were recrystallized from ether (100 mg), mp 155-156 °C: ^{1}H NMR ($CDCl_3$) δ 7.54 (m, 14 H), 3.68 (s, 2 H), 1.75 (s, 6 H); IR ($CHCl_3$) 3030 (m), 1595 (s), 1490 (s), 1440 (s), 1375 (m), 1025 (m) cm^{-1}; MS, *m/e* (%) (EI) 495, 493, 491 (M - HBr - Br, 1:2:1, 2), 414, 412 (M - HBr - 2Br, 1:1, 15) 413, 411 (M - 2HBr - Br, 1:1, 82), 333 (M - HBr - 3Br, 31), 332 (M - 2Br - 2HBr, 100), 331 (M - 3HBr - Br, 86), 318 (M - 3Br - HBr - CH_3, 9), 317 (M - 2Br - 2HBr - CH_3, 35), 316 (M - Br - 3HBr - CH_3, 29), 255 (M - 2Br - 2HBr - C_6H_5, 11), 254 (M - Br - 3HBr - C_6H_5, 19), 253 (M - 4HBr - C_6H_5, 33), 239 (M - 3HBr - Br - CH_3 - C_6H_5, 23), 129 ($HCCCCH_3C_6H_5$, 8); (CI) 577, 575, 573, 571 (M - Br, 1:3:3:1, 1), 495, 493, 491 (1:2:1, 12), 414, 412 (1:1, 18), 413, 411 (1:1, 48), 334 (M - 4Br, 13), 333 (48), 332 (100), 331 (81), 105 ($C_6H_5CHCH_3$, 53).

1,2-Dimethyl-1,2-diphenylnaphtho[*b*]cyclobutane (25). To a stirred and cooled (-30 °C) solution of **28** (100 mg, 0.15 mmol) in dry ether (60 mL, N_2) was added 1 mL of a 5% solution of MeLi in ether. After 1.5 h at -30 °C and quenching with water, the organic layer was washed with water (2 × 60 mL), dried ($MgSO_4$), concentrated to afford a yellowish viscous oil (48 mg, 96%), recrystallized from ether-methanol, and identified as the title compound, mp 125-26 °C: ^{1}H NMR ($CDCl_3$) δ 7.80 (m, 2 H), 7.65 (s, 2 H), 7.35 (m, 2 H), 6.85 (s, 10 H), 1.90 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 148.9 (C-10), 144.59 (C-13), 134.64 (C-11), 128.41, 127.44, 127.21, 125.48, 125.04, 121.21 (C-9, C-8, C-7, C-14, C-15, C-16), 61.19 (C-1), 23.90 (CH_3); IR (CCl_4) 3040 (m), 3005 (m), 2940 (s), 2870 (m), 1595 (w), 1485 (m), 1415 (m), 1290 (s), 1195 (s), 1015 (m), 905 (s) cm^{-1}; UV (cyclohexane) λ_{max}, nm, 232 (ϵ_{max} = 109 166), 262 (20 000), 271 (21 250, 281 (20 000), 294 (15 000), 307 (9160), 321 (7080); MS, *m/e* (%) (EI) 334 (M, 100), 319 (M - CH_3, 89), 304 (M - 2CH_3, 40), 257 (M - C_6H_5, 25), 256 (M - C_6H_6, 56), 242 (M - C_6H_5 - CH_3, 19), 241 (M - C_6H_6 - CH_3, 26), 229 (M - C_6H_6 - C_2H_3, 11), 228 (M - C_6H_6 - C_2H_4, 18), 153 ($C_{12}H_9$, 17); (CI) 335 (M + 1, 100), 257 (65) 207 (40). Anal. Calcd for $C_{26}H_{22}$: C, 93.15; H, 6.61. Found: C, 93.36, H, 6.63.

Kinetic Measurements. Kinetic measurements were performed by the use of ^{1}H NMR, by following the rate of decrease in substrate concentration with respect to a constant concentration of an inert reference. A weighed quantity of diallenes **5**, **12**, **14**, and **16** was dissolved in 1 mL of the appropriate solvent (CCl_4, $CDCl_3$, or CD_3CN) containing *p*-dimethoxybenzene as reference. About 0.5 mL of this solution was transferred to an NMR tube and immersed in a constant temperature bath after sealing. At appropriate time intervals the change in integration of the allenic protons around δ 6.34 and 5.58 for **14** and **16**, respectively, and of the γ-methyl protons at δ 1.76 for both **5** and **12**, with respect to the integration of the methoxy protons at δ 3.76, was recorded. In each case, control runs using *p*-dimethoxybenzene in a separate tube and immersed in the NMR tube, as an external reference, were also performed. The rate constants were calculated from the first-order kinetic expression $k = (2.303/t) \log (a/(a - x))$, where a represents the ratio of the allenic proton area and the methoxy proton area at $t = 0$, while $(a - x)$ is the same ratio after t. Plots of log $(a - x)$ vs time gave good straight lines for each run. Errors were calculated by means of an IBM 360/50 computer, using the APL language.

Registry No. **3**, 2223-64-5; **3a**, 67560-59-2; **4**, 61838-62-8; **4a**, 127229-20-3; **5**, 61838-63-9; **6**, 61838-59-3; **7**, 61838-61-7; **9**, 61838-58-2; **11**, 61838-57-1; **12**, 67560-52-5; **13**, 127208-21-3; **14**, 67560-57-0; **15**, 67560-58-1; **16**, 67560-54-7; **17**, 67560-56-9; **25**, 127208-22-4; **27**, 127208-23-5; **28**, 127208-24-6; isopropyltriphenylphosphonium bromide, 1530-33-2; 2-bromopropane, 75-26-3; 1-phenylethyltriphenylphosphonium bromide, 53213-26-6; 1-bromo-1-phenylethane, 585-71-7; phthaldialdehyde, 643-79-8; cetone-d_6, 666-52-4; 1,1,1,3,3,3-hexadeuterio-2-propanol, 3976-29-2; 1,1,1,3,3,3-hexadeuterio-2-bromopropane, 52809-76-4; 1,1,1,3,3,3-hexadeuterio-2-propyltriphenylphosphonium bromide, 127208-25-7; diisobutenyl ether, 764-51-2; 3,3-dimethyl-1-bromoallene, 6214-32-0; α,α-dimethylpropargyl bromide, 6214-31-9; 2-methyl-3-butyn-2-ol-d_6, 57444-27-6; acetylene, 74-86-2; 3-methyl-3-bromo-1-butyne-d_6, 67560-55-8.

Spherands Containing Cyclic Urea Units[1a,b]

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Contribution from the Department of Chemistry and Biochemistry of the University of California at Los Angeles, Los Angeles, California 90024. *Received January 8, 1990*

Abstract: Three new spherands (**1-3**) and one new hemispherand (**4**) are reported, all having in common two $(CH_2)_3N_2C{=}O$ cyclic urea units, three anisyl units, and one CH_2ACH_2 unit. In **1**, **2**, and **3** A = O, S, and $C(CO_2Et)_2$, respectively, and these together with the other units provide 18-membered macrorings whose enforced cavities are lined by (roughly) octahedrally arranged heteroatoms. In **4** A = 1,2-$C_6H_4O_2$ (catechol), and the macroring is 21-membered and is partially preorganized. Crystal structures are reported for **1**,**1**·Na picrate, **2**·$NaSbF_6$, **4**, and **10**·H_2O. The association constants (K_a, M^{-1}) and free energies of binding ($-\Delta G°$, kcal mol^{-1}) were determined at 25 °C for Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and $(CH_3)_3CNH_3^+$ picrates in $CDCl_3$ saturated with D_2O. Peak binding was observed for **1** and **2** with Na^+ (19.5 and 19.1 kcal mol^{-1}, respectively), for **3** with Li^+ (16.1 kcal mol^{-1}), and for **4** with K^+ (12.4 kcal mol^{-1}). The results further illustrate the utility of the principles of complementarity and preorganization. The rates of complexation-decomplexation during $CHCl_3$-water extractions were rapid on the human time scale. The greatest specificity was shown by **2** toward the physiologically important Li^+, Na^+, and K^+ ions: $K_a^{Na^+}/K_a^{Li^+}$ = 250; $K_a^{Na^+}/K_a^{K^+}$ = 10 000.

Cyclic trimethylene ureas ($(CH_2)_3N_2C{=}O$) have proven to be strongly binding ligands[2] for alkali metal, ammonium, and alkylammonium ions when incorporated along with anisyl units into 20-membered macroring systems, as in **5-8**.[2b] Hosts **5-8** bind

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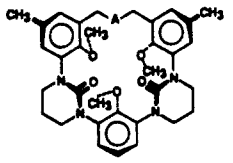
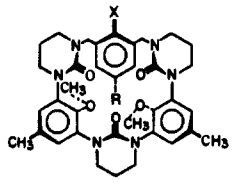


1, A = O; 2, A = S

3, A = $C(CO_2Et)_2$; 4, A = 1,2-C_6H_4O



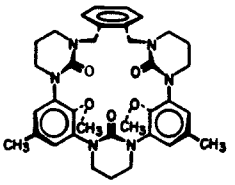
5, X = R = H; 6, X = Br, R = H

7, X = OCH_3, R = CH_3; 8, X = CO_2CH_3, R = H

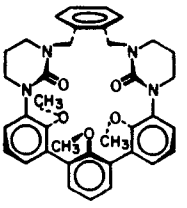
Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and $(CH_3)_3CNH_3^+$ picrates with $-\Delta G°$ values at 25 °C in $CDCl_3$ saturated with D_2O that range between a high of 15.5 to a low of 11.6 kcal mol^{-1}.[2b] Thus these systems are very strong but indiscriminate binders for all eight cations, and they also possess the desirable property of possessing extraction rates of guest salt from water into host in $CHCl_3$ that are essentially instantaneous on the human time scale. Hosts **5** and **6** contain only five ligating sites,[2b] and crystal structures of complexes of **7** and **8**[2b,c] suggest that the ligating sites at 12 o'clock in the drawing might not be used. The modest degree of preorganization in these hosts is partially offset by the powerful ligating strength of the urea units. The flexibility of these 20-membered rings allows the larger cations such as Rb^+ and Cs^+ to be bound nearly as strongly as Li^+ and Na^+. These hosts also are almost ideally preorganized for tripod binding of NH_4^+ and RNH_3^+,[2c-f] a property put to use in the synthesis of partial protease mimics.[2e,f]

In **9** and **10**, the macrocyclic ring atoms were decreased in number to 19, and those of the potential binding sites were decreased to five.[2c] As a result, the $-\Delta G°$ values of **9** and **10** binding Li^+ increased to ~18.3 and 16.6 kcal mol^{-1}, respectively, and the binding of Na^+ increased to 16.3 and 15.4 kcal mol^{-1}, respectively, whereas the $-\Delta G°$ values for the larger ions decreased markedly. Hosts **9** and **10** in CPK molecular models have small enforced cavities preorganized to bind the smaller ions and were thus thought to be true spherands. The stronger binding exhibited by **9** compared to **10** was attributed to the fact that **9** contains three cyclic urea and two anisyl moieties, whereas **10** contains two cyclic urea and three anisyl units.[2c]

We report here the design, synthesis, crystal structures, and binding properties of the three more highly preorganized hosts, **1–3**, whose macrorings are 18-membered. Examination of Corey–Pauling–Koltun (CPK) molecular models of these systems indicates that the three methoxy groups of the anisyl units at 2, 6, and 10 o'clock of drawings **1–3** must all lie on the remote side of the best plane of the macroring, and that the two carbonyls and heteroatoms of the A groups are located on the near side. In addition, the CH_3 of the CH_3–O groups must occupy conformations that diverge from the cavity. The result is a somewhat deformed octahedral arrangement of potential binding sites to give a cavity shielded on one face by three methyl groups and open on the other for entrance and egress of guests. The much more conformationally mobile system, **4**, contains a 21-membered macroring and was included in the study for comparative purposes.



9



10

The first section of this paper describes the syntheses of **1–4**. The second section reports the crystal structures of some of the hosts and complexes, including that of **10**·H_2O. The binding properties of **1–4** are described in the third part and compared to those of **10**. In the fourth section, correlations between structure and binding are discussed.

Results and Discussion

Syntheses. The syntheses of **1–4** started with hydroxymethylphenol **11** whose preparation has been described.[2g] Alkylation of **11** with $(CH_3)_2SO_4$–THF–NaH gave **12** (73%), reduction of which with H_2–Pt–EtOAc gave aniline derivative **13** (95%). The known acid chloride,[2g] **14**, was converted to its bisacylazide (**15**) with NaN_3 in aqueous acetone. Since during isolation of **15** a low-grade explosion occurred in successive runs, the compound without isolation was transferred to a solution in toluene, which was dried ($MgSO_4$). The dry toluene solution of **15** was heated to produce by a Curtius rearrangement the bisisocyanate **16**, which again without isolation was converted to bis-urea compound **17** by the addition of 2 mol of **13** to provide a 49% overall yield for the three steps, **14** → **15** → **16** → **17**. The two urea groups of **17** were bridged with $TsO(CH_2)_3OTs$–NaOH–H_2O–C_6H_6–$C_6H_5CH_2NEt_3Br$ in a two-phase reaction to provide key intermediate **18**, which was isolated by reverse-phase chromatography on alkylated silica gel[3] with CH_3OH–H_2O–NaBr as the mobile phase (53%). Apparently podand **18** is a strong enough ligand to complex NaBr under these conditions. Hydrogen bromide gas was bubbled through a $CHCl_3$ solution of **18** to provide dibromide **19** (91%). This dibromide was heated in a solution of acetone–water–$NaHCO_3$ to give dibenzyl alcohol **20** (93%), whose properties were identical with those of a sample of the same compound prepared previously by a much less satisfactory route.[2g]

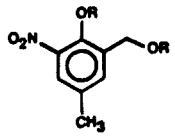
The key macrocyclic ring closures involved either diol **20** or dibromide **19** as starting materials. Host **1** was prepared by slowly adding via a double syringe pump separate THF solutions of **20** and *p*-toluenesulfonyl chloride to a refluxing, well-stirred mixture of NaH in THF to give **1**·NaBr (11%) isolated by reverse-phase chromatography[3] with CH_3OH–H_2O–NaBr as the mobile phase. The NaBr was extracted out of spheraplex **1**·NaBr by washing a CH_2Cl_2 solution of the complex five times with deionized water. Sulfa host **2** was formed by slowly adding an absolute ethanol solution of dibromide **19** to a suspension of $Na_2S·9H_2O$ in absolute ethanol to give **2**·NaBr (21%), which was purified and converted to free host **2** as **1**·NaBr was converted **1**. The diethyl malonate bridge was introduced into **3** by slowly adding a THF solution of dibromide and diethyl malonate **19** to a vigorously stirred mixture of THF·NaH held at reflux to give **3**·NaBr purified as before (2%) and converted to **3** as were the other spheraplexes. The catechol bridge was introduced into **4** by slowly adding a solution in THF of catechol and dibromide **19** to a vigorously stirred mixture of NaH in refluxing THF. Pure **4**·NaBr (19%) was obtained and converted to **4** by the techniques applied to the other hosts. All four hosts were easily purified by reverse-phase

(1) (a) Host–Guest Complexation 54. (b) The authors warmly thank the Division of Basic Sciences of the Department of Energy for support of the research on part of the synthesis and all of the binding of metal ions; we warmly thank the U.S. Public Health Service for Grant No. 12640, which supported the research on part of the synthesis, the crystal structures, and the ammonium ion binding.

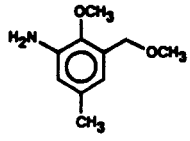
(2) (a) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25* 1039–1057. (b) Stewart, K. D.; Miesch, M.; Knobler, C. B.; Maverick, E. F.; Cram, D. J. *J. Org. Chem.* **1986**, *51*, 4327–4337. (c) Cram, D. J.; Dicker, I. B.; Lauer, M.; Knobler, C. B.; Trueblood, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7150–7167. (d) Doxsee, K. M.; Feigel, M.; Stewart, K. D.; Canary, J. W.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1987**, *109*, 3098–3107. (e) Cram, D. J.; Lam, P. Y.-S. *Tetrahedron* **1986**, *42*, 1607–1615. (f) Cram, D. J.; Lam, P. Y.-S.; Ho, S. P. *J. Am. Chem. Soc.* **1986**, *108*, 839–841. (g) Katz, H. E.; Cram, D. J. *J. Am. Chem. Soc.* **1984**, *106*, 4977–4987.

(3) Kühler, T. C.; Lindsten, G. R. *J. Org. Chem.* **1983**, *48*, 3589–3591.

Chart I



11, R = H; 12, R = CH_3



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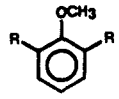
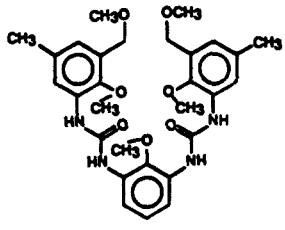


14, R = COCl; 15, R = CON_3; 16, R = N=C=O



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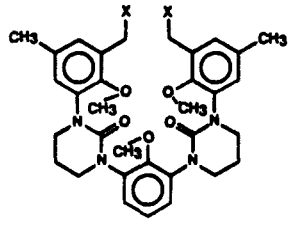


18, X = OCH_3; 19, X = Br; 20, X = OH

chromatography of their NaBr complexes with solutions of NaBr in CH_3OH–H_2O as the mobile phase.

Crystal Structures. Crystal structures have been determined for **1**, **1**·Na picrate, **2**·$NaSbF_6$, **4**, and **10**·H_2O. Chart II provides drawings of the substances depicting the conformations that match the stereoviews of the crystal structures. The picrate$^-$ and SbF_6^- counterions have been omitted from the two drawings for clarity. Comparison of the crystal structures for **1** with that of **1**·Na^+ shows that the free host is essentially completely preorganized, since it possesses the same structure before and after complexation. Thus **1** is a true spherand, and **1**·Na^+ is a spheraplex.[2a] Unfortunately, we were unable to grow suitable crystals of free host **2**. Comparison of CPK molecular models of **1** and **1**·Na^+ and **2** and **2**·Na^+ suggests that **2** is as preorganized for binding Na^+ as is **1**, and hence it is probably also an authentic spherand. Host **4** contains seven potential binding sites and a 21-membered macroring. Examination of CPK molecular models indicates the system is flexible enough to fill its own cavity with either inward-turned methyl or methylene groups, although the five oxygens of the three anisyl and two cyclic urea groups appear to prefer an alternate down-up-down-up-down arrangement, as drawn in Chart II. The crystal structure of **4** indicates that this alternation exists and that the methyl group of the methoxyl at 10 o'clock of the drawing is turned inward.

The crystal structure of **10**·H_2O provides a nice example of a neutral complex between what is most certainly a preorganized host and water. Molecular models of **10**·H_2O indicate that 1 mol of HOH beautifully spans the two carbonyl groups of **10** and could also occupy this position in **1**, **2**, and **4**. It is highly likely that in chloroform saturated with water, all four of these hosts are complexed with 1 mol of water in the absence of other guests.

Table I lists the Na^+···ligand distances in spheraplexes **1**·Na^+ and **2**·Na^+. The van der Waals radius of oxygen is 1.40 Å, and the ionic radius of Na^+ is 1.02 Å,[4] the sum being 2.42 Å. The four $N_2C{=}O{\cdots}Na^+$ distances in the two complexes range between 2.24 and 2.39 Å to give an average of 2.31 Å. These distances are ~0.1 Å shorter than the average of the six $Ar(CH_3)O{\cdots}Na^+$ distances of 2.42 Å (range of 2.29 to 2.55 Å). The longest distance in **1**·Na^+ is 2.55 Å for $(CH_2)_2O{\cdots}Na^+$, whose oxygen is a macroring member, rather than being forced inward by attachment to macroring members, as with the other binding sites. The van der Waals radius of covalent sulfur is 1.84 Å,[4] which added to that of Na^+ (1.02 Å) provides the standard value of 2.86 Å, close to the value of 2.93 Å observed for $(CH_2)_2S{\cdots}Na^+$ in **2**·Na^+.

The C–L···Na^+ binding angles are also listed in Table I. Those involving $N_2C{=}O{\cdots}Na^+$ are particularly interesting because of

Table I. Sodium Ion to Ligating Atom Distances and Binding Angles

	ligating heteroatom (L)			
complex	clock position[a]	ligand type	distance to Na^+, Å	angle, deg C–L···Na^+
1·Na^+	12	$(CH_2)_2O$	2.55	117, 119
	2	$Ar(CH_3)O$	2.29	101
	4	$N_2C{=}O$	2.30	121
	6	$Ar(CH_3)O$	2.44	112
	8	$N_2C{=}O$	2.24	121
	10	$Ar(CH_3)O$	2.32	99
2·Na^+	12	$(CH_2)_2S$	2.93	101, 100
	2	$Ar(CH_3)O$	2.49	106
	4	$N_2C{=}O$	2.39	116
	6	$Ar(CH_3)O$	2.55	113
	8	$N_2C{=}O$	2.31	122
	10	$Ar(CH_3)O$	2.44	107

[a] See Chart I for formulas.

the question of whether delocalized electron pairs or nonbonding electron pairs are involved in the binding of Na^+.[5] The average for the four $N_2C{=}O{\cdots}Na^+$ binding angles in **1**·Na^+ and **2**·Na^+ is 120° (range 116° to 122°), which is close to those angles observed for the $C{=}O{\cdots}Na^+$ binding angle (133°) where the carbonyl is part of a $ArCO_2CH_3$ group, and for the N–O···Na^+ binding angle (140°) where the oxygen is part of a $ArNO_2$ group.[6] If one uses the O···Na^+ binding distance as a criterion of binding power, the order of binding power for the largely preorganized units is $(CH_2)_3N_2C{=}O > ArCO_2CH_3 > ArNO_2 > R_2O$. If one uses the binding angles as a criterion of hybridization at oxygen, these systems are between sp^2–p and sp–p^2 hybridized at oxygen, the former at the extreme requiring a 120° and the latter a 180° binding angle. The strong binding of the cyclic urea unit by cations located in planes perpendicular to the plane of the $N_2C{=}O$ atoms invites molecular orbital calculations to be made to provide a theoretical framework to aid correlations and predictions.

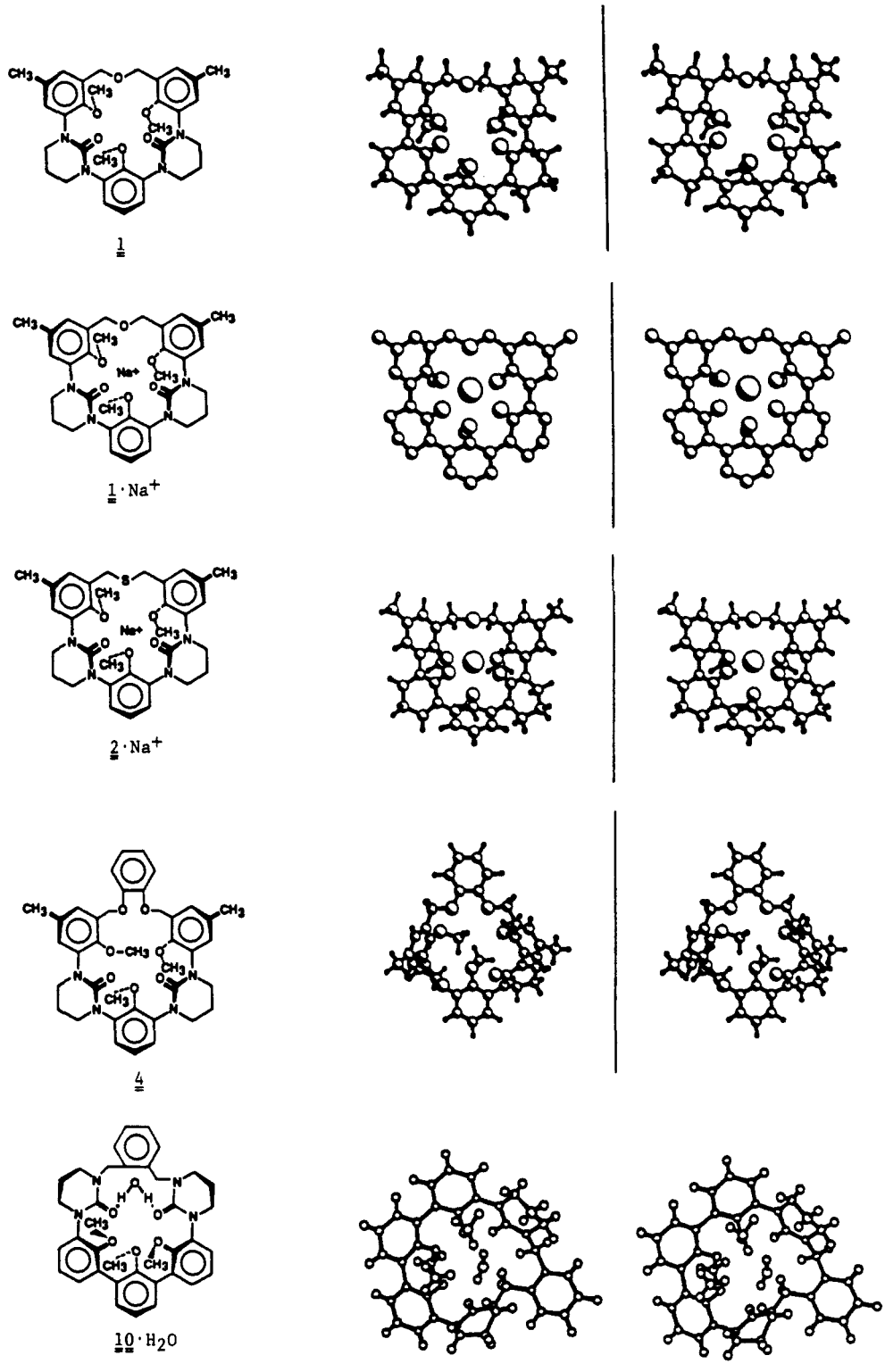
Association Constants and Binding Free Energies. Association constants (K_a, M^{-1}) and binding free energies ($-\Delta G°$, kcal mol^{-1}) for hosts **1**–**4** and the picrate salt guests of Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and $(CH_3)_3CNH_3^+$ were determined at 25 °C in $CDCl_3$ saturated with D_2O. Table II records the values obtained by either of two methods. Most of the determinations were made by distributing the picrate salts between the aqueous and chloroform phases in the presence and absence of host. The

(4) Waser, J.; Trueblood, K. N.; Knobler, C. M. *Chem. One*; McGraw-Hill Book Co.: New York, 1976; p 283.

(5) (a) Taylor, R.; Kennard, O.; Versichel, W. J. *J. Am. Chem. Soc.* **1983**, *105*, 5761–5766. (b) Murray-Rust, P.; Glusker, J. P. *Ibid.* **1984**, *106*, 1018–1025.

(6) Helgeson, R. C.; Bryant, J. A.; Knobler, C. B.; deGrandpre, M. P.; Cram, D. J. *J. Org. Chem.* In press.

Chart II. Crystal Structures of Hosts and Their Complexes



host and its complexes essentially are soluble only in the organic phase, and the free picrate salts are only very slightly soluble in the organic phase.[7] Values for **1** binding Li picrate were determined by equilibrating **1**·Li picrate with **21**, whose K_a and $-\Delta G°$ values for binding this salt at 25 °C in chloroform saturated with water are known and are very close to those for **1**·Li picrate.[8] Values for **1** and **2** binding sodium picrate under the same conditions were determined by equilibrating **1**·sodium picrate with **22**, whose K_a and $-\Delta G°$ values for binding this salt are known, and are very close to those for **1**·sodium picrate and **2**·sodium picrate.[8] Because of the very strong binding by **1** of CH_3NH_3 picrate and $(CH_3)_3CNH_3$ picrate, only lower limits were set for

(7) (a) Koenig, K. E.; Lein, G. M.; Stückler, P.; Kaneda, T.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3553–3566. (b) Helgeson, R. C.; Weisman, G. R.; Toner, J. L.; Tarnowski, T. L.; Chao, Y.; Mayer, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 4928–4941. (c) The 1.0 mM scale is identical with the method described in ref 7a and 7b except the host and guest concentrations are ca. 1.0 m instead of ca. 15 mM and the two phases are diluted by a factor of 49:1 instead of 499:1 before measuring their UV absorbances. A 6% decrease in the extinction coefficient of picrate anion at 380 nm on going from pure acetonitrile to 49:1 acetonitrile/water as solvent was taken into account (see: Ericson, J. L. Ph.D. Dissertation, Department of Chemistry and Biochemsitry, University of California at Los Angeles, 1988).

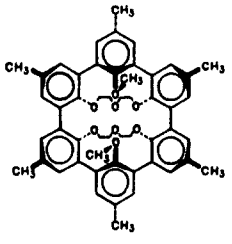
(8) Cram, D. J.; Lein, G. M. *J. Am. Chem. Soc.* **1985**, *107*, 3657–3668.

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

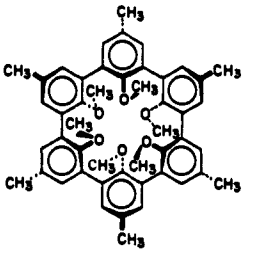
host no.	host central A group[a]	$-\Delta G^{a-c}$ or $K_a^{b,d}$	guest cation Li^+	Na^+	K^+	Rb^+	Cs^+	NH_4^+	$CH_3NH_3^+$	$(CH_3)_3CNH_3^+$
1	O	$-\Delta G°$	17.3[e]	19.5[f]	16.6	15.2	14.7	14.9	>14	>14
2	S	$-\Delta G°$	15.8	19.1[f]	13.7	12.5	12.1	13.3	12.9	14.2
3	$C(CO_2Et)_2$	$-\Delta G°$	16.1	15.2	11.6	10.9	10.6	11.0	10.6	12.4
4	1,2-$C_6H_4O_2$	$-\Delta G°$	10.4	10.2	12.4	11.6	11.5	11.0	10.6	11.0
9[g]		$-\Delta G°$	~18.3	16.3	12.4	11.4	11.8	11.8	12.1	13.2
10[g]		$-\Delta G°$	16.6	15.4	10.8	9.4	10.5	10.4	9.7	7.8
1	O	K_a	4.7×10^{12}	1.9×10^{14}	1.4×10^{12}	1.4×10^{11}	5.8×10^{10}	8.2×10^{10}	$>1.8 \times 10^{10}$	$>1.8 \times 10^{10}$
2	S	K_a	3.7×10^{11}	9.7×10^{13}	1.1×10^{10}	1.4×10^{9}	7.3×10^{8}	5.5×10^{9}	2.8×10^{9}	2.5×10^{10}
3	$C(CO_2Et)_2$	K_a	6.2×10^{11}	1.4×10^{11}	3.1×10^{8}	9.6×10^{7}	5.8×10^{7}	1.1×10^{8}	5.8×10^{7}	1.2×10^{9}
4	1,2-$C_6H_4O_2$	K_a	4.1×10^{7}	3.0×10^{7}	1.2×10^{9}	3.1×10^{8}	2.6×10^{8}	1.1×10^{8}	5.8×10^{7}	1.1×10^{8}
9[g]		K_a	2.5×10^{13}	8.7×10^{11}	1.2×10^{9}	2.2×10^{8}	4.4×10^{8}	4.4×10^{8}	7.3×10^{8}	4.6×10^{9}
10[g]		K_a	1.4×10^{12}	1.9×10^{11}	8.1×10^{7}	6.9×10^{7}	4.9×10^{7}	4.1×10^{7}	1.1×10^{7}	5.2×10^{5}

[a] Compounds first reported in this paper. [b] Unless otherwise noted, derived by extraction method at 1.0 mM concentrations of host and guest (see ref 7c). [c] kcal mol^{-1}. [d] M^{-1}. [e] Determined by partitioning guest between **1** and host **21** of known binding power (see ref 8); average of two determinations. [f] Determined by partitioning guest between **1** or **2** and host **22** of known binding power (see ref 8). [g] Taken from ref 2c.

the values of K_a and $-\Delta G°$ (determined by the extraction method).[7c]

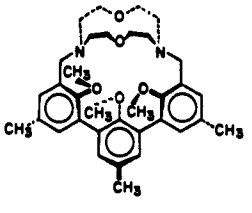


21

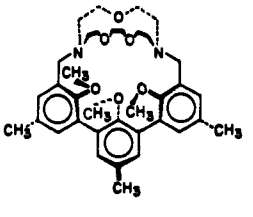


22

Correlation between Structure and Binding. The $-\Delta G°$ values for **1** and **4** range from a high of 19.5 kcal mol^{-1} for spherand **1** binding Na^+ to a low of 10.2 kcal mol^{-1} for hemispherand **4** binding the same ion. As expected from CPK molecular model examination, the very high degree of preorganization of **1** and the complementarity to Na^+ of its cavity lined with six oxygens contribute to this high value. Under the same conditions, prototype spherands **21** and **22** bind sodium picrate with 18.7 and 19.3 kcal mol,[8] respectively, whereas the values for cryptahemispherands **23** and **24** are 20.6 and 21.0 kcal mol^{-1}, respectively.[9a] Thus **1** is among the most strongly sodium ion binding systems known, being exceeded only by **23** and **24**, which possess more ligating sites (by one and two, respectively), and by the remarkable torand,



23



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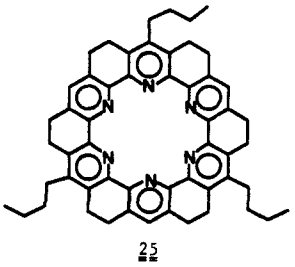

25

25 ($-\Delta G°$ = 20 kcal mol^{-1}).[9b] Although spherand **22** possesses more symmetrical (square-antiprism) and ideal arrangement of binding sites than **1**,[10] the superior binding by the two cyclic urea units in **1** vs the two additional anisyl units in **22** appears to compensate for the less than ideal arrangement of oxygens in **1**·Na^+. The higher degree of preorganization of **1** (18-membered) for binding both Na^+ (19.7 kcal mol^{-1}) and K^+ (16.6 kcal mol^{-1}) appears responsible for its greater binding power than the tris-urea, 20-membered cycle, **7**, whose respective $-\Delta G°$ values are 14.5 and 15.2 kcal mol^{-1}.[2c] Like **7**, **1** is a universally strong binder, its lowest $-\Delta G°$ value being >14 kcal mol^{-1} (toward $CH_3NH_3^+$ and $(CH_3)_3CNH_3^+$).

The selectivity of these hosts for the physiologically important Li^+, Na^+, and K^+ ions is best expressed as a ratio of K_a values. Thus, for **1**, $K_a^{Na^+}/K_a^{Li^+} = 40$ and $K_a^{Na^+}/K_a^{K^+} = 135$, less impressive than ratios for **9** and **10**. For tris-urea cycle **9**, $K_a^{Li^+}/K_a^{Na^+} = 29$ and $K_a^{Na^+}/K_a^{K^+} = 725$, whereas for bis-urea cycle **10**, $K_a^{Li^+}/K_a^{Na^+} = 7$ and $K_a^{Na^+}/K_a^{K^+} = 2300$. In CPK molecular models, both **9** and **10** appear to be more rigidly preorganized and to have a smaller cavity than **1**.

Host **2**, which contains a CH_2SCH_2 unit in place of the CH_2OCH_2 unit of **1**, is the most interesting of the four new hosts. Surprisingly, its $-\Delta G°$ value for binding Na^+ is 19.1 kcal mol^{-1}, comparable to that of **1**. The $-\Delta G°$ values for **2** binding the other cations are all several kcal mol^{-1} lower than those for **1**, as expected. Accordingly, the specificity for **2** binding Na^+ is substantially greater than is observed for **1**. Thus for **2**, $K_a^{Na^+}/K_a^{Li^+} = 260$ and $K_a^{Na^+}/K_a^{K^+} = 8800$. These high values make **2** a good candidate for structural manipulation at positions distant from the cavity that can act as indicator systems for Na^+ analyses.[11,12] The crystal structure of **2**·Na^+ in Chart II definitely shows the sulfur acts as a ligating site for Na^+.

Host **3** containing a malonic ester bridging group again showed a high level of $-\Delta G°$ values, ranging from 10.6 kcal mol^{-1} for Cs^+ and $CH_3NH_3^+$ to 16.1 kcal mol^{-1} for Li^+. In CPK models, one of the ester groups is oriented inward toward the cavity decreasing its size, whereas the other ester group orients outward. The $-\Delta G°$ (kcal mol^{-1}) values decrease monotonically with a decrease in alkaline earth ionic diameter: for Li^+, 16.6; Na^+, 15.2; K^+, 11.6; Rb^+, 10.9; and Cs^+, 10.6. Compound **3** is one of the few hosts that provide Li^+ specificity over Na^+ ($K_a^{Li^+}/K_a^{Na^+} = 4$), and much more specificity of Na^+ over K^+ ($K_a^{Na^+}/K_a^{K^+} = 450$.

Host **4** containing a catechol-derived central unit in CPK molecular models is conformationally mobile and adaptable to guest size. The 21-membered macroring provides greater flexibility and a larger cavity than **1–3**. Its $-\Delta G°$ values range from

(9) (a) Cram, D. J.; Ho, S. P. *J. Am. Chem. Soc.* **1986**, *108*, 2998–3005. (b) Bell, T. W.; Firestone, A.; Ludwig, R. *J. Chem. Soc., Chem. Commun.* **1989**, 1902–1904.

(10) Cram, D. J.; Kaneda, T.; Helgeson, R. C.; Brown, S. B.; Knobler, C. B.; Maverick, E.; Trueblood, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 3645–3657.

(11) Cram, D. J.; Carmack, R. A.; Helgeson, R. C. *J. Am. Chem. Soc.* **1988**, *110*, 571–577.

(12) Helgeson, R. C.; Czech, B. P.; Chapoteau, E.; Gebauer, C. R.; Kumar, A.; Cram, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 6339–6350.

a low of 10.2 for Na^+ to a high of 12.4 kcal mol^{-1} K^+ to provide a $K_a^{K^+}/K_a^{Na^+}$ ratio of 40. The compound is a strong general but indiscriminate binder, on average about 3 kcal mol^{-1} weaker than **7**, which contains *three* (rather than *two*) cyclic urea units as parts of a 20-membered macrocyclic ring.[2b] System **4** possesses a structure, five of whose seven oxygens are roughly preorganized, but whose two catechol oxygens and two methylene groups are probably organized for binding only during the complexing process. Its generally high level of complexing power is undoubtedly due to the presence of the two cyclic urea units incorporated in the ring system.

An attractive characteristic of hosts **1–10** is that they combine strong binding with rates of complexation, decomplexation, and extraction, which are high on the human time scale. Their ion specificity is low except when the cyclic urea units are incorporated in 19- and 18-membered macrorings, and thus far, it is limited to Na^+ or Li^+, as in **2** for the former, and **9** and **10** for the latter. Contrary to our conclusion based on CPK molecular model examination,[2c] the crystal structure of **10**·H_2O is not completely preorganized for binding, and therefore it is a hemispherand. This mistake emphasizes our ultimate dependence on crystal structure comparisons in assessing the degree of preorganization of hosts.

Experimental Section

General. All air-sensitive reactions were performed under a N_2 atmosphere in glassware oven dried for at least 6 h at 150 °C. For cyclizations, the oven-dried glassware was assembled under a flow of N_2 and flame dried. All compounds were dried according to the procedure that provided a correct C, H analysis prior to any further synthetic manipulations and before determining association constants. Tetrahydrofuran (THF) and Et_2O were freshly distilled from benzophenone ketyl. Toluene was dried over 3 Å sieves for at least 72 h prior to use. Tosyl chloride, catechol, and diethyl malonate were purified before use. Gravity column chromatography was performed on E. Merck silica gel 60 (70–230 mesh). Silica thin-layer chromatography was done on E. Merck plastic or aluminum-backed plates (silica gel 60, F_{254}, 0.2 mm). Reverse-phase chromatography was performed on the support (C_{18}-capped silica gel) described by Kühler and Lindsten.[3] Reverse-phase thin-layer chromatography was done on Whatman 0.2 mm $KC_{18}F$ octadecylsilane-bonded coated glass plates. All melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 297 spectrometer. Electron impact mass spectra were performed on a Kratos AE-1 Model MS-9 spectrometer. Fast atom bombardment mass spectra were determined on a ZAB SE instrument with *m*-nitrobenzyl alcohol (NOBA) as the matrix. Hydrogen NMR spectra were obtained on Bruker instruments (AM-500, AM-360, or WP-200), and all NMR spectra are referenced to tetramethylsilane as an internal standard at 0.00 ppm. Ultraviolet measurements were made on a Perkin-Elmer Lambda 4B instrument.

Benzene, 2-Methoxy-1-(methoxymethyl)-5-methyl-3-nitro- (12). A solution of 2-(hydroxymethyl)-4-methyl-6-nitrophenol (**11**)[2g] (31.1 g, 0.17 mol) in THF was slowly added to a suspension of NaH (60% oil dispersion, 13.6 g, 0.34 mol) in 700 mL of THF over 30 min. After H_2 gas evolution had subsided $(CH_3)_2SO_4$ (48.3 mL, 0.51 mol) was added over 1 h, and the mixture was stirred for an additional 12 h. Ammonium hydroxide was carefully added, and the THF was removed in vacuo. The residue was extracted with ether and water. The organic layer was washed with brine and dried ($MgSO_4$). Chromatography on silica gel (CH_2Cl_2) provided 26.2 g of **12** (73%): R_f (silica gel 10% EOAc in CH_2Cl_2) 0.7; ^1H NMR (200 MHz, $CDCl_3$) δ 2.38 (s, 3 H, ArCH_3), 3.46 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 4.52 (s, 2 H, ArCH_2OCH$_3$), 7.47 (s, 1 H, Ar*H*), 7.59 (s, 1 H, Ar*H*); high-resolution MS calcd $C_{10}H_{13}NO_4$ MW = 211.0844, found $C_{10}H_{13}NO_4$ MW = 211.0840 (89%).

Benzenamine, 2-Methoxy-3-(methoxymethyl)-5-methyl- (13). Compound **12** (22.9 g, 0.11 mol) was dissolved in EtOAc and shaken with PtO_2 under 3 atm of H_2 pressure for 3 h. The mixture was filtered and the solvent removed to give **13** (19.8 g, 95%) as an oil: R_f (silica gel, 10% EtOAc in CH_2Cl_2) 0.3; IR ($CDCl_3$), doublet in 3440 and 3360 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.23 (s, 3 H, ArCH_3), 3.42 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 4.44 (s, 2 H, ArCH_2OCH$_3$), 6.54 (s, 1 H, Ar*H*), 6.59 (s, 1 H, Ar*H*); high-resolution MS calcd $C_{10}H_{15}NO_2$ MW = 181.1103, found $C_{10}H_{15}NO_2$ MW = 181.1099 (100%).

***N*,*N*″-(2-Methoxy-1,3-phenylene)bis[*N*′-[2-methoxy-3-(methoxymethyl)-5-methylphenylurea]] (17).** Acid chloride **14**[2g] (12.8 g, 55 mmol) was dissolved in 500 mL of acetone and submerged in an ice bath at 0 °C. Sodium azide (9.6 g, 139 mmol) in 75 mL of water was added dropwise to the acid chloride, and the solution was stirred an additional 2 h. Toluene was added and the layers were separated. The aqueous layer was extracted with additional toluene. The organic layers were combined, dried ($MgSO_4$), and filtered. This drying procedure was repeated two more times with drying periods of 12 and 4 h, respectively. *This procedure is superior to other drying procedures for this bis(acylazide) which involve isolating the explosive acylazide as a solid.* After being filtered from $MgSO_4$, the toluene solution was heated to 80–90 °C for 45 min. Aniline derivative **13** (21.9 g, 121 mmol) was dissolved in toluene and added dropwise to this solution. The mixture was stirred for 4 h at 90 °C, during which time a precipitate began to form. The mixture was stirred overnight at 25 °C and filtered, and the product was washed with toluene and petroleum ether. This procedure yielded 14.8 g of **17**, and overall yield for the three steps from **14** to **17** being 49%: ^1H NMR (200 MHz, $(CD_3)_2SO$) δ 2.26 (s, 6 H, ArCH_3), 3.33 (s, 6 H, OCH_3), 3.71 (s, 6 H, OCH$_3$), 3.74 (s, 3 H, OCH_3), 4.41 (s, 4 H, ArCH_2OCH$_3$), 6.79 (s, 2 H, ArH), 6.96 (t, 1 H, Ar*H*, *J* = 8 Hz), 7.78 (d, 2 H, Ar*H*, *J* = 8 Hz), 7.95 (s, 2 H, Ar*H*), 8.94 (s, 4 H, N*H*); MS (FAB, NOBA) *m/e* 553 (M + H^+, 75%). Anal. (dried at 110 °c, 10^{-5} Torr, 24 h, drying at higher temperatures caused decomposition) Calcd for $C_{29}H_{36}N_4O_7 \cdot 2H_2O$: C, 59.17; H. 6.85. Found: C, 59.07; H, 6.09.

1,1′-(2-Methoxy-1,3-phenylene)bis[tetrahydro-3-[2-methoxy-3-(methoxymethyl)-5-methylphenyl]-2(1*H*)-pyrimidinone] (18). The unbridged urea **17** (14.37 g, 26 mmol) and 1,3-propaneditosylate (25 g, 65 mmol) were dissolved in 500 mL of benzene. Sodium hydroxide (75 g) was dissolved in 150 mL of water and added. Benzyltriethylammonium bromide (5.5 g, 20 mmol) was added, and the mixture was stirred at reflux for 3 days. The layers were separated, and the aqueous layer was washed with CH_2Cl_2. The organic layers were combined and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was preabsorbed on 50 mL of reverse-phase silica gel and chromatographed through this support, eluting with 1% w/v NaBr in a 13:7 mixture of MeOH–H_2O. This provided 8.6 g (53%) of **18** isolated as a foam: R_f (reverse-phase silica gel, 1% w/v NaBr in 65:35 CH_3OH–H_2O) 0.3; ^1H NMR (200 MHz, $CDCl_3$) δ 2.21–2.28 (s and m overlapping, 10 H, RNCH$_2$*CH*$_2$CH$_2$NR and Ar*CH*$_3$), 3.41 (s, 6 H, O*CH*$_3$), 3.73 (m, 8 H, RN*CH*$_2$CH$_2$*CH*$_2$NR), 3.85 (s, 6 H, O*CH*$_3$), 3.90 (s, 3 H, O*CH*$_3$), 4.47 (s, 4 H, Ar*CH*$_2$OCH$_3$), 7.05–7.10 (overlapping peaks, 5 H, Ar*H*), 7.20 (d, 2 H, Ar*H*); MS (FAB, NOBA), *m/e* 633 (M + H^+, 93%), *m/e* 655 (M + Na^+, 10%). Anal. (dried at 80 °C, 10^{-5} Torr, 12 h) Calcd for $C_{35}H_{44}N_4O_7$: C, 66.44; H, 7.01. Found: C, 66.27; H, 7.14.

1,1′-(2-Methoxy-1,3-phenylene)bis[tetrahydro-3-[2-methoxy-3-(bromomethyl)-5-methylphenyl]-2(1*H*)-pyrimidinone] (19). The bis(methoxymethyl) compound **18** (1.03 g, 1.6 mmol) was dissolved in $CHCl_3$. Hydrogen bromide gas was bubbled through the solution for 1 h. Water was added, and the layers were separated. The organic layer was dried ($MgSO_4$, for several min), and the solvent was removed in vacuo. This provided 1.06 g (91%) of **19**, isolated as a foam: R_f (silica gel, 5% CH_3OH in CH_2Cl_2) 0.4; MS (70 eV), *m/e* 730 (M^+); ^1H NMR (200 MHz, $CDCl_3$) δ 2.22–2.27 (s and m overlapping, 10 H, RNCH$_2$*CH*$_2$CH$_2$NR and Ar*CH*$_3$), 3.75 (m, 8 H, RN*CH*$_2$CH$_2$*CH*$_2$NR), 3.89 (s, 3 H, O*CH*$_3$), 3.96 (s, 6 H, O*CH*$_3$), 4.53 (s, 4 H, Ar*CH*$_2$Br), 7.08–7.12 and 7.20–7.24 (overlapping peaks, 7 H, ArH). This spectrum is identical with that of a sample of **19** prepared by a different method by Ho.[13] Anal. (dried at 80 °C, 10^{-5} Torr, 3 h) Calcd for $C_{33}H_{38}N_4Br_2O_5$: C, 54.26; H, 5.24. Found: C, 54.33; H, 5.27.

1,1′-(2-Methoxy-1,3-phenylene)bis[tetrahydro-3-(2-methoxy-3-(hydroxymethyl)-5-methylphenyl)-2(1*H*)-pyrimidinone] (20). The bis(benzyl bromide) **19** (1.53 g, 2.1 mmol) was dissolved in 140 mL of acetone. Sodium bicarbonate in 30 mL of water was added, and the mixture was stirred at reflux for 10 h. The acetone was removed in vacuo, CH_2Cl_2 was added, and the layers were separated. The organic layer was dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Compound **20** was obtained as a white solid (1.2 g, 93%): R_f (9:1 CH_2Cl_2–MeOH) 0.35; ^1H NMR was identical with that previously reported for **20** prepared by a different method[2g] (200 MHz, $CDCl_3$), 2.22–2.27 (s and m overlapping, 10 H, RNCH$_2$*CH*$_2$CH$_2$NR and Ar*CH*$_3$), 3.74 (m, 8 H, RN*CH*$_2$CH$_2$*CH*$_2$NR), 3.87 (s, 6 H, OCH$_3$), 3.90 (s, 3 H, O*CH*$_3$), 4.65 (br s, 4 H, Ar*CH*$_2$OH), 7.05–7.19 and 7.22–7.26 (overlapping peaks, 7 H, Ar*H*).

29,30,32-Trimethoxy-19,27-dimethyl-23-oxa-2,6,12,16-tetraazahexacyclo[23.3.1.1^{2,6}.1^{7,11}.1^{12,16}.1^{17,21}]tritriaconta-1(29),7,9,11(32),17,19,21-(30),25,27-nonaene-31,33-dione (1). Sodium hydride (0.4 g, 60% oil dispersion) in 300 mL of THF was stirred vigorously at reflux. Diol **20** (0.643 g, 1.06 mmol) was dissolved in 50 mL of THF and added to a syringe. Toluenesulfonyl chloride (0.203 g, 1.06 mmol) was dissolved in 50 mL of THF and added to a separate syringe. The contents of the two syringes were added to the above solution over 12 h via a syringe pump.

(13) Ho, S. P. Ph.D. Dissertation, Department of Chemistry and Biochemistry, University of California, Los Angeles, 1985.

When the addition was complete, additional toluenesulfonyl chloride (44 mg in 10 mL of THF) was added dropwise. The mixture was refluxed an additional 20 h and cooled to 25 °C, and water was carefully added. The THF was removed in vacuo, and the residue partitioned between CH_2Cl_2 and water. The organic extract was preabsorbed on 10 mL of reverse-phase silica gel and chromatographed through an additional 60 mL of this support, eluting with 1% (w/v) NaBr in 13:7 MeOH–H_2O. The fractions corresponding to the product were combined. Complex **1**·NaBr crystallized out of the column eluent upon partial evaporation of the solvent to provide 81 mg (11%) of material. A CH_2Cl_2 solution of **1**·NaBr was decomplexed by washing it five times with deionized water and evaporating the solvent to provide **1**: R_f (reverse-phase silica gel, 1% w/v NaBr in 13:7 CH_3OH–H_2O) 0.4; ^1H NMR (360 MHz, $CDCl_3$) δ 2.17 (s, 6 H, ArCH_3), 2.36 (br m, 4 H, RNCH$_2$$CH_2CH_2$NR), 3.81 (br m, 8 H, RN$CH_2CH_2$$CH_2$NR), 3.93 (s, 6 H, O$CH_3$), 3.97 (s, 3 H, O$CH_3$), 4.38 (br m, 2 H, Ar$CH_2$O), 4.73 (br m, 2 H, Ar$CH_2$O), 6.89–6.94 (overlapping peaks, ArH, 5 H), 7.07 (d, 2 H, ArH, J = 11 Hz); MS (FAB, NOBA), m/e 587 (M + H^+, 100%). Anal. (dried at 150 °C, 10^{-5} Torr, 3 h) Calcd for $C_{33}H_{38}N_{38}N_4O_6$: C, 67.56; H, 6.53. Found: C, 67.47; H, 6.58.

23-Thia-2,6,12,16-tetraazahexacyclo[23.3.1.1^{2,6}.1^{7,11}.1^{12,16}.1^{17,21}]tritriaconta-1(29),7,9,11(32),17,19,21(30),25,27-nonanene-31,33-dione, 29,30,32-Trimethoxy-19,27-dimethyl- (2). A suspension of Na_2S·9H_2O (0.876 g, 3.65 mmol) in 300 mL of absolute EtOH was vigorously stirred. The bis(benzyl bromide) **19** (0.812 g, 1.1 mol) was dissolved in 50 mL of absolute EtOH and added via a syringe pump over 20 h. The mixture was stirred an additional 24 h. The solvent was removed in vacuo and the residue partitioned between CH_2Cl_2 and H_2O. The organic extract was preabsorbed on 15 mL of reverse-phase silica gel and chromatographed through an additional 70 mL of this support, eluting with 1% (w/v) NaBr in 4:1 MeOH–H_2O. The complex, **2**·NaBr, crystallized upon partial evaporation of the column eluate. The cycle was decomplexed by washing a CH_2Cl_2 solution of **2**·NaBr five times with deionized water to give 0.142 g (21%) of **2** as a white solid: R_f (reverse-phase silica gel, 1% w/v NaBr in 4:1 CH_3OH–H_2O) 0.6; ^1H NMR (500 MHz, $CDCl_3$) δ 2.17 (s, 6 H, ArCH_3), 2.25–2.38 (br m, 4 H, RNCH$_2$$CH_2CH_2$NR), 3.80–4.20 (overlapping peaks, 21 H, OCH_3, RNCH_2CH$_2$$CH_2NR, ArCH_2SCH_2$Ar), 6.85 (s, 2 H, Ar$H$), 6.87 (s, 2 H, Ar$H$), 6.97 (t, 1 H, Ar$H$, J = 8 Hz), 7.10 (d, 2 H, ArH, J = 8 Hz); MS (FAB, NOBA), m/e 625 (M + Na^+, 100%), m/e 603 (M + H^+, 0.2%). Anal. (dried at 80 °C, 10^{-5} Torr, 6 h) Calcd for $C_{33}H_{38}SN_4O_5$: C, 65.76; H, 6.35. Found: C, 65.55; H, 6.28.

2,6,12,16-Tetraazahexacyclo[23.3.1.1^{2,6}.1^{7,11}.1^{12,16}.1^{17,21}]tritriaconta-1(29),7,9,11(32),17,19,21(30),25,27-nonaene-23,23-dicarboxylic Acid, 29,30,32-Trimethoxy-19,27-dimethyl-31,33-dione-, Diethyl Ester (3). Sodium hydride (0.4 g, 60% oil dispersion) in 500 mL of THF was stirred vigorously at reflux. Bis(benzyl bromide) **19** (1.106 g, 1.52 mmol) and diethyl malonate (0.23 mL, 1.52 mmol) were both dissolved in the same 80 mL of THF. The solution was added to the above mixture via a constant rate addition funnel over 5 h. The mixture was refluxed an additional 1 h and then cooled to 25 °C. After removal of the solvent under reduced pressure, CH_2Cl_2 and water were added, and the layers were separated. The organic residue was preabsorbed on 15 mL of reverse-phase silica gel and chromatographed through an additional 60 mL of this support, eluting with 1% (w/v) NaBr 3:1 MeOH–H_2O. Fractions corresponding to **3**·NaBr were combined, but a small impurity was present. Crystallization of **3**·NaBr from CH_2Cl_2/CCl_4 provided analytically pure complex (2%). The free host, **3**, was obtained by washing a CH_2Cl_2 solution of **3**·NaBr five times with deionized water; R_f (reverse-phase silica gel, 1% w/v NaBr in 4:1 CH_3OH–H_2O) 0.5. The ^1H NMR spectrum of the free cycle was useless due to many overlapping peaks, so that of **3**·NaBr is recorded: ^1H NMR (200 MHz, $CDCl_3$) δ 0.74 (t, 3 H, $CO_2CH_2CH_3$, J = 7 Hz), 1.46 (t, 3 H, $CO_2CH_2CH_3$, J = 7 Hz), 2.22 (s, 6 H, ArCH_3), 2.49 (br m, 4 H, RNCH$_2$$CH_2CH_2$NR), 3.35 (q, 2 H, $CO_2CH_2CH_3$, J = 7 Hz), 3.61, 3.71 (dd, 4 H, ArCH$_2$CH_2CH$_2$Ar, J = 9 Hz), 4.02 (m, 8 H, RNCH_2CH$_2$$CH_2$NR), 4.22 (s, 6 H, O$CH_3$), 4.31 (s, 3 H, O$CH_3$), 4.45 (q, 2 H, $CO_2CH_2CH_3$, J = 7 Hz), 6.93–7.31 (overlapping peaks, 7 H, ArH); R_f (reverse-phase chromatography on silica gel, 1% w/v NaBr in 4:1 CH_3OH–H_2O) 0.5; MS (FAB, NOBA), m/e 751 (M + Na^+, 100%), 729 (M + H^+, 0.2%). Analysis (dried at 80 °C, 10^{-5} Torr, 3 h) of uncomplexed **3**. Calcd for $C_{40}H_{48}N_4O_9$: C, 65.92; H, 6.64. Found: C, 65.90; H, 6.71.

9*H*,19*H*,28*H*-8,12:18,22-Dimethano-3,7:13,17:23,27-trimetheno-2*H*-1,29,8,12,18,22-benzodioxatetraazacyclohentriacontine-35,37-dione, 10,11,20,21-Tetrahydro-34,36,38-trimethoxy-5,25-dimethyl- (4). Sodium hydride (0.3 g, 60% oil dispersion) in 500 mL of THF was stirred vigorously at reflux. Dry catechol (0.156 g, 1.4 mmol) and bis(benzyl bromide) **19** (1.1 g, 1.4 mmol) were dissolved in 150 mL of THF and added to the reaction mixture via a constant rate addition funnel over 20 h. The reaction was refluxed an additional 24 h and cooled, and the solvent was removed in vacuo. The residue was partitioned between CH_2Cl_2 and water. The layers were separated and the CH_2Cl_2 was evaporated. The residue was preabsorbed on 15 mL of reverse-phase silica gel and chromatographed through an additional 70 mL of this support, eluting with 1% (w/v) NaBr in 4:1 MeOH–H_2O. Product crystallized out of the reverse-phase eluent upon partial evaporation of the solvent to give 0.18 g (19%) of **4**·NaBr. This material was decomplexed by washing a CH_2Cl_2 solution of it five times with deionized water; R_f (reverse-phase silica gel, 1% w/v NaBr in 4:1 CH_3OH–H_2O) 0.5; ^1H NMR (200 MHz, $CDCl_3$) δ 2.17 (s, 6 H, ArCH_3), 2.29 (br m, 4 H, RNCH$_2$$CH_2CH_2$NR), 3.78–4.01 (br m, 8 H, RNCH_2CH$_2$$CH_2$NR), 3.78 (s, 3 H, O$CH_3$), 3.87 (s, 6 H, O$CH_3$), 4.66 (d, 2 H, Ar$CH_2$O, J = 9 Hz), 5.12 (d, 2 H, ArCH_2O, J = 9 Hz), 6.96–7.20 (overlapping peaks, ArH, 11 H); MS (FAB, NOBA) m/e 701 (M + Na^+, 100%), 679 (M + H^+). Anal. (dried at 110 °C, 10^{-5} Torr, 3 h) Calcd for $C_{39}H_{42}N_4O_7$2H_2O: C, 65.53; H, 6.49. Found: C, 65.12; H, 6.37.

Binding Studies. Volumetric flasks were washed with chromerge, aqueous ammonium hydroxide, and deionized water. Deuteriochloroform (minimum isotopic purity 99.96%) was saturated with D_2O. Stock solutions of **1**·sodium picrate, **2**·sodium picrate, and **22** were prepared by dissolving the appropriate amount in D_2O-saturated $CDCl_3$ to give 2.65 mM solutions. Aliquots (400 μL) of free host and complexed host were mixed in an NMR tube. The ^1H NMR spectra were taken at periods of 1–2 h, 24 h, and 2 weeks. Only slight changes (~10%) occurred in the position of the equilibria in each experiment after 1–2 h. After 24 h equilibration was complete, and no further change in the ratio of peaks was observed after that time and for up to 2 weeks. A relaxation delay of 5 s was used to ensure complete relaxation of all protons. The ^1H NMR signals for free and complexed forms of **22** at 2.85 and 2.95 ppm were distinguished and integratable. The integral of these peaks along with those of the picrate peak at 8.76 ppm were used to calculate the association constants.[8,9] Similar experiments were conducted involving **1**·lithium picrate and uncomplexed **21**.[8] Integrals of the aryl hydrogens of free and complexed **21** at 7.34 and 7.56 ppm (respectively) and of the picrate peak at 8.77 ppm were used to follow the equilibration for 2 weeks. The values of K_a and $-\Delta G°$ for **1** complexing lithium picrate were calculated from the known values for **21** complexing lithium picrate and these integrals.[8,9]

Crystal Structure Data. All structures except **10**·H_2O were examined at 25 °C, and all were determined by direct methods.

Compound **1** crystallized from CH_2Cl_2/CCl_4 as colorless parallelepipeds in the monoclinic system $P2_1/a$. Unit cell dimensions are as follows: a = 31.240 (3) Å, b = 9.845 (1) Å, c = 13.183 (1) Å, β = 92.134 (3)°, V = 4061 Å^3, Z = 4. The crystal was examined on a diffractometer constructed by Professor C. E. Strouse of this department, with Mo Kα radiation. Refinement of 232 parameters (1893 reflections >3$\sigma(I)$) has an agreement value, R, currently at 0.20. The crystal contains two molecules of CH_2Cl_2 per molecule of **1**.

Complex **1**·sodium picrate crystallized from CH_2Cl_2/CH_3OH as yellow parallelepipeds in the orthorhombic system *Pcab* (standard setting *Pbca*). Unit cell dimensions are as follows: a = 12.290 (2) Å, b = 23.982 (3) Å, c = 26.914 (4) Å, V = 7933 Å^3, Z = 8. The crystal was examined on a modified Picker FACS-1 diffractometer, with Mo Kα radiation. Refinement of 256 parameters (2193 reflections >3$\sigma(I)$) has an agreement value currently at 0.19.

Complex **2**·$NaSbF_6$ crystallized from acetone–H_2O as colorless plates in the monoclinic system $P2_1/n$. Unit cell dimensions are as follows: a = 16.607 Å, b = 8.9715 (7) Å, c = 25.328 (2) Å, β = 98.419 (4)°, V = 3733 Å^3, Z = 4. The crystal was examined on a diffractometer constructed by Professor C. E. Strouse with Mo Kα radiation. Refinement of 255 parameters (1770 reflections >2$\sigma(I)$) has an agreement value currently at 0.10.

Compound **4**·2CH_3OH crystallized from CH_3OH–CH_2Cl_2 as colorless parallelepipeds in the monoclinic system $P2_1/c$. Unit cell parameters are as follows: a = 12.160 (2) Å, b = 22.798 (4) Å, c = 14.283 (2) Å, β = 111.120 (6)°, V = 3694 Å^3, Z = 4. The crystal was examined on a modified Syntex P$\bar{1}$ diffractometer with Cu Kα radiation. Refinement of 287 parameters (2501 reflections >3$\sigma(I)$) has an agreement value currently at 0.10. A methanol is hydrogen bonded to an oxygen of a cyclic urea group. A second methanol is disordered and is located between host molecules.

Compound **10**·H_2O was crystallized from EtOH–H_2O as colorless parallelepipeds in the orthorhombic system $P2_12_12_1$. Unit cell dimensions are as follows: a = 11.527 (1) Å, b = 15.023 (2) Å, c = 17.691 (2) Å, V = 3064 Å^3, Z = 4. The crystal was examined at 128 K on a locally modified Picker FACS 1 diffractometer with Mo Kα radiation. Refinement of 195 parameters (2296 reflections >3$\alpha(I)$) has an agreement value of 0.05. The host is hydrogen bonded to water at the oxygens of the two urea groups. Further crystallographic details will be published elsewhere.