Host–Guest Complexation. 28. Hemispherands with Four Self-Organizing Units[1]

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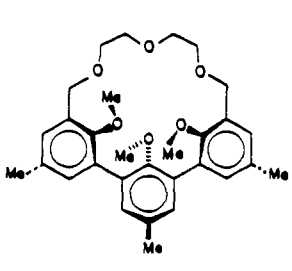
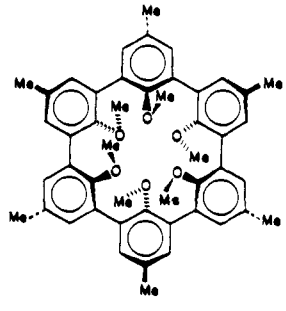
Abstract: Twenty new hemispherands and two open-chain analogues have been synthesized and examined for their differential binding properties toward the alkali metal and ammonium ions. All new hosts contain four self-organizing methoxybenzene or ethoxybenzene units attached to one another, and at their ends they are attached to other units. These units and their points of attachment are symbolized by the letters under their structures in Chart I. The macrocyclic host structures are indicated by the letter sequences. They are classified by macroring size: 18 membered, $A(CH_2O)_2E$ (**1**), $A(CH_2O)_2F$ (**2**), $B(CH_2O)_2F$ (**3**), $A(CH_2O)_2J$ (**4**), $A(CH_2O)_2K$ (**5**); 19 membered, $A(CH_2O)_2P$ (**6**), $B(CH_2O)_2P$ (**7**), $A(CH_2O)_2L$ (**8**); 20 membered, $A(CH_2O)_2M$ (**9**), $A(CH_2O)_2N$ (**10**); 21 membered, $A(CH_2OE)_2O$ (**11**), $B(CH_2OE)_2O$ (**12**), $A(CH_2OCH_2)_2T$ (**13**), $B(CH_2OCH_2)_2T$ (**14**), $A(CH_2OCH_2)_2Py$ (**15**), $A(CH_2OE)_2S$ (**16**), $A(CH_2OE)_2SO$ (**17**), $A(CH_2OE)_2SO_2$ (**18**); 22 membered, $A(UCH_2)_2F$ (**19**) and $A(CH_2U)_2V$ (**20**). Two open-chain systems were also prepared, $A(UH)_2$ (**21**) and $A(UCH_3)_2$ (**22**). All of these hosts were synthesized through HO_2CACO_2H (**23**) or HO_2CBCO_2H (**24**) as key intermediates, which in turn were prepared from dibenzofuran. The critical ring-closing reaction yields varied from a low of 11% for $A(UCH_2)_2V$ (**20**) to a high of 55% for $A(CH_2OE)_2O$ (**11**). These reactions involved $BrCH_2ACH_2Br$ or $BrCH_2BCH_2Br$ reacting in base with either nitrogen or oxygen nucleophiles. Association constants (K_a) between host and guest to give complexes were determined by extracting picrate salts (guests) from D_2O into $CDCl_3$ in the absence and presence of hosts at 25 °C. The free energies for complexation for the 22 hosts with the picrate salts of Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and t-$BuNH_3^+$ were calculated. These $-\Delta G°$ values (kcal mol^{-1}) ranged from a high of 13.5 to a low of <5. Interesting selectivity ratios for a host distinguishing between two similar guests ($K_a^G/K_a^{G'}$) are as follows: Na^+/Li^+, $A(CH_2O)E$, 4×10^4; Na^+/K^+, $A(CH_2O)E$, 120; K^+/Na^+, $B(CH_2OE)_2T$, 2×10^3; K^+/Rb^+, $A(CH_2O)_2E$, 60; Rb^+/K^+, $A(CH_2OE)_2Py$, 2; Rb^+/Cs^+, $A(CH_2O)_2M$, 11; Cs^+/Rb^+, $A(CH_2U)_2V$, ~1, $NH_4^+/CH_3NH_3^+$, $A(CH_2O)_2F$, 210; $CH_3NH_3^+/t$-$BuNH_3^+$, $A(CH_2OCH_2)T$, 3×10^3. Correlations between structures of hosts and guests and their free energies of binding are interpreted in terms of the principles of complementarity and of preorganization. The use of A as a potentially chiral unit in hosts has been examined through use of ^1H NMR techniques. The energy barrier for ring inversion of three of the anisole units of the 18-membered ring host $A(CH_2O)_2K$ (**5**) at ambient temperature is >21 and <27 kcal mol^{-1}. Ring inversion in complexed host can occur only by dissociation. Dynamic ^1H NMR techniques were used to estimate decomplexation rate constants of potassium picrate complexes of $A(CH_2O)_2F$ (**2**), $A(CH_2O)_2P$ (**6**), $A(CH_2O)_2L$ (**8**), and $B(CH_2OE)_2O$ (**12**) at 25 °C in $CDCl_3$ saturated with D_2O. They varied from 4 to 27 s^{-1}. These and the association constant were used to estimate the association rate constants. They varied from 10^7 to 10^9 (mol^{-1} s^{-1}).

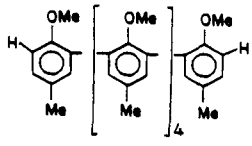
Hemispherands have been defined as hosts, at least half of whose structures are composed of units unable to fill their own potential cavities by conformational reorganizations. The binding properties have been reported for several such hosts, of which **25** is a prototype.[2,3] This macrocycle contains three contiguous anisyl units, whereas others contain cyclic urea units substituted for the central anisyl unit.[4] These 18-membered macrocycles were completed with conformationally mobile $(CH_2OCH_2)_3$ units or their equivalents. As hosts, they are somewhat stronger binding and more discriminating toward the alkali metal ions than chorand 18-crown-6 and its analogues.[5]



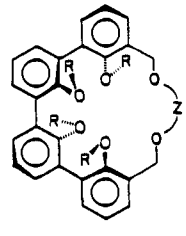
25



26



27, $H(p\text{-}CH_3C_6H_2OCH_3)_6H$



28

Although anisyl units are intrinsically poor ligands for metal ions, the relatively rigid placements of their oxygens during synthesis rather than during complexation are undoubtedly responsible for the enhanced binding and selectivity of the hemispherands. The effect of preorganization is dramatically illustrated by the fact that the full spherand **26** binds Li^+ by >17 kcal mol^{-1} more than its open-chain analogue **27** and Na^+ by >13 kcal mol^{-1}. The former is perfectly organized to bind these ions during its synthesis and is not conformationally changed during complexation. The latter possesses over 1000 conformations, only two of which allow all six oxygens to act cooperatively.[6]

This paper reports the synthesis and binding properties of a series of hemispherands that possess the general structures **28**, in which R is methyl or ethyl and Z consists of the units formulated in Chart I. Macrocycles **1**–**20** and two open-chain analogues, **21** and **22**, as well as some intermediates, will be identified in line formulas composed of sequences of letters that signify the kinds and points of attachment of the various units that complete the structures. Hosts **28** contain four contiguous anisyl-type units

(1) Support for the research involving hosts **1**, **3**, **4**, **6**–**8**, and **11**–**20** by the Department of Energy, Contract AT(04-3) is gratefully acknowledged. We thank the National Science Foundation, Grant NSF CHE 81-09532, for support of the research involving hosts **2**, **5**, **9**, and **10**.

(2) Koenig, K. E.; Lein, G. M.; Stückler, P.; Kaneda, T.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3553-3566.
(3) Cram, D. J.; Moran, J. R.; Maverick, E. F.; Trueblood, K. N. *J. Chem. Soc., Chem. Commun.* **1983**, 647-648.
(4) Cram, D. J.; Dicker, I. B.; Lein, G. M.; Knobler, C. B.; Trueblood, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 6827-6828.
(5) Cram, D. J.; Trueblood, K. N. *Top. Curr. Chem.* **1981**, *98*, 43-106.
(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.

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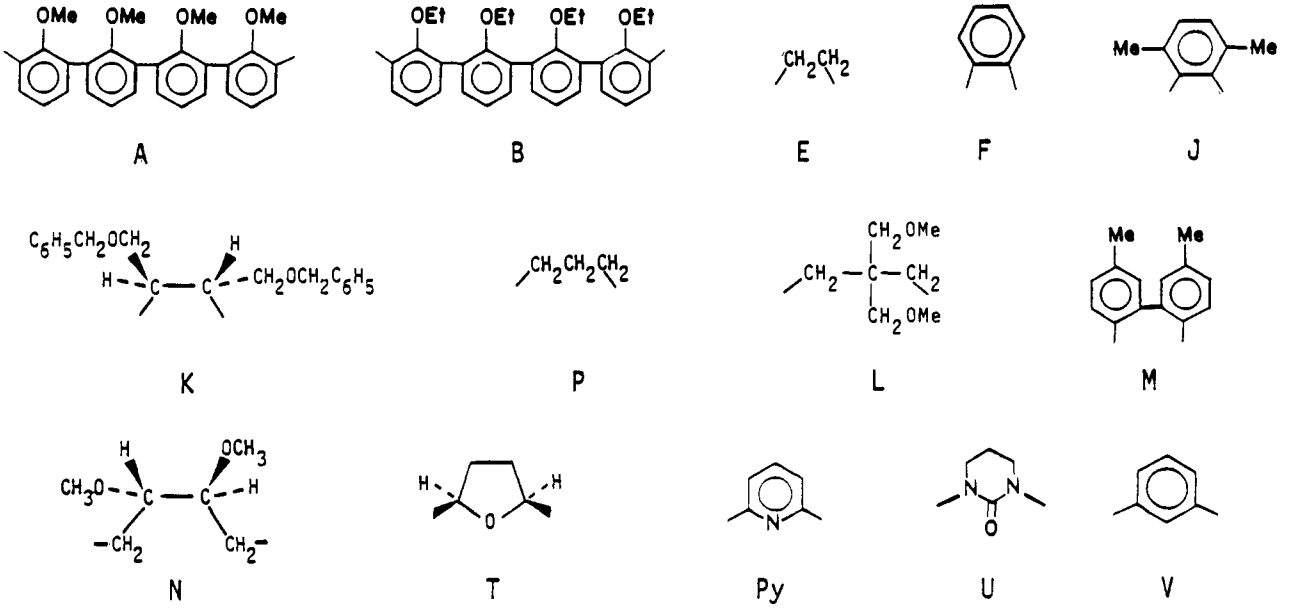
Chart I



which in CPK molecular models appear to possess the conformations drawn, which are particularly enforced when the Z chains are two to four atoms in length. Spherand **26** is extremely ion selective, but the *extraction rates* of guests from water into chloroform solution of hosts such as **26** are slow. In homogeneous media ($CDCl_3$), complexation rates are fast. Hemispherand **25** is much less ion selective, but its extraction rates are relatively high.[5] We had hoped that compounds **28** would exhibit high ion selectivity as well as fast extraction rates.

A second desirable feature of hosts such as **28** is their chirality. Molecular models (CPK) of **28** with Z bridges of two- to four-atom chains appear to have the enforced conformation for the anisyl-like units drawn in general structure **28**. In this conformation, the tetraaryl unit is chiral, contains a C_2 axis, and can undergo enantiomerization only by three of the four alkoxy units passing through the middle of the ring. The temperatures at which enantiomers of **28** interconvert should be a function of the length and rigidity of the Z chain and the bulk of the R groups. If the Z element also contains a C_2 axis, the compounds are nonsided. By varying the character of R and Z, **28** is subject to extensive tailoring to provide a chiral environment for carbanions ion paired with bound metal cationic guests. Previous work demonstrated that weakly binding hosts containing binaphthyl chiral elements act as turnover catalysts in Michael additions to convert prochiral starting materials into chiral products of very high enantiomeric purity.[7]

Results

Syntheses. Dibenzofuran was monometallated with *n*-butyllithium, and the resulting organometallic was oxidatively coupled with $Fe(acac)_3$ to give **29**[8] (70%) (Scheme I).[9] This compound was dilithiated with *n*-butyllithium, and the resulting organometallic was carbonated to provide diacid **30** (~100%). The two furan rings of **30** were opened in molten NaOH–KOH to give after acidification the diacid tetraphenol, **31** (95%). This tetraphenol when methylated ($(CH_3)_2SO_4$–K_2CO_3) went to **32** (74%), whose carboxyls were reduced ($BH_3 \cdot O(CH_2)_4$) to give diol **33** (77%), which when treated with PBr_3 provided dibromide **34** (80%). Similarly, **31** was ethylated (EtI–K_2CO_3) to give **36** (72%), which was reduced to diol **37** (78%), which in turn was brominated to provide dibromide **38** (80%).

The macrocyclic rings were closed by slowly adding a mixture of the appropriate diol and dibromide (either **34** or **38**) to a refluxing suspension of NaH in $(CH_2)_4O$ under conventional high dilution conditions. Table I lists the reactants, products, and yields of the macrocycles prepared in this manner. Sulfide $A(CH_2OE)_2S$ (**16**) was oxidized to its corresponding sulfoxide, $A(CH_2OE)_2SO$ (**17**, 67%), and to its sulfone, $A(CH_2OE)_2SO_2$ (**18**, 79%). Diacid **32** through its bis(acid chloride) was converted to its diazide, which was subjected to a Curtius rearrangement. The resulting bisisocyanate mixed with $H_2N(CH_2)_3Br$ gave the bisurea **35** ($A[NHCONH(CH_2)_3Br]_2$ 61% overall), which when treated with KOBu-*t* gave $A(UH)_2$ (**21**, 78%). Methylation of **21** with CH_3I–NaH gave $A(UCH_3)_2$ (**22**, 66%). Cyclization of $A(UH)_2$ with *o*-$C_6H_4(CH_2Br)_2$ by the same procedure applied to the diols gave $A(UCH_2)_2F$ (**19**, 40%). Treatment of 1,3-diaminobenzene with $OCN(CH_2)_3Cl$ gave the bisurea $V[NHCONH(CH_2)_3Cl]_2$, which when doubly ring closed with KOBu-*t* gave $V(UH)_2$ (**39**, 94% overall).[10] Cyclization of $BrCH_2ACH_2Br$ with $V(UH)_2$ by the standard procedure produced macrocycle $A(CH_2U)_2V$ (**20**, 11%). Attempts to ring close $A(UH)_2$ with $ClCH_2Br$, $C_6H_5POCl_2$, ClCOCOCl, and $C_6H_5CHBr_2$ and base failed to provide isolable macrocycles.

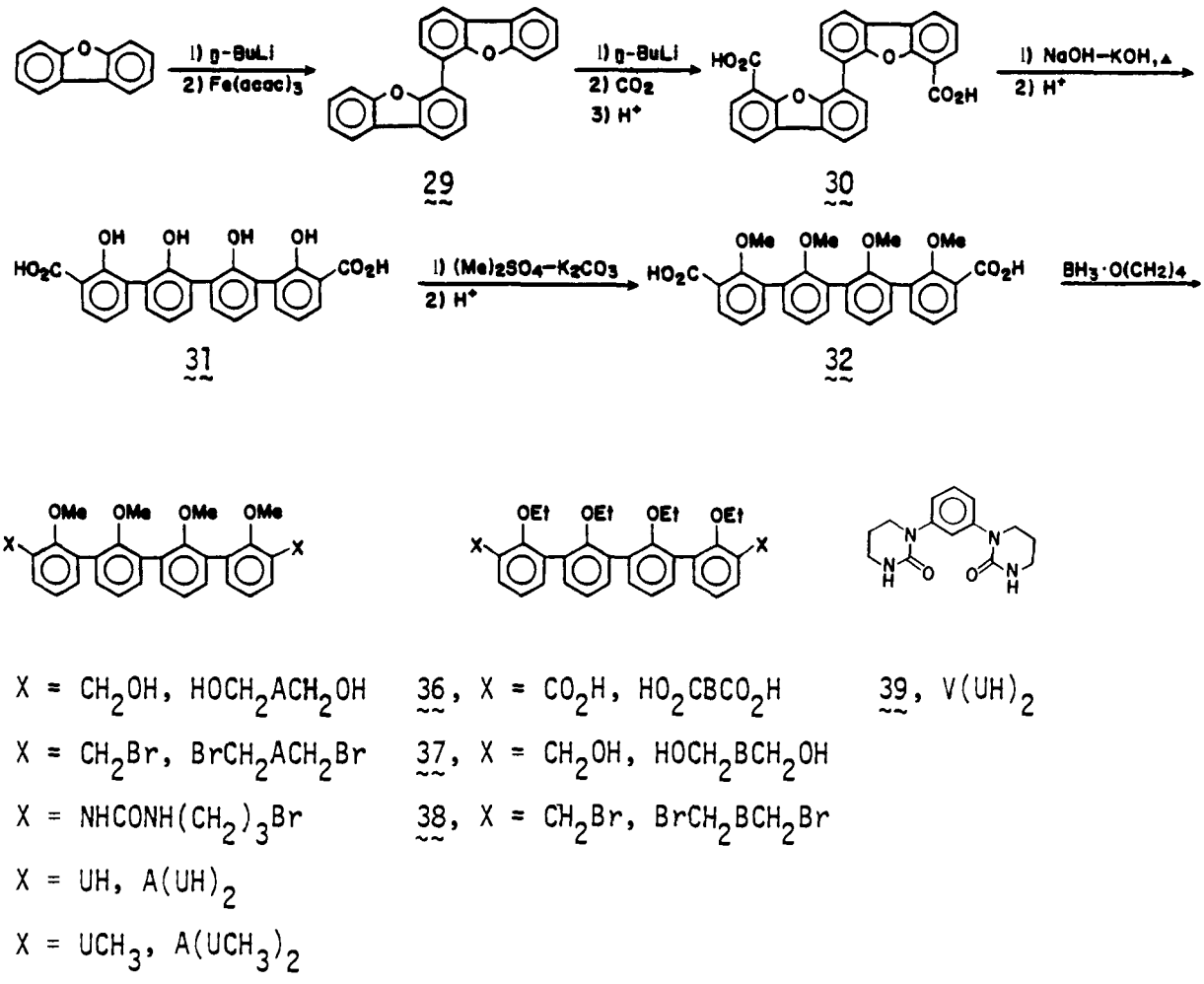
Complexation Properties. The association constants (K_a) and free energies of association ($-\Delta G°$) of cyclic hosts **1**–**20** and open-chain systems **21** and **22** in $CDCl_3$ saturated with D_2O at 25 °C were measured by the picrate extraction method.[11,12] Solutions of Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and $(CH_3)_3CNH_3^+$ picrates in D_2O were extracted with $CDCl_3$ in the absence and presence of host. The hosts and their complexes are soluble essentially only in the $CDCl_3$ layer. The K_a and $-\Delta G°$ values at 25 °C in $CDCl_3$ saturated with D_2O were calculated from the results and are found in Table II along with the detailed structures and line formulas of the hosts. This method provided precisions in $-\Delta G°$ values that vary between ±1.4 and ±3.1%. The results are the average of two determinations.

Discussion

Correlation of Structure with Binding Free Energy. The structure-binding free energy relationships will be discussed in terms of the principle of complementarity and the principle of preorganization. The principle of complementarity states that "in complexes of substantial stability, binding sites of host and guest components must simultaneously contact and attract one

(7) Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625–628.
(8) Gilman, H.; Weipert, E. A.; Dietrich, J. J.; Hayes, F. N. *J. Org. Chem.* **1958**, *23*, 361–362.
(9) We warmly thank Dr. M. Lauer for developing this procedure.
(10) We warmly thank Dr. R. J. M. Nolte for preparing this compound (see Experimental Section).
(11) 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.
(12) Lein, G. M.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1982**, 301–304.

Scheme I



another." The principle of preorganization states that "the more highly hosts and guests are organized for binding and for low solvation *prior* to their complexation, the more stable will be their complexes". Although these principles are intuitively obvious and are implicit in many discussions of complexation,[5,6] their central importance to the design of host–guest relationships justifies their explicit statement.

Of the hosts of this study, those containing 18-membered rings (**1–5**) exhibit both the highest $-\Delta G°$ values and, generally, the most discrimination between the guest ions studied. Molecular model (CPK) examinations of **1–5** suggest that the methyl or ethyl groups attached to the aryl oxygens possess the self-organizing (during synthesis) up–down–up–down arrangement formulated in Table I. Alternative arrangements appear highly strained sterically. However, the benzylmethylenes in the macrocycles of **1–5** and even one of the methylenes of the CH_2CH_2 group in $A(CH_2O)_2E$ (**1**) can easily turn inward to fill the cavity in these uncomplexed hosts. Thus the A units appear preorganized, but parts of the remaining units are conformationally mobile in these noncomplexed hosts. The ^1H NMR spectra of **1–5** are compatible with these structural predictions. Unfortunately, crystals suitable for X-ray diffraction study have not yet come to hand. However, the crystal structure host **25**, an 18-membered ring analogue of **1**, showed the three anisyl units to possess the indicated up–down–up structure, with the cavity filled with inward turned CH_2 groups of the aliphatic bridge.[5]

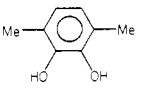
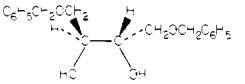
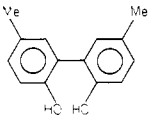
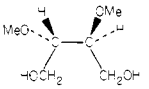
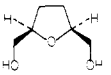
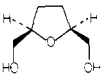
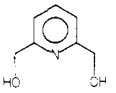
Host $A(CH_2O)_2E$ (**1**) is the strongest binder of Na^+ and shows the greatest discrimination for this ion. The $-\Delta G°$ values (kcal mol^{-1}) are as follows: Li^+, 7.2; Na^+, 13.5; K^+, 10.7; Rb^+, 8.4; Cs^+, 7.1; NH_4^+, 8.7; $CH_3NH_3^+$, 6.2; t-$BuNH_3^+$, <5.0. Thus **1** binds Na^+ 6.3 kcal mol^{-1} (factor of 4×10^4) better than Li^+ and 2.8 kcal mol^{-1} better than K^+ (factor of 116). Molecular models of **1** in the conformation drawn show its cavity diameter to be in the 1.8–2.0 Å range, and thus complementary to that of Na^+. In models, Li^+ can contact simultaneously only three to four of the oxygens and K^+ can nest in the cavity, but only by deforming the benzene rings and other bond angles. This host favors K^+ over Rb^+ by 2.3 kcal mol^{-1} (factor of 43) and Rb^+ over Cs^+ by 1.3 kcal mol^{-1} (factor of 10). Models indicate these ions to be too big to nest in the cavity. Rather they perch on four of the oxygens. The NH_4^+ ion is favored over $CH_3NH_3^+$ by 1.5 kcal mol^{-1}, which in turn is favored as a guest over t-$BuNH_3^+$ by > 1.2 kcal mol^{-1}.

As expected form model examination, $A(CH_2O)_2E$ (**1**) is more preorganized, more strongly binding, and more discriminating in its binding than its three anisyl unit analogue, **25**. That host best binds Na^+ (12.2 kcal mol^{-1}) and K^+ next to the best (11.8 kcal mol^{-1}).[4] In contrast, the fully preorganized spherand only binds Li^+ and Na^+ (>23 and 19.2 kcal mol^{-1}, respectively).[12]

The other four hosts that contain 18-membered rings show similar patterns but are less discriminating and not as strong binders. Substitution of *o*-phenylene unit F for the CH_2CH_2 unit (E) of **1** provides $A(CH_2O)_2F$ (**2**), which is the most similar to **1**. Substitution of the methyl groups of **2** with ethyl groups of $B(CH_2O)_2F$ (**3**) resulted in a generally similar pattern except that the larger ions were somewhat more strongly bound than in the methyl analogue, $A(CH_2O)_2F$ (**2**). Apparently ethyl–ethyl repulsions slightly expand the cavity. The two methyls ortho to the oxygens on the *o*-phenylene unit of $A(CH_2O)_2J$ (**4**) strongly inhibit binding by deforming the cavity (CPK model examination), but the system still discriminates between Na^+ and K^+. This discrimination is lowered somewhat in $A(CH_2O)_2K$ (**5**), possibly because the side-chain oxygens are involved in complexing the larger ion.

The three 19-membered ring hosts, $A(CH_2O)_2P$ (**6**), $B(CH_2O)_2P$ (**7**), and $A(CH_2O)_2L$ (**8**) are both poor and nondiscriminating ligand systems. In models, the conformations of CH_2C-

Table I. Reactants, Products, Yields, and Ring Sizes of Products

reactants			products		
dibromide or sulfide	nucleophile or oxidant	structure	no.	yield, %	ring size
$BrCH_2ACH_2Br$	$HOCH_2CH_2OH$	$A(CH_2O)_2E$	**1**	13	18
$BrCH_2ACH_2Br$	*o*-HOC_6H_4OH	$A(CH_2O)_2F$	**2**	38	18
$BrCH_2BCH_2Br$	*o*-HOC_6H_4OH	$B(CH_2O)_2F$	**3**	52	18
$BrCH_2ACH_2Br$		$A(CH_2O)_2J$	4	16	18
$BrCH_2ACH_2Br$		$A(CH_2O)_2K$	5	46	18
$BrCH_2ACH_2Br$	$HOCH_2CH_2CH_2OH$	$A(CH_2O)_2P$	6	34	19
$BrCH_2BCH_2Br$	$HOCH_2CH_2CH_2OH$	$B(CH_2O)_2P$	7	44	19
$BrCH_2ACH_2Br$	$(CH_3OCH_2)_2C(CH_2OH)_2$	$A(CH_2O)_2L$	8	54	19
$BrCH_2ACH_2Br$		$A(CH_2O)_2M$	9	49	20
$BrCH_2ACH_2Br$		$A(CH_2O)_2N$	10	54	20
$BrCH_2ACH_2Br$	$O(CH_2CH_2OH)_2$	$A(CH_2OE)_2O$	11	55	21
$BrCH_2BCH_2Br$	$O(CH_2CH_2OH)_2$	$B(CH_2OE)_2O$	12	51	21
$BrCH_2ACH_2Br$		$A(CH_2OCH_2)_2T$	13	24	21
$BrCH_2BCH_2Br$		$B(CH_2OCH_2)_2T$	14	27	21
$BrCH_2ACH_2Br$		$A(CH_2OCH_2)_2Py$	15	36	21
$BrCH_2ACH_2Br$	$S(CH_2CH_2OH)_2$	$A(CH_2OE)_2S$	16	45	21
$A(CH_2OE)_2S$	*m*-$ClC_6H_4CO_3H$	$A(CH_2OE)_2SO$	17	67	21
$A(CH_2OE)_2S$	*m*-$ClC_6H_4CO_3H$	$A(CH_2OE)_2SO_2$	18	79	21
o-$C_6H_4(CH_2Br)_2$	$A(UH)_2$	$A(UCH_2)_2F$	19	40	22
$BrCH_2ACH_2Br$	$V(UH)_2$	$A(CH_2U)_2V$	20	11	23

H_2CH_2 units in **6** and **7** can be anti in the uncomplexed state but must become gauche to open up the cavity for complexation. Expanding the macrorings by one member (from 18 to 19) results in K^+ being the favored guest rather than Na^+.

The two 20-membered ring hosts, $A(CH_2O)_2M$ (**9**) and $A(CH_2O)_2N$ (**10**), show peak binding with K^+ but are less discriminating than **1–3** and **5**. Models suggest that the biphenyl unit of $A(CH_2O)_2M$ (**9**) rigidifies the host in a conformation reasonably conducive to binding, whereas in $A(CH_2O)_2N$ (**10**) a methoxyl of the $CH_2CH(OCH_3)CH(OCH_3)CH_2$ unit occupies the cavity and must be driven out during complexation. As a result, **9** is the better binder of the two.

The 21-membered ring hosts, **11–15**, share the following features. They all show peak binding with Rb^+ or K^+ at about the 10–12 kcal mol^{-1} level and favor K^+ over Na^+ by at least 1.5 kcal mol^{-1} ($A(CH_2OCH_2)_2Py$, **15**) and by as much as 4.5 kcal mol^{-1} (factor of 2000 for $B(CH_2OCH_2)_2T$ (**14**)). They show little discrimination between the larger ions K^+, Rb^+, Cs^+, and NH_4^+. They favor NH_4^+ over $CH_3NH_3^+$ by 0.8–1.5 kcal mol^{-1} but discriminate between $CH_3NH_3^+$ and *t*-$BuNH_3^+$, favoring the former by 4.6–4.8 kcal mol^{-1} (factor of 3200 for $A(CH_2OCH_2)_2T$, **13**). Thus at the two ends of the scale of guest size, these hosts show handsome structural recognition factors, but not in the middle of the scale.

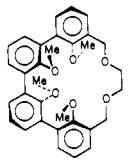
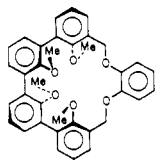
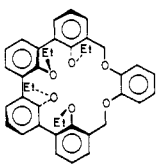
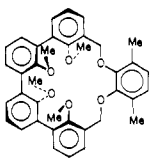
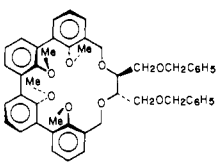
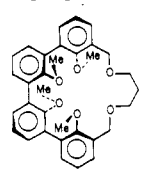
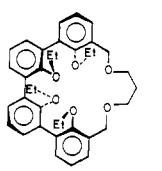
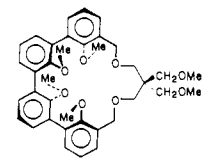
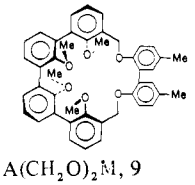
Molecular models show these hosts to be very conformationally mobile, particularly $A(CH_2OE)_2O$ (**11**) and $B(CH_2OE)_2O$ (**12**). Their cavity sizes match or adapt well to the diameters of the ions they bind well but very poorly to Li^+, Na^+, and *t*-$BuNH_3^+$. Models of $A(CH_2OCH_2)_2T$ (**13**) and $B(CH_2OCH_2)_2T$ (**14**) are both rigidified by the presence of the *cis*-tetrahydrofuran (T) unit and bind better and somewhat more discriminatingly than $A(CH_2OE)_2O$ (**11**) and $B(CH_2OE)_2O$ (**12**). Substitution of ethyl for methyl groups in two sets of hosts (**11** vs. **12**, or **13** vs. **14**) has the effect of increasing the discrimination for K^+ over Na^+ by a substantial amount. It is harder to compress the oxygens carrying four ethyl groups than those carrying four methyls to accommodate the relatively small diameter of Na^+. Host $A(CH_2OCH_2)_2Py$ (**15**) is a poorer and less discriminating binder than the "all oxygen" systems, in spite of its containing the rigidifying pyridyl group.

The three sulfur-containing hosts, **16–18**, also contain 21-membered rings. They are all relatively poor binders, peak with K^+ as guest, and exhibit only low selectivity. Although the sulfoxide unit of $A(CH_2OE)_2SO$ (**17**) is undoubtedly an intrinsically good ligand for K^+, this host is poorer at binding than either its companion sulfide, $A(CH_2OE)_2S$ (**16**), or its sulfone, $A(CH_2OE)_2SO_2$ (**18**). The poorer binding properties of $A(CH_2OE)_2SO$ (**17**) illustrate in a negative way the principle of preorganization. The bridge of **17** contains a multitude of nonbinding conformations which must be frozen out to provide a nest for a guest in the cavity.

Hosts **19–22** contain the cyclic urea unit (U), which when organized as parts of 19-membered rings in spherands provides some of the most Li^+- and Na^+-selective ligand systems known.[13] Compound $A(UCH_2)_2F$ (**19**) is 22-membered, and in models is

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

Table II. 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

host structure	guest cation	K_a, M^{-1}	$-\Delta G°$, kcal mol^{-1}
	Li	2.0×10^5	7.2
	Na[a]	8.0×10^9	13.5
	K	6.9×10^7	10.7
	Rb	1.6×10^6	8.4
	Cs	1.6×10^5	7.1
	NH_4	2.3×10^6	8.7
	CH_3NH_3	3.6×10^4	6.2
$A(CH_2O)_2E$, **1**	*t*-$BuNH_3$		<5
	Li	1.7×10^5	7.1
	Na	4.1×10^9	13.1
	K	1.1×10^8	11.0
	Rb	6.7×10^6	9.3
	Cs	9.0×10^5	8.1
	NH_4	5.5×10^6	9.2
	CH_3NH_3	6.9×10^4	6.6
$A(CH_2O)_2F$, **2**	*t*-$BuNH_3$		<5
	Li	1.6×10^5	7.1
	Na[a]	1.6×10^9	12.5
	K[a]	4.2×10^8	11.8
	Rb	4.0×10^7	10.4
	Cs	3.4×10^6	8.9
	NH_4	2.3×10^7	10.0
	CH_3NH_3	2.0×10^5	7.2
$B(CH_2O)_2F$, **3**	*t*-$BuNH_3$		<5
	Li	1.8×10^4	5.8
	Na	1.0×10^7	9.6
	K	1.4×10^5	7.0
	Rb	3.3×10^4	6.2
	Cs	1.7×10^4	5.8
	NH_4		<5
	CH_3NH_3	7.3×10^3	5.3
$A(CH_2O)_2J$, **4**	*t*-$BuNH_3$		<5
	Li	4.1×10^4	6.3
	Na	1.0×10^9	12.3
	K	4.7×10^7	10.5
	Rb	3.3×10^6	8.9
	Cs	3.7×10^5	7.6
	NH_4	4.4×10^6	9.1
	CH_3NH_3	9.0×10^4	6.8
$A(CH_2O)_2K$, **5**	*t*-$BuNH_3$		<5.0
	Li	1.2×10^5	5.6
	Na	1.4×10^5	7.0
	K	5.5×10^5	7.8
	Rb	3.2×10^4	6.2
	Cs	2.5×10^4	6.0
	NH_4	7.7×10^4	6.7
	CH_3NH_3	9.3×10^3	5.4
$A(CH_2O)_2P$, **6**	*t*-$BuNH_3$		<5
	Li	1.2×10^4	5.6
	Na	1.4×10^4	5.6
	K	5.0×10^4	6.4
	Rb	2.5×10^4	6.0
	Cs	2.2×10^4	5.9
	NH_4	1.6×10^4	5.7
	CH_3NH_3		<5
$B(CH_2O)_2P$, **7**	*t*-$BuNH_3$		<5
	Li	1.7×10^4	5.8
	Na	2.8×10^5	7.4
	K	1.5×10^6	8.4
	Rb	9.7×10^4	6.8
	Cs	3.8×10^4	6.2
	NH_4	2.9×10^5	7.4
	CH_3NH_3		<5
$A(CH_2O)_2L$, **8**	*t*-$BuNH_3$		<5
	Li	7.1×10^4	6.6
	Na	1.5×10^7	9.8
	K	1.6×10^8	11.2
	Rb	3.1×10^7	10.2
	Cs	2.9×10^6	8.8
	NH_4	1.8×10^7	9.9
	CH_3NH_3	1.1×10^6	8.3
$A(CH_2O)_2M$, **9**	*t*-$BuNH_3$		<5

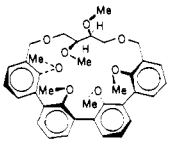
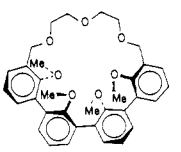
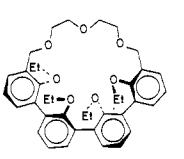
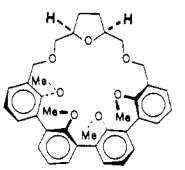
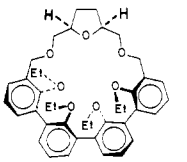
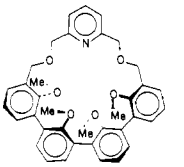
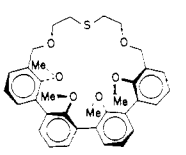
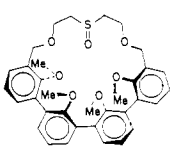
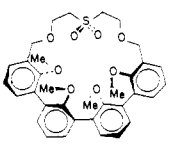
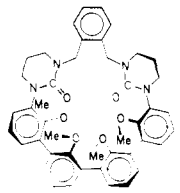
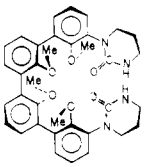
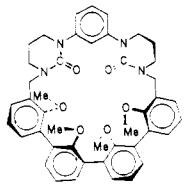
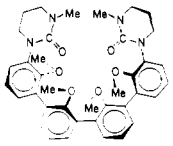
host structure	guest cation	K_a, M^{-1}	$-\Delta G°$, kcal mol^{-1}
	Li	2.4×10^4	6.0
	Na	1.1×10^5	6.9
	K	2.7×10^6	8.8
	Rb	8.5×10^5	8.1
	Cs	1.8×10^5	7.2
	NH_4	2.5×10^6	8.7
	CH_3NH_3	1.8×10^4	5.8
$A(CH_2O)_2N$, **10**	*t*-$BuNH_3$		<5
	Li	1.5×10^4	8.4
	Na	3.5×10^6	8.9
	K	1.4×10^8	11.1
	Rb	1.5×10^8	11.2
	Cs	1.2×10^8	11.0
	NH_4	6.6×10^7	10.7
	CH_3NH_3	1.2×10^7	9.6
$A(CH_2OE)_2O$, **11**	*t*-$BuNH_3$		<5
	Li	5.5×10^4	6.5
	Na	1.4×10^5	7.0
	K	6.5×10^7	10.6
	Rb[a]	1.1×10^8	11.0
	Cs[a]	7.5×10^7	10.7
	NH_4	3.4×10^7	10.3
	CH_3NH_3	4.0×10^6	9.0
$B(CH_2OE)_2O$, **12**	*t*-$BuNH_3$		<5
	Li	2.6×10^6	8.8
	Na	5.8×10^6	9.2
	K	7.6×10^8	12.1
	Rb	9.2×10^8	12.2
	Cs	1.1×10^8	11.0
	NH_4	1.1×10^8	11.0
	CH_3NH_3	1.8×10^7	9.9
$A(CH_2OCH_2)_2T$, **13**	*t*-$BuNH_3$	5.6×10^3	5.1
	Li	5.8×10^4	6.5
	Na	1.6×10^5	7.1
	K[a]	3.2×10^8	11.6
	Rb[a]	2.3×10^8	11.4
	Cs[a]	4.2×10^7	10.4
	NH_4	7.6×10^7	10.8
	CH_3NH_3	6.4×10^6	9.3
$B(CH_2OCH_2)_2T$, **14**	*t*-$BuNH_3$		<5
	Li	2.2×10^5	7.3
	Na	8.2×10^5	8.1
	K	1.0×10^7	9.6
	Rb	2.1×10^7	10.0
	Cs	1.2×10^7	9.7
	NH_4	6.3×10^6	9.3
	CH_3NH_3	1.7×10^6	8.5
$A(CH_2OCH_2)_2Py$, **15**	*t*-$BuNH_3$		<5
	Li	2.8×10^4	6.1
	Na	7.8×10^4	6.7
	K	6.5×10^6	9.3
	Rb	5.5×10^6	9.2
	Cs	1.6×10^6	8.5
	NH_4	2.3×10^6	8.7
	CH_3NH_3	9.2×10^4	6.8
$A(CH_2OE)_2S$, **16**	*t*-$BuNH_3$		<5
	Li	3.4×10^4	6.2
	Na	6.6×10^5	7.9
	K	1.5×10^6	8.4
	Rb	5.9×10^5	7.9
	Cs	2.8×10^5	7.4
	NH_4	5.1×10^5	7.8
	CH_3NH_3	1.1×10^4	5.5
$A(CH_2OE)_2SO$, **17**	*t*-$BuNH_3$		<5
	Li	1.1×10^4	5.5
	Na	1.6×10^6	8.5
	K	5.8×10^6	9.2
	Rb	1.2×10^6	8.3
	Cs	1.6×10^5	7.1
	NH_4	5.0×10^5	7.8
	CH_3NH_3	8.8×10^3	5.4
$A(CH_2OE)_2SO_2$, **18**	*t*-$BuNH_3$		<5

Table II (*Continued*)

host structure	guest cation	K_a, M^{-1}	$-\Delta G^\circ$, kcal mol^{-1}	host structure	guest cation	K_a, M^{-1}	$-\Delta G^\circ$, kcal mol^{-1}
	Li	2.2×10^5	7.3		Li	9.1×10^4	6.8
	Na	9.7×10^7	10.9		Na	3.1×10^5	7.5
	K	3.0×10^7	10.2		K	1.3×10^6	8.3
	Rb	1.8×10^6	8.5		Rb	4.5×10^5	7.7
	Cs	1.8×10^5	7.2		Cs	3.2×10^5	7.5
	NH_4	2.4×10^6	8.7		NH_4	2.4×10^5	7.3
	CH_3NH_3	4.7×10^5	6.4		CH_3NH_3	4.5×10^4	6.4
$A(UCH_2)_2F$, 19	*t*-$BuNH_3$		<5	$A(UH)_2$, 21	*t*-$BuNH_3$	5.4×10^3	5.1
	Li	5.9×10^4	6.5		Li	1.1×10^4	5.5
	Na	8.4×10^4	6.7		Na	3.0×10^4	6.1
	K	1.3×10^6	8.3		K	2.5×10^5	7.4
	Rb	7.2×10^5	8.0		Rb	1.2×10^5	6.9
	Cs	5.2×10^5	7.8		Cs	6.7×10^4	6.6
	NH_4	3.0×10^5	7.5		NH_4	1.1×10^5	6.9
	CH_3NH_3	9.8×10^4	6.8		CH_3NH_3	2.2×10^4	5.9
$A(CH_2U)_2V$, 20	*t*-$BuNH_3$	2.1×10^4	5.9	$A(UCH_3)_2$, 22	*t*-$BuNH_3$		<5

[a] Based on host and guest concentrations of 0.001 M. All other values are based on 0.015 M concentrations.

very conformationally mobile. It binds Na^+ and K^+ with 10.9 and 10.2 kcal mol^{-1}, respectively, and the other ions less well by at least 1.5 kcal mol^{-1}, showing low ion selectivity. Host $A(CH_2U)_2V$ (**20**) is 23-membered and in models is even less well organized for binding because of its variety of conformations. Accordingly it is one of the poorest hosts in the series, both in binding power and in selectivity. Its binding pattern resembles that of the nonmacrocycle $A(UH)_2$ (**21**). Both systems exhibit peak binding at K^+ (8.3 kcal mol^{-1}) and give similar values for most of the other ions. Molecular models of $A(UH)_2$ suggest the possibility that the terminal U units are joined by a NH···O=C hydrogen bond, thus providing some macrocyclic effect similar to what is observed in some of the antibiotic ionophores. If present, such a ring hardly reduced the adaptability of the binding sites to the various ions, since the maximum difference in $-\Delta G^\circ$ values is 1.9 kcal mol^{-1} (excluding the *t*-$BuNH_3^+$ ion). Replacement of the two N–H bonds of $A(UH)_2$ with two N–CH_3 bonds as in $A(UCH_3)_2$ (**22**) reduces the binding of each ion by about 1 kcal mol^{-1}, which suggests the hydrogen bond in **21** plays some role.

A comparison of $A(UH)_2$ (**21**) and $A(UCH_3)_2$ (**22**) with H-(*p*-$CH_3C_6H_2OCH_3)_6$H (**27**) is instructive. The first two systems are composed of four bound anisyl units terminated at each end by cyclic urea units. The last system (**27**) possesses six bound *p*-methylanisole units and no cyclic urea units. Whereas complexation of $A(UH)_2$ with all eight ions and $A(UCH_3)_2$ with seven of the eight ions are on scale, no complexation is observed with H(*p*-$CH_3C_6H_2OCH_3)_6$H. The superior ligating properties of the cyclic urea units at the ends of $A(UH)_2$ and $A(UCH_3)_2$ appear to force more organization on the intervening anisyl units than is observed when anisyl units themselves occupy the terminal positions. In $A(UCH_3)_2$, the two cyclic urea units may be held together in the free host by 1 mol of water hydrogen bonding the two carbonyl groups.

Generalizations extracted from this study are as follows. (1) The smaller cycles favor the smaller ions, and the larger cycles, the larger ions (principle of complementarity). (2) The smaller cycles that are more rigidly preorganized for binding are stronger binders and are more ion selective. For example, $A(CH_2O)_2E$ (**1**) binds Na^+ 116 times better than K^+ (principle of preorganization). (3) The smaller cycles that are more rigidly preorganized for *nonbinding* are poor binders and are nonselective. For example, $B(CH_2O)_2P$ (**7**) is the poorest and least selective host in the series since it is preorganized for nonbinding. (4) The larger cycles that are the most rigidly preorganized for binding are the strongest and most selective binders of the larger ions. For example, $A(CH_2OCH_2)_2T$ (**13**) binds $CH_3NH_3^+$ 3000 times better than *t*-$BuNH_3^+$, and $B(CH_2OCH_2)_2T$ (**14**) binds K^+ 2000 times better than Na^+ (principle of preorganization). (5) By varying structural parameters, selectivity can be enhanced in a rational way. For example, substitution of ethyl for methyl groups in three sets of analogues enhanced the binding of K^+ relative to that of Na^+. (6) The two ions most alike in their binding free energies of the 22 hosts examined are Rb^+ and NH_4^+. Except for $A(CH_2O)_2J$ (**4**), whose NH_4^+ value for $-\Delta G^\circ$ is off scale, the maximum $-\Delta G^\circ$ difference is 1.2 kcal mol^{-1} (for $A(CH_2OCH_2)_2T$ (**13**)). The overall average difference for the 21 hosts with values on scale is less than 0.5 kcal mol^{-1}. (7) Of the eight ions examined as guests, peak binding was accomplished for only Na^+, K^+, and Rb^+ ions although the ring size was varied from 18 to 23 members and the types of potential binding units employed were 16 in number.

Symmetry Properties and Ring Inversions in Hosts. Molecular model examination of **1–18** indicates that the only stable conformations for the tetraanisole-like units A and B place their alternate oxygens on opposite sides of the best plane of the macroring and their attached methyl or ethyl groups in positions remote from the center of the macroring. This provides the A and B units with a C_2 axis and makes them intrinsically chiral. Thus compounds **1–20** are intrinsically chiral. All of the combinations of units that compose the bridges that connect the ends of the A and B units have C_2 axes as well, except those containing the *cis*-tetrahydrofuran (T) or sulfoxide units. Hosts **1–12**, **15**, **16**, and **18–20** all have C_2 axes as their only symmetry element. Except for $A(CH_2O)_2K$ (**5**) and $A(CH_2O)_2N$ (**10**), which contain asymmetric carbon centers, the other cyclic hosts should be racemates whose enantiomers might interconvert at some temperature by ring inversions of any three of the four anisole-like units. In principle, this could occur by either passing the nonsubstituted parts of the aryls (*syn rotations*) or passing the OR substituted parts of the aryls (*anti rotations*) through the center of the ring. Molecular model examination indicates that only syn rotations are possible except for the hosts $A(UCH_2)_2F$ (**19**) and $A(CH_2U)_2V$ (**20**), which contain 22 and 23 ring members, respectively.

Dynamic ^1H NMR studies were undertaken for several hosts containing C_2 axes by following the changes with temperature of the signals due to the diastereotopic protons of the ring $ArCH_2O$ groups.[14] In 10:1 hexachlorobutadiene:$(CD_3)_2SO$, host $A(CH_2OE)_2O$ (**11**) showed no coalescence of its benzylic protons at temperatures up to 130 °C, which means that the free energy for enantiomer interconversion is $\Delta G^\ddagger_{403} > 19.5$ kcal mol^{-1} in this 21-membered ring system. Host $A(CH_2O)_2N$ (**10**) contains a 20-membered ring and consists of a mixture, present in a 4:3 ratio (^1H NMR), of two enantiomerically pure diastereoisomers as-

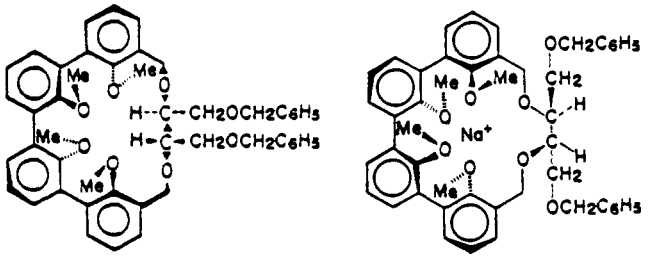
(14) Lambert, J. B.; Shurvell, H. F.; Verbit, L.; Cooks, R. C.; Stout, G. H. "Organic Structural Analysis"; MacMillan: New York, 1976; pp 116–123.

sociated with the presence of both asymmetric carbons and the tetraaryl chiral element. The diastereomers failed to interconvert in this same solvent at 130 °C, which means $\Delta G^{\ddagger}_{403} > 19.5$ kcal mol^{-1} for ring inversion of three anisoles in this system as well. Host A$(CH_2O)_2$M (**9**) also contains a 20-membered ring as well as a chiral bitolyl unit (M) in its bridge. It exists as a 3.2:1 ratio of diastereomerically related racemates (^{1}H NMR). In the same solvent, coalescence of the inner methoxyl methyl signals of the A group occurred at 110 °C ($\Delta G^{\ddagger}_{383} = 21.0$ kcal mol^{-1}) and of the methyl signals of the $CH_3C_6H_3$–$C_6H_3CH_3$ (M) unit at 120 °C ($\Delta G^{\ddagger}_{393} = 21.3$ kcal mol^{-1}). Although epimer interconversion in principle could occur either within the tetraaryl (A) or within the biaryl (M) units to produce these results, ring inversion in the biaryl unit is undoubtedly responsible for the observed results.

Attempts were made to separate the enantiomers of the 18-membered ring host A$(CH_2O)_2$F (**2**). Resolution into two bands of equal intensity was observed when **2** was chromatographed (5 min) on an analytical silicate column to which was attached a chiral π-acid (TAPA column).[15] However, a preparative cellulose chromatograph column[16] failed to produce resolved material. Crystalline complexes between **2** and the sodium salt of L-(+)-mandelic acid and that of camphor-10-*d*-sulfonic acid were obtained, but their optical activity was lost during decomplexation (30 min at 25 °C).

Both A$(CH_2O)_2$K (**5**) and A$(CH_2O)_2$N (**10**) are mixtures of diastereomers configurationally homogeneous at their chiral carbons in their K and N units but configurationally heterogeneous in their A units. Thick layer chromatography of A$(CH_2O)_2$N (**10**) gave a band due to each isomer, but each gave the same epimeric mixture (**1H** NMR) by the time their components were isolated. Thus the A unit in **10** undergoes ring inversion at 25 °C at a rate rapid on the human time scale.

Fortunately, A$(CH_2O)_2$K (**5**) crystallized as a single epimer (α-5). When dissolved in $CDCl_3$ at −58 °C, the ^{1}H NMR spectrum showed the presence of only α-**5** from −58 to −23 °C, but an 11:1 equilibrium mixture of α-5 to β-5 was rapidly produced at 0 °C. When a solution of excess sodium picrate in cold



$\underset{\sim}{\alpha}$-5 $\underset{\sim}{\beta}$-5·Na$^+$

$(CD_3)_2CO$ was added to a cold (−58 °C) solution of α-**5** in $CDCl_3$, only α-**5**·Na$^+$ was formed. This complex, to equilibrate, had to be heated to 50 °C for 2 weeks. The resulting mixture was 1:1.5, α-**5**·Na$^+$:β-**5**·Na$^+$. When $(CD_3)_2SO$ was added to α-**5**·Na$^+$ in the same medium, equilibration occurred in 0.5 h at 25 °C.

These results point to the following conclusions. (1) Since epimerization can occur only by ring inversion, only noncomplexed host can epimerize (Na$^+$ and CH_3 cannot occupy the limited space in the cavity at the same time). (2) Epimerization of free host is rapid on the human time scale but slow on the ^{1}H NMR time scale at working temperatures. (3) Addition of $(CD_3)_2SO$ to the $CDCl_3$–$(CD_3)_2CO$ solution lowers the value of the host–guest association constant, probably by competitive association (S→O··Na$^+$ ligation). (4) In thermodynamic stability, α-**5** > β-**5** but β-**5**·Na$^+$ > α-**5**·Na$^+$.

Crystals suitable for X-ray structures of the epimers of **5** and **5**·Na$^+$ could not be obtained. Molecular model examinations of the two sets of epimers provide clues as to their configurations, which are provisionally assigned by the labeling of structures with the experimentally based α and β symbols. The structure assigned to α-**5** provides the longest possible bridge across the constrained A unit. This structure orients the ring benzyl oxygens anti to one another (and away from their near methoxy neighbors), fills the cavity with two inward-turned methine hydrogens, and thrusts the long side chains away from the cavity gauche to one another. The structure assigned to β-**5**·Na$^+$ provides a near octahedral arrangement of the six oxygens, places the ring benzyl oxygens gauche to one another, and places the long side chains anti to one another. The oxygens in the benzyl side chains of β-**5**·Na$^+$ can cooperate in the binding only by eclipsing the ring benzyl oxygens with the side chains.

An energy barrier to ring inversion of about 27 kcal mol^{-1} is required to preserve configurational integrity at room temperature. Thus the free energy barrier to ring inversions of the A units in the hosts containing up to 21-membered rings must be >21 and <27 kcal mol^{-1}. Substitutions of ethoxy for methoxy groups are reported to increase by a factor of 6, the half-life for racemizations of 2,2′-dialkoxybiphenyl compounds.[17] This factor is much too small for comparisons of the B with the A units in our hosts because of the ring-enforced convergent arrangement of four alkoxy groups. Since A$(CH_2O)_2$F (**2**) appears to be close to preserving its configurational integrity at room temperature, it is likely that B$(CH_2O)_2$F (**3**) does so. Substitution of as few as two benzyloxys for two methoxys in any of the 18-membered ring cycles should guarantee maintaining configurational integrity of the tetraaryl units at working temperatures since at least three alkoxy units must ring invert to alter the configuration. In molecular models, it is impossible for a benzyloxy unit to pass through the center of the macrocycle without breaking bonds.

Of hosts **1**–**20**, only **1**–**8** with 18- or **19**-membered rings appear in molecular models to be true hemispherands. In the larger macrocycles, at least one of the methyl or ethyl groups of the A or B units can turn inward to occupy the cavity.

Rates of Complexation and Decomplexation. Dynamic ^{1}H NMR methods[14,18] were used to estimate decomplexation rates for a few representative hosts (**2**, **6**, **8**, and **12**) of differing ring sizes complexed with potassium picrate. Solutions of 1:1 molar ratios of host to complex at about the 0.01 M concentration level were prepared in $CDCl_3$ saturated with D_2O. At available temperatures, certain proton signals (200-MHz machine) for free and complexed hosts of equal intensities were clearly differentiated and their differences in chemical shifts ($\Delta\nu$) determined. The solutions were then heated to the coalescence temperature (t_c) and the rate constants for decomplexation (k_{-1}) were calculated.[14,18]

In this treatment, we assume that exchange occurs by a dissociative (unimolecular) mechanism. Different protons involving the same host coalesce at different temperatures and thus k_{-1} and $\Delta G^{\ddagger}_c$ values for decomplexation were calculated at two different temperatures. These $\Delta G^{\ddagger}_c$ values were then extrapolated to 25 °C, and the k_{-1} values at this temperature were estimated. Since the association constant (K_a) for these same hosts and guests in this medium were known (Table II), the association rate constants (k_1) were estimated. Table III records the relevant results.

The complexation rate constants (k_1) range from a low of 10^7 for A$(CH_2O)_2$P (**6**) to a high of 2×10^9 mol^{-1} s^{-1} for A$(CH_2O)_2$F (**2**). These values are higher than those for the anisyl spherands binding Na$^+$ in the same medium (10^5–10^6 mol^{-1} s^{-1})[12] but lower than those observed for the hemispherands containing two to three cyclic urea units binding *t*-BuNH$_3^+$ (10^{11}–10^{12} mol^{-1} s^{-1}).[18] Of these three types of hosts, the anisyl spherands are the most preorganized, and entrance to the cavity is the most hindered, so complexation is relatively slow. The tetraanisyl hemispherands are the next most preorganized, entrance to the cavity is hindered

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(16) Hess, H.; Burger, G.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 612–614.
(17) Adams, R.; Li, C. C. *J. Am. Chem. Soc.* **1935**, *57*, 1565–1569.
(18) Anthonsen, T.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1983**, 414–416.

Table III. Estimated Rate Constants for Complexation (k_1) and Decomplexation (k_{-1}) for Hosts and Potassium Picrate in $CDCl_3$ Saturated with D_2O at 25 °C

host					kcal mol^{-1}			
structure	no.	protons obsd	$\Delta\nu$, Hz at T, K	T_c, K	$\Delta G^{\ddagger}_c$[a]	$\Delta G^{\ddagger}_{298}$[b]	k_1, mol^{-1} s^{-1}	k_{-1}, s^{-1}
$A(CH_2O)_2F$	2	inner OCH_3[c]	18.68 (217)	327	16.80	15.90	2×10^9	14
$A(CH_2O)_2F$	2	$ArCH_2$ (upfld)[d]	26.80	338	17.14			
$A(CH_2O)_2P$	6	inner OCH_3	6.40 (214)	267	14.15	15.50	1×10^7	27
$A(CH_2O)_2P$	6	$ArCH_2$ (dnfld)[e]	19.24	315	16.11			
$A(CH_2O)_2P$	6	$ArCH_2$ (upfld)[d]	41.97	328	16.29			
$A(CH_2O)_2L$	8	inner OCH_3[c]	11.36 (213)	297	15.46	15.48	4×10^7	26
$A(CH_2O)_2L$	8	$ArCH_2$ (upfld)[d]	29.80	327	16.20			
$B(CH_2OE)_2O$	12	inner CCH_3[f]	1.50 (270)	285	15.99	16.69	2×10^8	4
$B(CH_2OE)_2O$	12	outer CCH_3[g]	2.00	330	18.43			

[a] Free energy of activation for decomplexation at coalescence temperature. [b] Free energy of decomplexation at 298 K. [c] $Ar(OCH_3)Ar(OCH_3)Ar(OCH_3)Ar(OCH_3)$. [d] Upfield. [e] Downfield. [f] $Ar(OCH_2CH_3)Ar(OCH_2CH_3)Ar(OCH_2CH_3)Ar(OCH_2CH_3)$. [g] $Ar(OCH_2CH_3)Ar(OCH_2CH_3)Ar(OCH_2CH_3)Ar(OCH_2CH_3)$.

from all but two directions, and complexation is fast. The cyclic urea hemispherands studied were relatively less preorganized, contact with the binding sites of the cavity is little hindered, and complexation is diffusion controlled. Of the four hosts of the current study, k_1 values decrease in the order $A(CH_2O)_2F$ (**2**, 2×10^9) > $B(CH_2OE)_2O$ (**12**, 2×10^8) > $A(CH_2O)_2L$ (**8**, 4×10^7) > $A(CH_2O)_2P$ (**6**, 10^7 mol^{-1} s^{-1}). This order is roughly that of decreasing preorganization of the host for binding, as well as the order for decreasing values of the $-\Delta G°$ for their complexes (11.0, 10.6, 8.4, and 7.8 kcal mol^{-1}, respectively).

The decomplexation rate constants (k_{-1}) of **2**, **6**, **8**, and **12** vary only from values of 4 to 27 s^{-1}, which is much less than was observed among either of the spherands[12] or of the cyclic urea hemispherands,[18] whose decomplexation rates decreased with their increased binding power. With the tetraanisyl-like hosts of the present study, the complexation free energies correlate better with the complexation rates than with the decomplexation rates.

Experimental Section

General. Benzene was distilled from $LiAlH_4$ before use, CH_2Cl_2 twice from CaH_2, and Et_2O and $(CH_2)_4O$ (THF) from sodium benzophenone ketyl under N_2. Dimethylformamide (DMF) was distilled at reduced pressure from alumina and was stored under argon over 4-Å molecular sieves. Pyridine was fractionally distilled from solid NaOH and stored over 4-Å sieves, *t*-BuOH from CaH_2, and toluene and $(CH_3)_2NCH_2CH_2N(CH_3)_2$ (TMEDA) were dried over 4-Å sieves. All diols used for ring closure were dried before use, as was $Fe(acac)_3$ (100 °C at 0.1 mm).

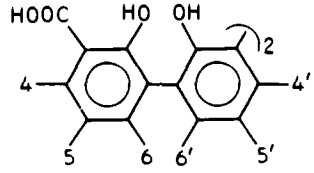
Chromatography was performed on Silica Gel 60 (E. Merck, 2-mm thickness). Gel permeation chromatography was performed on either of two 20 ft × 0.375 in. (o.d.) columns packed with 200 g of 100-Å Styragel (Waters Associates) each using CH_2Cl_2 as eluant at flow rates of 3.8–4.1 mL/min and back pressures of 250–500 psi. Column A had been exposed to salts and complexes. Column B had only been exposed to neutral materials.

Infrared spectra were recorded on a Perkin-Elmer 297 spectrometer. Absorbance readings in the UV for association constants were taken on a Gilford Model 252 photometer utilizing a Beckmann DU monochrometer. The mass spectra were recorded on an AE-1 model MS-9 double-focusing spectrometer interfaced by Kratos Company to a Data General Nova 3. The nuclear magnetic spectra were recorded on either a Bruker WP-200 (200 MHz) spectrometer or a Jeol FX90Q (90 MHz) spectrometer. All new compounds were submitted to elemental analyses, and the values found were within 0.30% of theory in all cases.

1,1′-Bidibenzofuran (29).[9] Dibenzofuran (33.4 g for 0.200 mol) was dissolved in 400 mL of dry THF. The solutions was cooled to −20 °C under nitrogen, and 95 mL of a 2.3 M solution of *n*-BuLi in hexane (0.22 mol) was added with stirring. The solution was allowed to come to 25 °C where it was stirred for 4 h. It was then cooled to −40 °C, and a solution of 100 g (0.28 mol) of dry $Fe(acac)_3$ in 400 mL of dry benzene was added rapidly, which brough the temperature of the stirred mixture to about 25 °C. If the temperature goes higher, the yield is reduced. The mixture was stirred for 16 h, the solvent was evaporated under reduced pressure, and the residue was shaken with 200 mL of 2 N hydrochloric acid and 200 mL of CH_2Cl_2. The organic layer was washed five times with successive portions of 1 N hydrochloric acid, dried, and 200 mL of ethanol was added. The mixture was concentrated to about 150 mL, and the product that separated was collected and recrystallized from toluene to give 24.1 g (70%) of **29**: mp 192 °C, of product pure to thin layer chromatography [lit.[8] mp 191 °C].

[1,1′-Bidibenzofuran]-8,8′dicarboxylic Acid (30). To 22.02 g (0.067 mol) of 1,1′-bidibenzofuran dissolved in 800 mL of THF stirred under dry argon was added by syringe 128 mL of 1.3 M *n*-butyllithium. After the solution had stirred for 7 h, a stream of dry CO_2 was passed through the solution for 20 min. After standing for 4 h the mixture was acidified, and the precipitate was collected. Concentration of the mother liquor yielded additional solid. The combined solids were triturated with 200 mL of acetone. The acetone wash was concentrated to 50 mL, and the solid that separated was collected. The combined solids were triturated with 100 mL of CH_2Cl_2 and dried at 0.1 mm to give 28.3 g (100%) of **30**: mp >340 °C; ^{1}H NMR (200 MHz, $(CD_3)_2SO$) δ 7.542 (H 3), 8.053 (H 2), 8.276 (H 4), (ABC, 2 × 3 H, $J_{2,3} = J_{3,4} = 6.7$, $J_{2,4} \approx 0$), 7.630 (H 6), 8.309 (H 5), 8.482 (H 7), (ABC, 2× 3, $J_{5,6} = 6.7$, $J_{6,7} = 7.3$, $J_{5,7} \approx 0$); IR (KBr) 3300–2500 (OH), 1700 (CO), 1482, 1430, 1299, 1195, 750 cm^{-1}; MS (70 eV, 230 °C) *m/e* M$^+$ 422. Anal. Calcd for $C_{26}H_{14}O_6$: C and H.

2,2′,2″,2‴-Tetrahydroxy-[1,1′:3′,1″:3″,1‴:3‴,1⁗-quaterphenyl]-3,3‴dicarboxylic Acid (31). In a steel crucible were mixed thoroughly 28.29 g (0.67 mol) of finely powdered diacid **30**, 75.1 g (1.14 mol) of 85% KOH, and 53.6 g (1.34 mol) of NaOH. The flask containing the mixture was heated with a Woods metal bath whose temperature was 200 °C. After the mixture liquified (10 min) efficient mechanical stirring was started. The temperature of the bath was raised to 275–300 °C (higher temperature decreased the yield), and after 1 h the pasty material was quickly transferred to a metal cookie tray with a steel spatula. The paste solidified. The solid was broken into small pieces and dissolved in 2 L of water. The solution was filtered, and the filtrate was acidified to pH 1 with a hydrochloric acid–ice mixture. The flocculent solid was collected on a medium glass-fritted filter and dried at 0.1 mm. This material was dissolved in refluxing acetone, cyclohexane was added, the solution was concentrated, and the product which separated (**31**) was collected and dried, 29.13 g (95%): mp 275 °C; ^{1}H NMR (200 MHz, $(CD_3)_2CO$) δ 6.989 (H 5), 7.537 (H 6), 7.862 (H 4), (ABC, 2 × 3 H, $J_{5,6} = 7.4$, $J_{4,5} = 7.8$, $J_{4,6} = 1.5$), 7.049 (H 5′), 7.228 (H 4′), 7.329 (H 6′) (ABC, 2 × 3 H, $J_{4',5'} = 7.4$, $J_{5',6'} = 7.6$, $J_{4',6'} = 1.5$); MS (16 eV, 220 °C) *m/e* M$^+$ 458. Anal. Calcd for $C_{26}H_{18}O_8$: C and H.



2,2′,2″,2‴-Tetramethoxy-[1,1′:3′,1″:3″,1‴:3‴,1⁗-quaterphenyl]-3,3‴-dicarboxylic Acid (32). A mixture of 10.12 g (22.1 mol) of **31**, 20.14 g (145.8 mmol) of K_2CO_3, 13.8 mL (145.8 mmol) of dimethyl sulfate, and 450 mL of acetone was stirred for 24 h. After addition of 20 mL more of dimethyl sulfate the mixture was refluxed for 2 days. The solvent was removed under reduced pressure. The residue was partitioned between acidic water (pH 1) and diethyl ether. The aqueous layer was extracted with a second portion of diethyl ether. The combined organic layers were washed with brine, dried, and concentrated. The residue was refluxed in a solution of 10 g of KOH, 40 mL of water, and 200 mL of ethanol for 3 h. The mixture was cooled, the solvent was evaporated, and the residue was acidified with hydrochloric acid. The resulting suspension was continuously extracted with CH_2Cl_2 for 2 days. Cyclohexane was added to the organic layer, which was concentrated. The product separated and was collected and dried to give 8.36 g (74%) of **31**, which after recrystallization from methanol gave mp 232–233 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.267 (s, inner OCH_3 2 × 3 H), 3.635 (s, outer OCH_3,

2 × 3 H), 7.26–8.22 (7, ArH, 12 H); IR (KBr) 3250–2700, 1699, 1240, 1020 cm^{-1}; MS (70 eV, 180 °C) *m/e* 514. Anal. Calcd for $C_{30}H_{26}O_8$: C and H.

2,2′,2″,2‴-Tetraethoxy-[1,1′:3′,1″:3″,1‴-quaterphenyl]-3,3‴-dicarboxylic Acid (36). To a 500-mL flask under an argon atmosphere were added 10.7 g (23.4 mmol) of **31**, 22.6 g (163.4 mmol) of K_2CO_3, and 18.83 mL (234 mmol) of iodoethane in 300 mL of dry DMF. The solution was stirred for 24 h. The solution was heated to 50 °C, followed by addition of 10 mL of iodoethane every 24 h. On the fifth day, 5 g of K_2CO_3 was added, followed by 10 mL of iodoethane. Two additional 10-mL portions of iodoethane were added on the sixth and seventh days. After a total of 8 days, the DMF was removed under reduced pressure. The residue was partitioned between 400 mL of diethyl ether and 400 mL of 1 M hydrochloric acid. The organic layer was washed with 400 mL of brine and concentrated under reduced pressure. This oil was refluxed in a mixture of 10 g of KOH, 40 mL of water, and 250 mL of ethanol for 3 h to hydrolyze ester that had formed. The solution was concentrated under reduced pressure and acidified with 1 M hydrochloric acid to pH 1. The solution was extracted twice with 400 mL of diethyl ether. The organic phase was washed with brine and dried ($MgSO_4$). After addition of cyclohexane, the organic solution was concentrated to give 9.53 g (71.6%) of **36**: mp 169–170 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 0.779_X and 3.428_A (A_2X_3, inner OEt, 2 × 5 H, J = 7.0), 1.204_X and 3.824_A (A_2X_3, outer OEt, 2 × 5 H, J = 7.1), 7.250_B and 7.406_A and 7.481_C (ABC, inner ArH, 2 ×3 H, J_{AB} = 7.4, $J_{B,C}$ = 7.7, J_{AC} = 1.9), 7.333_B and 7.657_C and 8.201_A (ABC, outer ArH (A is ortho to acid and C is para to acid), 2 × 3 H, J_{AB} = 7.8, J_{BC} = 7.6, J_{AC} = 1.8), 11.6 (bs, OH, 2 H); IR (KBr) 3500–2500 (OH), 1735, 1698, 1079, 1026 cm^{-1}; MS (70 eV, 180 °C) *m/e* M^+ 570. Anal. Calcd for $C_{34}H_{34}O_8$: C and H.

2,2′,2″,2‴-Tetramethoxy-[1,1′:3′,1″:3″,1‴-quaterphenyl]-3,3‴-dimethanol (33). To a dry solution of 2.18 g (4.24 mmol) of diacid **32** in 200 mL of dry THF stirred under N_2 was added 16.9 mL (16.9 mmol) of 1 M BH_3·THF by syringe. A stringy precipitate formed. The mixture was stirred for 3 h at 25 °C and 3 h at reflux. The mixture was cooled, and excess reagent was cautiously decomposed with water. Water (40 mL) saturated with K_2CO_3 was added, and the resulting mixture was stirred for 12 h. The solvent was evaporated under reduced pressure, and the residue was partitioned between acidic water and 150 mL of ethyl acetate. The aqueous layer was extracted with two 150-mL portions of ethyl acetate and the combined organic layers were washed twice with 100-mL portions of brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the oil was chromatographed over 100 g of silica gel in CH_2Cl_2. The column was developed with 1–20% (v:v) Et_2O in CH_2Cl_2, and product was eluted with 3% CH_3OH in CH_2Cl_2, 1.59 g (77%), a small sample of which was crystallized from methanol: mp 91–97 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 2.65–2.75 (bs, OH, 2 H), 3.264 (s, inner OCH_3, 6 H), 3.484 (s, outer OCH_3, 6 H), 4.755 (s, CH_2O, 4 H), 7.14–7.39 (m, ArH, 12 H); IR (KBr) 3600–3200, 2950, 1470, 1420, 1235, 1010, 785 cm^{-1}; MS (70 eV, 180 °C) *m/e* 486. Anal. Calcd for $C_{30}H_{30}O_6$: C and H.

2,2′,2″,2‴-Tetraethoxy-[1,1′:3′,1″:3″,1‴-quaterphenyl]-3,3″-dimethanol (37). To a solution of 2.0 g (3.51 mmol) of diacid **36** in 150 mL of dry THF stirred under argon was added by syringe 10.1 mL of a 1 M BH_3·THF solution. After 10 min, a white suspension appeared. The mixture was stirred an additional 2 h and then refluxed for 3 h. Heating was stopped and the reaction mixture was stirred with 20 mL of saturated aqueous K_2CO_3 solution. The mixture was concentrated under reduced pressure and acidified to pH 4. The aqueous solution was extracted twice with 200 mL of diethyl ether. The combined ether phases were washed once with brine and dried ($MgSO_4$). The solution was concentrated under reduced pressure. The residue was chromatographed through 100 g of silica gel in Et_2O–CH_2Cl_2 (1:10). Product was eluted with CH_2Cl_2–EtOH (20:1, v:v), R_f 0.24. This diol (**37**) was isolated as a foam, which was dried at high vacuum, 1.49 g (78.3%); ^1H NMR (200 MHz, $CDCl_3$) δ 0.783_X and 3.463_A (A_2X_3, inner OCH_2CH_3, 2 × 5 H, J_{AX} = 7.0), 1.119_X and 3.681_A (A_2X_3, outer OCH_2CH_3, 2 × 5 H, J_{AX} = 7.0), 2.05–2.15 (bs, OH, 2 H), 4.784 (s, CH_2O, 4H), 7.14–7.44 (m, ArH, 12 H); MS (70 eV, 200 °C) *m/e* M^+ 542. Anal. Calcd for $C_{34}H_{38}O_6$: C and H.

3,3‴-Bis(bromomethyl)-2,2′,2″,2‴-tetramethoxy-1,1′:3′,1″:3″,1‴-quaterphenyl (34). To 0.505 g (1.04 mmol) of diol **33** dissolved in 5 mL of CH_2Cl_2 was added 50 mL of C_6H_6. To this stirred solution, 0.29 g (1.07 mmol) of PBr_3 was added, and the mixture was stirred for 30 h. The reaction mixture was mixed with 50 mL of Et_2O, and the resulting solution was quickly washed with two 50-mL portions of water saturated with K_2CO_3, once with 50 mL of water, and with two 50-mL portions of brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The resulting oil was flash chromatographed through 50 g of silica gel with CH_2Cl_2 as the mobile phase. The material from the column was crystallized from hexane to give 0.52 g (82%) of **34**: mp 113–114 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 3.152 (s, inner OCH_3, 2 × 3 H), 3.430 (s, outer OCH_3, 2 × 3 H), 4.523 (s, CH_2Br, 4 H), 6.95–7.38 (m, ArH, 12 H); IR (KBr) 2950, 1481, 1399, 1239, 1015, 765 cm^{-1}; MS (70 eV, 150 °C) *m/e* M^+ 610 (^{79}Br). Anal. Calcd for $C_{30}H_{28}Br_2O_4$: C, H, and Br.

3,3‴-Bis(bromomethyl)-2,2′,2″,2‴-tetraethoxy-1,1′:3′,1″:3″,1‴-quaterphenyl (38). To a stirred solution of diol **37** (1.49 g, 2.75 mmol) in 100 mL of C_6H_6 was added 0.26 mL (2.75 mmol) of PBr_3. The solution was stirred under dry conditions for 20 h, and 100 mL of Et_2O was added. The resulting solution was washed with 100 mL of water saturated with K_2CO_3 and 100 mL of brine. The solution was dried ($MgSO_4$), and the organic layer was concentrated under reduced pressure. The residual oil was flash chromatographed on 50 g of silica gel with CH_2Cl_2 as the mobile phase. The eluted product was isolated as a foam, which was dried under high vacuum to give 1.47 g (80%) of dibromide **38**: ^1H NMR (200 MHz, $CDCl_3$) δ 0.783_X and 3.467_A (A_2X_3, inner OCH_2CH_3, 2 × 5 H, J = 7.0), 1.137_X and 3.724_A (A_2X_3, outer OCH_2CH_3, 2 × 5 H, J = 7.0), 4.665 (s, CH_2Br, 4 H), 7.11–7.47 (m, ArH, 12 H); MS (70 eV, 190 °C) *m/e* 666 (^{79}Br). Anal. Calcd for $C_{34}H_{36}Br_2O_4$: C and H.

Cyclization Reactions. The ring closures were accomplished by either of two similar high-dilution methods. Method A was applied to the preparations of **1**,**2**,**4**,**6**, and **8**–**11**. Method B was used to make **3**, **5**, **7**, **12**, **14**, and **16**. Better control of the rates of addition of reactants and less solvent needed for isolation of product made method B superior to A. Method A will be illustrated by the synthesis of **11** and B by the synthesis of **12**.

Method A. 30,31,32,33-Tetramethoxy-18,21,24-trioxapentacyclo[24.3.1.1^{2,6}.1^{7,11}.1^{12,16}]tritriaconta-1(30),2,4,6(33),7,9,11(32),12,14,16(31),26,28-dodecaene (11). A flask fitted in series with a reflux-return, diluting and mixing thimble of ~30 mL volume, a condenser, and a Hershberg addition funnel was dried at 200 °C and flushed with dry argon while hot, and allowed to cool under argon. A 50% NaH dispersion in mineral oil washed free of mineral oil with dry THF (0.25 g of NaH, 5.1 mmol) was mixed in the flask with 125 mL of freshly dried and distilled THF under dry argon (mixture A). A solution of 0.90 g (1.47 mmol) of dibromide $BrCH_2ACH_2Br$ (**34**) and 0.158 g (1.48 mmol) of dry 2,2′-oxybisethanol in 200 mL of freshly dried and distilled THF was placed in the addition funnel (solution B). Mixture A was heated to vigorous reflux while being stirred. After the reflux-return thimble was full, a slow, even addition of solution B through the condenser was initiated and continued for 30 h while mixture A was stirred at vigorous reflux. After the addition was complete, the mixture was stirred at reflux for an additional 30 h and cooled. The solvent was evaporated under reduced pressure to give residue C, which was partitioned between 200 mL of a dilute hydrochloric acid solution and 200 mL of CH_2Cl_2. The aqueous phase was extracted with 200 mL of CH_2Cl_2. The combined organic phases were washed with three successive portions of deionized water, dried ($MgSO_4$), and concentrated under reduced pressure to give residue D. Gel permeation chromatography of residue D (column B, R_v = 156 mL) gave residue E, trituration of which with ethanol gave 0.45 g (55%) of host **11**: mp 195 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 2.977 (s, inner OCH_3, 6 H), 3.584 (s, outer OCH_3, 6 H), 3.590 (bs, OCH_2CH_2O, 8 H), 4.300 and 4.775 (AB, $ArCH_2O$, 4 H, J = 10.7), 7.10–7.40 (m, ArH, 12 H); IR (KBr) 2945, 2900, 1455, 1410, 1230, 1090, 1010 cm^{-1}; MS (70 eV, 210 °C) *m/e* M^+ 556. Anal. Calcd for $C_{34}H_{36}O_7$: C and H.

28,29,30,31-Tetramethoxy-18,22-dioxapentacyclo[22.3.1.1^{2,6}.1^{7,11}.1^{12,16}]hentriaconta-1(28),2,4,6(31),7,9,11(30),12,14,16(29),24,26-dodecaene (6). Mixture A was made by suspending 0.11 g of washed NaH in 200 mL of dry THF. Solution B was prepared by dissolving 0.3421 g (0.56 mmol) of dibromide (**34**) and 0.0457 g (0.60 mmol) of dry 1,3-propanediol in 200 mL of dry THF. The addition time was 40 h, and the total reflux time was 52 h.

Residue C was partitioned between 200 mL of ethyl acetate and 100 mL of dilute hydrochloric acid solution. The organic phase was washed with 100 mL of dilute hydrochloric acid, 100 mL of water, and 100 mL of brine. It was dried ($MgSO_4$) and concentrated to give 0.10 g (34%) of host **6** as needles: mp 235 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 1.80–1.95 (m, CCH_2C, 2 H), 2.879, (s, inner OCH_3, 6 H), 3.206 (s, outer OCH_3, 6 H), 3.39–3.49 (m, OCH_2CCH_2O, 4 H), 4.416 and 4.716 (AB, $ArCH_2O$, 4 H), J = 12.0), 7.08–7.47 (m, ArH, 12 H); MS (70 eV, 210 °C) *m/e* M^+ 526. Anal. Calcd for $C_{33}H_{34}O_6$: C and H.

33,34,35,36-Tetramethoxy-2,31-dimethyl-6*H*,27*H*-7,11:12,16:17,21:22,26-tetramethenodibenzo[*b*,*d*][1,6]dioxacyclooctacosin (9). Mixture A was prepared by suspending 0.23 g of washed NaH in 100 mL of dry THF. Solution B was prepared by dissolving 1.000 g (1.63 mmol) of **34** and 1.020 g (1.66 mmol) of 5,5′-dimethyl-1,1′-biphenyl-2,2′-diol[2] in 150 mL of dry THF. The addition time was 24 h,

and the total reflux time was 48 h. Residue D was subjected to gel permeation chromatography on column B (R_v = 156 mL), and residue E was crystallized from ethyl acetate. The solid was dried in vacuo to give 0.53 g (49%) of host **9**: mp 143–144 °C; ^{1}H NMR (200 MHz, $CDCl_3$) showed two epimers in a ratio of 1.4:1.0, major δ 2.242 (s, $ArCH_3$, 6 H), 2.718 (s, inner OCH_3, 6 H), 3.321 (s outer, OCH_3, 6 H), 4.786 and 5.273 (AB, $ArCH_2O$, 4 H, J = 10.8), 6.85–7.50 (m, ArH, 18 H); minor δ 2.242 (s, $ArCH_3$, 6 H), 2.659 (s, inner OCH_3, 6 H), 3.025 (s, outer OCH_3, 6 H), 4.895 and 5.469 (AB, $ArCH_2O$, 4 H, J = 13.2), 6.85–7.50 (m, ArH, 18 H); MS (70 eV, 220 °C) m/e M^+ 664. Anal. Calcd for $C_{44}H_{40}O_6$: C and H. A small sample of host was dissolved in $CDCl_3$ and vortexed with potassium bromide–saturated deterium oxide. The organic layer gave ^{1}H NMR (200 MHz, $CDCl_3$) two epimers in a 3.2:1.0 ratio, major δ 2.286 (s, $ArCH_3$, 6 H), 2.825 (s, inner OCH_3, 6 H), 3.211 (s, outer OCH_3, 6 H), 4.863 and 5.470 (AB, $ArCH_2O$, 4 H, J = 12.2), 7.00–7.60 (m, ArH, 18 H); minor δ 2.262 (s, $ArCH_3$, 6 H), 2.825 (s, inner OCH_3, 6 H), 3.279 (s, outer OCH_3, 6 H), 4.661 and 5.623 (AB, $ArCH_2O$, 4 H, J = 10.1), 7.00–7.60 (m, ArH, 18 H).

29,30,31,32-Tetramethoxy-2*H*,23*H*-3,7:8,12:13,17:18,22-tetrametheno-1,24-benzodioxacyclohexacosin (2). Mixture A was made by suspending 0.274 g of NaH in 125 mL of dry THF. Solution B was prepared by dissolving 1.000 g (1.63 mmol) of **34** and 0.1816 g (1.65 mmol) of dry 1,2-benzenediol in 200 mL of dry THF. The addition time was 30 h, and the total reflux time was 48 h.

Residue D was chromatographed on column B (R_v = 160 mL). Residue E was crystallized from ethanol to give upon drying in vacuo 0.3463 g (37.9% of host **2**: mp 200 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.659 (s, inner OCH_3, 12 H), 3.142 (s, outer OCH_3, 6 H), 4.895 and 5.384 (AB, $ArCH_2O$, 4 H, J = 11.2), 6.79–7.44 (m, ArH, 16 H); IR (KBr) 2950, 1596, 1501, 1460, 1410, 1222, 1200 cm^{-1}; MS (70 eV, 210 °C) m/e M^+ 560. Anal. Calcd for $C_{36}H_{32}O_6$: C and H. A small sample of host **2** dissolved in $CDCl_3$ and shaken with sodium bromide–saturated deuterium oxide gave ^{1}H NMR (200 MHz) δ 2.901 (s, inner OCH_3, 6 H), 3.372 (s, outer OCH_3, 6 H), 5.155 and 5.428 (AB, $ArCH_2O$, 4 H, J = 10.9), 6.98–7.56 (m, ArH, 16 H).

(20*S*,21*S*)-(+)-29,30,31,32-Tetramethoxy-18,23-dioxapentacyclo[23.3.1.1^{2,6}.1^{7,11}.1^{12,16}]dotriaconta-1(29),2,4,6(32),7,9,11(31),12,14,16(30),25,27-dodecaene (10). Mixture A was made by suspending 0.247 g of washed NaH in 100 mL of dry THF. Solution B was prepared by dissolving 0.9417 g (1.54 mmol) of **34** and 0.223 g (1.49 mmol) of dry (2*S*,3*S*)-2,3-dimethoxybutane-1,4-diol[11] in 225 mL of dry THF. The addition time was 24 h, and the total reflux time was 48 h. Gel permeation chromatography was done on column B (R_v = 153 mL). Residue E was crystallized from ethanol, which after drying in vacuo gave 0.50 g (54%) of **10**: mp 154 °C; ^{1}H NMR (200 MHz, $CDCl_3$) showed two epimers in a 4:3 ratio, major δ 2.947 (s, inner OCH_3, 6 H), 3.339 (s, outer OCH_3, 6 H), 3.404 (s, bridge OCH_3, 6 H), 3.46–3.77 (m, OCH_2CH, 6 H), 4.363 and 4.652 (AB, $ArCH_2O$, 4 H, J = 9.9), 7.05–7.43 (m, ArH, 12 H); minor δ 2.969 (s, inner OCH_3, 6 H), 3.287 (s, outer OCH_3, 6 H), 3.359 (s, bridge OCH_3, 6 H), 3.47–3.77 (m, OCH_2CH, 6 H), 4.430 and 4.695 (AB, $ArCH_2O$, 4 H, J = 12.0), 7.05–7.43 (m, ArH, 12 H); MS (70 eV, 180 °C) m/e M^+ 600. Anal. Calcd for $C_{36}H_{40}O_8$: C and H.

20,20-Bis(methoxymethyl)-28,29,30,31-tetramethoxy-18,22-dioxapentacyclo[22.3.1.1^{2,6}.1^{7,11}.1^{12,16}]hentriaconta-1(28),2,4,6(31),7,9,11(30),12,14,16(29),24,26-dodecaene (8). Mixture A was made with 0.253 g of washed NaH and 125 mL of dry THF. Solution B was prepared by dissolving 0.9224 g (1.51 mmol) of **34** and 0.2471 g (1.51 mmol) of dry 2,2-bis(methoxymethyl)-1,3-propanediol[19] in 200 mL of dry THF. The addition time as 30 h, and the total reflux time was 48 h. Column B was used in the gel permeation chromatographic purification (R_v = 153 mL). Crystallization of residue E from ethanol gave 0.50 g (53.9%) of host **8**: mp 180–181 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.915 (s, inner OCH_3, 6 H), 3.193 (s, outer OCH_3, 6 H), 3.261 (s, bridge OCH_3, 6 H), 3.283 (s, CH_2OMe, 4 H), 3.283 and 3.383 (AB, OCH_2CCH_2O, 4 H, J = 10.1), 4.423 and 4.684 (s, $ArCH_2O$, 4 H, J = 11.5), 7.12–7.49 (m, ArH, 12 H); MS (70 eV, 180 °C), m/e M^+ 614. Anal. Calcd for $C_{37}H_{42}O_8$: C and H.

32,34,35,36-Tetramethoxy-18,26-dioxa-33-azahexacyclo[26.3.1.1^{2,6}.1^{7,11}.1^{12,16}.1^{20,24}]hexatriaconta-1(32),2,4,6(36),7,9,11(35),12,14,16(34),20,22,24(33),28,30-pentadecaene (15). Mixture A was made by suspending 0.30 g of washed NaH in 150 mL of dry THF. Solution **B** was prepared by dissolving 1.0019 g (1.636 mmol) of **34** and 0.2274 g (1.635 mmol) of 2,6-pyridinemethanol[20] in 250 mL of dry THF. The addition time was 40 h, and the total reflux time was 52 h. Gel permeation chromatography was done on column B (R_v = 158.8 mL). Crystallization of residue E from ethanol gave 0.35 g (36.3%) of host **15**: mp 198–199 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.964 (s, inner OCH_3, 6 H), 3.341 (s, outer OCH_3, 6 H), 4.538 and 4.587 (AB, OCH_2pyr, 4 H, J = 12.7), 4.495 and 4.891 (AB, $ArCH_2O$, 4 H, J = 11.1), 7.13–7.39 (m, ArH, 15 H); MS (70 eV, 230 °C) m/e M^+ 589. Anal. Calcd for $C_{37}H_{35}NO_6$: C and H.

27,28,29,30-Tetramethoxy-18,21-dioxapentacyclo[21.3.1.1^{2,6}1.^{7,11}.1^{12,16}]triaconta-1(27),2,4,6(30),7,9,11(29),12,14,16(28),23,25-dodecaene (1). Mixture A was made by suspending 0.31 g of washed NaH in 125 mL of dry THF. Solution B was prepared by dissolving 0.9983 g (1.63 mmol) of **34** and 0.1022 g (1.65 mmol) 1,2-ethanediol in 220 mL of dry THF. The addition time as 36 h, and the total reflux time as 48 h. Gel permeation chromatograhy was done on column B (R_v = 164 mL). Crystallization of residue E from ethanol gave 0.1073 g (12.8% of host **1**: mp 217–218 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.777 (s, inner OCH_3, 6 H), 3.184 (s, outer OCH_3, 6 H), 3.65–3.80 and 3.95–4.10 (AA′BB′, OCH_2CH_2O, 4 H), 4.464 and 4.631 (AB, $ArCH_2O$, 4 H, J = 11.3 Hz), 7.04–7.45 (m, ArH, 12 H); IR (KBr) 2945, 2852, 1590, 1460, 1421, 1403, 1392, 1237, 1085, 1010, 800, 760 cm^{-1}; MS (70 eV, 240 °C) m/e M^+ 512. Anal. Calcd for $C_{32}H_{32}O_6$: C and H. A small sample of host **1** in $CHCl_3$ was complexed with sodium bromide in water. The mixture was filtered through $MgSO_4$ and crystallized from ethyl acetate. The crystals darkened between 230–250 °C but did not melt up to 325 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.911 (s, inner OCH_3, 6 H), 3.355 (s, outer OCH_3, 6 H), 3.710 and 4.273 (AA′BB′, OCH_2CH_2O, 4 H, J_{AB} = 7.2, $J_{AB'}$ = 0), 4.282 and 4.897 (AB, $ArCH_2O$, 4 H, J = 9.5), 7.20–7.58 (m, ArH, 12 H); MS(70 eV, 260 °C) m/e (relative intensity) 512(58), 452 (56), 437 (93), 406 (100). Anal. Calcd for $C_{32}H_{32}BrNaO_6$: C and H.

25,28-Dimethyl-29,30,31,32-tetramethoxy-2*H*,23*H*-3,7:8,12:13,17:18,22-tetrametheno-1,24-benzodioxacyclohexacosin (4). Mixture A was made by suspending 0.28 g of washed NaH in 125 mL of dry THF. Solution B was prepared by dissolving 0.9201 g (1.50 mmol) of **34** and 0.2095 g (1.50 mmol) of 3.6-dimethyl-1,2-benzenediol[21] in 225 mL of THF. The addtion time as 24 h, and the total reflux time was 48 h. Gel permeation chromatography was performed on column B (R_v = 155). Crystallization of residue E in ethanol gave, after drying in vacuo, 0.142 g (16%) of **4**: mp 184 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.525 (s, $ArCH_3$, 6 H), 2.742 (s, inner OCH_3, 6 H), 3.243 (s, outer OCH_3, 6 H), 4.469 and 5.248 (AB, $ArCH_2O$, J = 9.1), 6.93–7.45 (m, ArH, 14 H); MS (70 eV, 200 °C) m/e M^+ 588. Anal. Calcd for $C_{38}H_{36}O_6$: C and H.

(20*R*,23*S*)-31,33,34,35-Tetramethoxy-18,25,32-trioxahexacyclo[25.3.1.1^{2,6}.1^{7,11}.1^{12,16}.1^{20,23}]pentatriaconta-1(31),2,4,6(35),7,9,11(34),12,14,16(33),27,29-dodecaene (13). Mixture A was made by suspending 0.295 g of washed NaH in 125 mL of dry THF. Solution B was prepared by dissolving 0.9381 g (1.53 mmol) of **34** and 0.2024 g (1.53 mL) of *cis*-tetrahydro-2,5-furandimethanol[22] in 200 mL of THF. The addition time as 24 h, and the total reflux time was 48 h. Gel permeation chromatography was done on column B (R_v = 158). Crystallization of residue E from ethanol gave, in two crops, 0.2179 g (24.4%) of host **13**: mp 221 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20–2.08 (m, CH_2CH_2, 4 H), 2.835 and 3.130 (s, inner OCH_3, 2 × 3 H), 3.392 and 3.490 (s, outer OCH_3, 2 × 3 H), 2.96–4.03 (m, OCH_2CHO, 6 H), 4.147 and 5.058 (AB, $ArCH_2O$, 2 H, J = 11.5), 4.427 and 4.651 (AB, $ArCH_2O$, 2 H, J = 11.4), 7.07–7.45 (m, ArH, 12 H); IR (KBr) 2950, 2905, 2875, 1461, 1410, 1225, 1092, 1003, 800, 747 cm^{-1}; MS (70 eV, 240 °C) m/e M^+ 582. Anal. Calcd for $C_{36}H_{38}O_7$: C and H.

Method B. 30,31,32,33-Tetraethoxy-18,21,24-trioxapentacyclo[24.3.1.1^{2,6}.1^{7,11}.1^{12,16}]tritriaconta-1(30),2,4,6(33),7,9,11(32),12,14,16(31),26,28-dodecaene (12). The same equipment was used as in method A except that the addition funnel was pressure equalizing and was equipped with a dual control Teflon stopcock. The same drying procedure was employed, and all reactions were conducted in an atmosphere of dry argon. Mixture A was composed of 0.095 g of a 50% NaH dispersion in mineral oil (which had been washed with dry THF) mixed with 100 mL of freshly distilled THF in the reaction flask. Solution B placed in the addition funnel was composed of 0.379 g (0.566 mmol) of $BrCH_2BCH_2Br$ (**38**) and 0.0601 g (0.567 mmol) of dry 2,2′-oxybisethanol dissolved in 50 mL of dry, freshly distilled THF. Mixture A was heated to vigorous reflux, and after the return thimble was full, solution B was added at a constant rate over 14 h. The reaction mixture was held at reflux for an additional 18 h and cooled, and 1 mL of 2 M hydrochloric acid was added. The solvent was evaporated under reduced pressure to

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give residue C. This material was partitioned between 20 mL of CH_2Cl_2 and 20 mL of deionized water. The mixture was placed in a centrifuge tube and vortexed for 1 min, and then centrifuged to separate the layers. The aqueous layer was pipetted off and discarded. In this fashion, the organic layer was washed five more times with 20-mL portions of deionized water. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed as in method A on column B (R_v = 152). The band containing the product was evaporated under reduced pressure to give residue D, which was crystallized from ethanol to give 0.1784 g (51.4%) of host **12**: mp 139–139.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.486 (t, inner $OCCH_3$, 6 H, J = 7.3), 0.984 (t, outer $OCCH_3$, 6 H, J = 7.0), 3.22–3.40 (m, inner O–CH_2Me, 4 H), 3.50–3.68 (m, outer OCH_2Me and OCH_2CH_2O, 12 H), 4.348 and 4.821 (AB, $ArCH_2O$, 4 H, J = 11.3), 7.10–7.36 (m, ArH, 12 H); IR (KBr) 2850, 1440, 1390, 1223, 1096, 779 cm^{-1}; MS (16 eV, 210 °C) m/e M$^+$ 612. Anal. Calcd for $C_{38}H_{44}O_7$: C and H.

28,29,30,31-Tetraethoxy-18,22-dioxapentacyclo[22.3.1.1^{2,6}.1^{7,11}.1^{12,16}]hentriconta-1(28),2,4,6(31),7,9,11(30),12,14,16(29),24,26-dodecaene (7). Mixture A was made by suspending 0.096 g of washed NaH in 100 mL of dry THF. Solution B was prepared by dissolving 0.3812 g (0.57 mmol) of **38** and 0.0434 g (0.60 mmol) of dry 1,3-propanediol in 100 mL of dry THF. The addition time was 24 h, the total reflux time was 48 h. Gel permeation chromatography was done on column B (R_v = 156.8 mL). Crystallization from ethanol of residue D gave 0.1479 g (44.4%) of host **7**: mp 241–242 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.471 (t, inner $OCCH_3$, 6 H, J = 6.9), 0.900 (t, outer $OCCH_3$, 6 H, J = 7.0), 1.77–1.95 (m, CCH_2C, 2 H), 2.79–3.30 (m, inner OCH_2Me, 4 H), 3.30–3.39 (m, OCH_2CCH_2O, 4 H), 3.40–3.58 (m, outer OCH_2Me, 4 H), 4.459 and 4.804 (AB, $ArCH_2O$, 4 H, J = 11.8), 7.05–7.43 (m, ArH, 12 H); ^{13}C NMR (90 MHz, $CDCl_3$, ^{1}H decoupled) δ 15.30 (2 CH_3), 30.41 (C–CH_2–C), 65.30, 67.95, 68.44, and 70.12 (4 CH_2O), 122.56, 122.99, 128.25, 129.77, 129.93, 130.25, 130.80, 132.26, 133.34, 134.05, 156.91, and 158.15 (12 Ar); MS (70 eV, 230 °C) m/e M$^+$ 582. Anal. Calcd for $C_{37}H_{42}O_6$: C and H.

29,30,31,32-Tetraethoxy-2*H*,23*H*-3,7:8,12:13,17:18,22-tetrametheno-1,24-benzodioxacyclohexacosin (3). Mixture A was made by suspending 0.166 g of washed NaH in 150 mL of dry THF. Solution B was prepared by dissolving 0.6588 g (0.986 mmol) of **38** and 0.1085 g (0.986 mmol) of dry 1,2-benzenediol in 100 mL of THF. The addition time as 36 h, and the total reflux time was 48 h. Gel permeation chromatography was done on column B (R_v = 160 mL). Crystallization from ethanol of residue D gave 0.3581 g (52%) of host **3**, mp 129–131 °C. This host crystallized as a solvate from several different solvents. The solvent was not removed by drying in vacuo. The analytical and spectral sample (^{1}H NMR, 20 MHz, $CDCl_3$) contained ethanol (s, 1.15 (t), and 3.60 (q)) and dichloromethane (δ 5.20 (s)) in the ratio to the host shown in the elemntal analysis, calculated. The spectra of **3** were as follows: δ 0.180 (t, inner $OCCH_3$, 6 H, J = 7.0), 0.836 (t, outer $OCCH_3$, 6 H, J = 7.0), 2.70–3.10 (m, inner OCH_2Me, 4 H), 3.30–3.45 (m, outer OCH_2Me, 4 H), 4.827 and 5.457 (AB, $ArCH_2O$, 4 H, J = 10.8), 6.78–7.45 (m, ArH, 16 H); MS (70 eV, 210 °C) m/e M$^+$ 616. Anal. Calcd for $C_{40}H_{40}O_6 \cdot CH_2Cl_2(0.85) \cdot C_2H_6O(0.2)$: C, 70.96; H, 6.19; Cl, 8.63. Found: C, 70.92; H, 6.20; Cl, 8.76. A small sample of **3** was sublimed (110 °C, 1 × 10^{-5} mmHg), mp 138 °C.

(20*R*,23*S*)-31,33,34,35-Tetraethoxy-18,25,32-trioxahexacyclo[25.3.1.1^{2,6}1^{7,11}.1^{12,16}.1^{20,23}]pentatriconta-1(31),2,4,6(35),7,9,11(34),12,14,16(33),27,29-dodecaene (14). Mixture A was made by suspending 0.16 g of washed NaH in 100 mL of dry THF. Solution B was prepared by dissolving 0.4872 g (0.73 mmol) of **38** and 0.1060 g (0.80 mmol) of dry *cis*-tetrahydro-2,5-furandimethanol[22] in 100 mL of dry THF. The addition time was 30 h, and the total reflux time was 48 h. Gel permeation chromatography was done on column B (R_v = 149 mL). Crystallization from ethanol of residue D gave 0.121 g (27.3%) of host **14**: mp 202–203 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40–1.62 (m, inner $OCCH_3$, 6 H), 1.90–2.05 (m, outer $OCCH_3$, 6 H), 1.35–2.00 (m, CCH_2CH_2C, 4 H), 2.95–4.00 (m, 2 OCH_2CHO and 4 OCH_2Me, 14 H), 4.34 and 4.83 (AB, $ArOCH_2$, 2 H, J = 11.8), 4.46 and 4.83 (AB, $ArOCH_2$, 2 H, J = 11.8), 7.05–7.40 (m, ArH, 12 H); MS (70 eV, 180 °C) m/e M$^+$ 638. Anal. Calcd for $C_{40}H_{46}O_7$: C and H.

(19*S*,20*S*)-19,20-Bis((phenylmethoxy)methyl)-27,28,29,30-tetramethoxy-18,21-dioxapentacyclo[21.3.1.1^{2,6}.1^{7,11}.1^{12,16}]triconta-1(27),2,4,6(30),7,9,11(29),12,14,16(28),23,25-dodecaene (5). Mixture A was made by suspending 0.23 g of washed NaH in 200 mL of dry THF. Solution B was prepared by dissolving 0.8222 g (1.34 mmol) of **34** and 0.4060 g (1.34 mmol) of (2*S*,3*S*)-(+)-1,4-bis(phenylmethoxy)-2,3-butanediol[11] in 100 mL of THF. The addition time was 24 h, and the total reflux time was 48 h. Gel permeation chromatography was done on column B (R_v = 147 mL). Two crystallizations from ethanol of residue D gave 0.4695 g (46.4%) of host **5**, mp 137–138 °C. A crystal dissolved in $CDCl_3$–CS_2 (4:1) at 215 K (–58 °C) gave ^{1}H NMR chemical shifts for only α-**5**. When warmed, the spectrum of the solution showed the absence of β-**5** up to 265 K.

At 275 K the spectrum of β-**5** started to appear, and by the time 305 K was reached, the epimers had reached equilibrium to give a ratio of α to β of 11.5:1. A crystal of α-**5** dissolved at 300 K gave an ^{1}H NMR spectrum (200 MHz, $CDCl_3$) for epimer α-**5** δ 2.808 (s, inner OCH_3, 6 H), 3.092 (s, outer OCH_3, 6 H), 3.60–3.75 (m) and 3.90–3.95 (d, J = 9.5) ($OCCH_2O$, 4 H), 4.30–4.39 (m, OCHCHO, 2 H), 4.427 and 4.957 (AB, $ArCH_2O$, 4 H, J = 11.8), 4.524 (s, $PhCH_2O$, 4 H), 7.02–7.44 (m, ArH, 22 H); and for epimer β-**5** (in part) δ 2.683 (s, inner OCH_3, 6 H), 3.048 (s, outer OCH_3, 6 H), 4.80–4.88 (1/2 AB, $ArCH_2O$, 2 H, J = 10.7); MS (16 eV, 200 °C) m/e M$^+$ 752. Anal. Calcd for $C_{48}H_{48}O_8$: C and H. When a crystal of α-**5** was dissolved in $CDCl_3$–$(CD_3)_2CO$ (10:1) at 205 K followed by addition of a 20% molar excess of sodium picrate in $(CD_3)_2CO$, the ^{1}H NMR spectrum of only α-**5**·NaPic was observed. After this solution had been heated at 323 K for 2 weeks, it gave an equilibrium mixture in the ratio of α-**5**·NaPic to β-**5**·NaPic of 1:1.5, whose ^{1}H NMR spectrum (200 MHz, 301 K) gave for α-**5**·NaPic δ 2.741 (s, inner OCH_3, 6 H), 3.202 (s, outer OCH_3, 6 H), 3.50–3.72 (m, $OCCH_2O$, 4 H), 3.91–4.04 (m, OCHCHO, 2 H), 4.413 and 5.045 (AB, $ArCH_2O$, 4 H, J = 10.2), 4.533 and 4.576 (AB, $PhCH_2O$, 4 H, J = 2.0), 7.10–7.68 (m, ArH, 22 H), 8.746 (s, pic H, 2 H); and for β-**5**·NaPic δ 2.507 (s, inner OCH_3, 6 H), 3.089 (s, outer OCH_3, 6 H), 3.40–4.00 (m, $OCHCH_2O$, 6 H), 4.207 and 5.099 (AB, $ArCH_2O$, 4 H, J = 10.4), 4.375 (bs, $PhCH_2O$, 4 H), 7.05–7.50 (m, ArH, 22 H), 8.666 (s, pic H, 2 H). When the same procedure was applied to a crystal of α-**5** in C_6D_5C-D_3–$(CD_3)_2SO$ (95:5) and in CD_3CN–$(CD_3)_2SO$ (95:5), both solutions reached an equilibrium mixture of epimeric complexes of **5** within 1 h of reaching 340 K in a ratio of α-**5**·NaPic to β-**5**·NaPic of 1:1.6.

30,31,32,33-Tetramethoxy-18,24-dioxa-21-thiapentacyclo[24.3.1.1^{2,6}.1^{7,11}.1^{12,16}]tritriaconta-1(30),2,4,6(33),7,9,11(32),12,14,16(31),26,28-dodecaene (16). Mixture A was made by suspending 0.27 g of washed NaH in 200 mL of dry THF. Solution B was prepared by dissolving 1.0047 g (1.64 mmol) of **34** and 0.2002 g (1.64 mmol) of 2,2′-thiobis(ethanol) in 200 mL of dry THF. The addition time was 30 h, and the total reflux time was 48 h. Gel permeation chromatography was done on column B (R_v = 156 mL). Crystallization of residue D from ethanol gave 0.4259 g (45.3%) of **16**: mp 146 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.61–2.90 (m, S-CH_2C, 4 H), 3.011 (s, inner OCH_3, 6 H), 3.495 (s, outer OCH_3, 6 H), 3.50–3.78 (m, OCH_2C, 4 H), 4.339 and 4.737 (AB, $ArCH_2O$, 4 H, J = 10.6), 7.05–7.49 (m, ArH, 12 H); IR (KBr) 2938, 2860, 1581, 1453, 1405, 1230, 1080, 1002, 762 cm^{-1}; MS (70 eV, 200 °C) m/e M$^+$ 572. Anal. Calcd for $C_{34}H_{36}O_6S$: C and H.

30,31,32,33-Tetramethoxy-18,24-dioxa-21-thiapentacyclo[24.3.1.1^{2,6}.1^{7,11}.1^{12,16}]tritriaconta-1(30),2,4,6(33),7,9,11(32),12,14,16(31),26,28-dodecaene 21-Oxide (17). A solution of 0.1561 g (0.273 mmol) of host **16** in 80 mL of CH_2Cl_2 was cooled to –77 °C. A solution containing 0.0554 g (0.273 mmol) of 85% *m*-chloroperbenzoic acid in 30 mL of CH_2Cl_2 was added. The resulting mixture was stirred 16 h while being slowly allowed to return to room temperature. The reaction mixture was concentrated to 20 mL and placed in a centrifuge tube. The organic layer was vortexed with 20 mL of a saturated aqueous Na_2SO_3 solution, centrifuged, and separated from the aqueous layer. In this manner the organic layer was washed successively with 20 mL of 0.6 M NaOH solution in water, 20 mL of a saturated $NaHCO_3$ solution in water, and six times with 20-mL portions of deionized water. Cyclohexane (10 mL) was added to the organic layer, and it was concentrated to 10 mL. The crystals that separated were collected and dried in vacuo to give 0.1072 g (66.7%) of **17**: mp 169 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.81–3.19 (m, $S(O)CH_2C$, 4 H), 2.965 and 3.017 (s, inner OCH_3, 2 × 3 H), 3.439 and 3.468 (s, outer OCH_3, 2 × 3 H), 3.82–4.02 (m, O–CH_2C, 4 H), 4.272 and 4.866 (AB, $ArCH_2O$, 2 H, J = 10.7), 4.354 and 4.793 (AB, $ArCH_2O$, 2 H, J = 10.1), 7.05–7.43 (m, ArH, 12 H); IR (KBr) 2945, 2855, 1460, 1405, 1222 (vs), 1090, 1002, 761 cm^{-1}; MS 770 eV, 230 °C) m/e M$^+$ 588. Anal. Calcd for $C_{34}H_{36}O_7S$: C and H.

30,31,32,33-Tetramethoxy-18,24-dioxa-21-thiapentacyclo[24.3.1.1^{2,6}.1^{7,11}.1^{12,16}]tritriaconta-1(30),2,4,6(33),7,9,11(32),12,14,16(31),26,28-dodecaene 21,21-Dioxide (18). Into 50 mL of CH_2Cl_2 cooled to 0 °C were stirred 0.1196 g (0.21 mmol) of sulfide **16** and 0.1272 g (0.63 mmol) of 85% *m*-chloroperbenzoic acid for 6 h. The mixture was concentrated to 20 mL and placed in a centrifuge tube. The organic solution was vortexed with 20 mL of water saturated with Na_2SO_3 solution, centrifuged, and separated from the aqueous layer by pipet. In the same manner the organic layer was washed with 20 mL of 0.6 M NaOH in water, 20 mL of $NaHCO_3$ in water, and five times with 20-mL portions of deionized water. Addition of cyclohexane, followed by concentration of the solution and cooling, gave 0.0996 g (78.8%) of sulfone **18**: mp 183–184 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.921 (s, inner OCH_3), 3.30–4.20 (m, $OCH_2CH_2S(O)$, 8 H), 3.325 (s, OCH_3, 6 H),

4.306 and 4.840 (AB, $ArCH_2O$, 4 H, J = 10.7), 7.05–7.43 (m, ArH, 12 H); IR (KBr) 2947, 1459, 1407, 1292, 1230, 1129, 1099, 1008, 761 cm^{-1}; MS (70 eV, 280 °C) m/e M^+ 604. Anal. Calcd for $C_{34}H_{36}O_8S$: C and H.

***N,N'''*-(2,2',2'',2'''-Tetramethoxy[1,1':3',1'':3'',1'''-quaterphenyl]-3,3'''-diyl)bis[*N'*-(3-bromopropyl)urea] (35).** A solution of 3.45 g (6.7 mmol) of diacid **32** dissolved in 20 mL of thionyl chloride was refluxed for 1.5 h. The solution was concentrated under reduced pressure. Residual thionyl chloride was removed as an azeotrope with 30 mL of dry benzene. The residue was dissolved in 21 mL of dry acetone (molecular sieves) and cooled to 0 °C. Sodium azide, 1.13 g (17.5 mmol), dissolved in 3.5 mL of water was added. After stirring for 20 min the solution was poured into 250 mL of cold water. The reaction mixture was extracted with cold toluene. The organic layer was washed with brine and dried ($MgSO_4$). The solution was filtered and dried ($MgSO_4$) a second time. Under a nitrogen atmosphere, the solution was brought to reflux for 1 h and cooled to 0 °C. Then 3.01 g (13.8 mmol) of 3-bromopropylamine hydrobromide and 1.78 g (13.7 mmol) of *N,N*-diisopropylethylamine were added to the stirred solution. After 24 h the solvent was removed in vacuo. The residue was triturated with 100 mL of methanol and filtered. Water was added to the filtrate to give a second crop of white solid. The combined solids were triturated with diethyl ether to give 3.22 g (61.2%) of **35**: mp 173–177 °C (dec); ^1H NMR (200 MHz, $(CD_3)_2SO$) δ 1.96–2.10 (m, C-CH_2-C, 4 H), 3.19–3.29 (m, CH_2N, 4 H), 3.193 (s, inner OCH_3, 2 × 3 H), 3.385 (s, outer OCH_3, 2 × 3 H), 3.559 (t, CH_2Br, 4 H, J = 6.3), 6.80–7.40 (m, ArH, 10 H), 8.167 (d, ArH ortho to urea, 2 H, J = 8.3); MS (16 eV, 240 °C) m/e 622 (M^+ − 2(HBr), 3.7), 496 (M^+ − 2($NH(CH_2)_3Br$), 8.3), 58 ($NHCH_2CH_2CH_2$, 100). A small amount was eluted (R_f = 0.5) on a thick layer silica gel plate with EtOH–CH_2Cl_2 (1:9) to give pure **35**. Anal. Calcd for $C_{36}H_{40}Br_2N_4O_6$: C and H.

2,2',2'',2'''-Tetramethoxy-3,3'''-bis(tetrahydro-2-oxo-1(2*H*)-pyrimidinyl)-1,1':3',1'':3'',1'''-quaterphenyl (21). A solution of 4.21 g (5.37 mmol) of **35** and 2.41 g (21.5 mmol) of KOBu-*t* in 250 mL of *t*-BuOH was allowed to stand for 24 h under a drying tube ($CaSO_4$). The mixture was poured into 1 L of water and stirred for 8 h. The suspension was filtered. The solid was dissolved in CH_2Cl_2–MeOH (9:1). Addition of ethyl acetate followed by concentration of the resulting solution gave two crops of a light yellow solid. The solid was placed in a soxhlet thimble and extracted with $CHCl_3$. The solid, which crystallized from $CHCl_3$, was collected. Addition of acetone to the mother liquor yielded more solid material. The combined solids were triturated with diethyl ether to give 2.60 g (77.8%) of **21**: mp 245–250 °C (dec); ^1H NMR (200 MHz, $CDCl_3$) δ 2.03–2.12 (m, C-CH_2-C, 4 H), 3.290 (s, inner OCH_3, 2 × 3 H), 3.42–3.49 (m, -CH_2NH, 4 H), 3.57–3.63 (m, -CH_2NAr, 4 H), 3.595 (s, outer OCH_3, 6 H), 4.800 (bs, NH, 2 H), 7.12–7.42 (m, ArH, 12 H); ^{13}C NMR (90 MHz, $CDCl_3$) 22.70 (t, C-CH_2-C, J_{CH} = 22.0), 41.12 (t, CH_2N, J_{CH} = 20.8), 49.08 (t, CH_2N, J_{CH} = 22.0), 60.70 (q, OCH_3, J_{CH} = 21.0), 61.00 (q, OCH_3, J_{CH} = 21.0), 123.6–136.7 (Ar), 154.4 (s, C-OMe), 155.81 (s, C-OMe), 156.02 (s, C=O); IR (KBr) 3400–2900, 2780, 2660, 1660 (vs), 1508, 1459, 1320, 1240, 1016, 765 cm^{-1}; MS (16 eV, 270 °C) m/e M^+ 622. Compound **21** always crystallized as a solvate and was hydroscopic. For analysis, a sample was sublimed (200 °C, 3 × 10^{-5} mmHg). Anal. Calcd for $C_{36}H_{38}N_4O_6$: C and H.

2,2',2'',2'''-Tetramethoxy-3,3'''-bis(tetrahydro-2-oxo-3-methyl-1-(1*H*)-pyrimidinyl)-1,1':3',1'':3'',1'''-quaterphenyl (22). Under dry conditions, 0.152 g (0.24 mmol) of dry **21** and 0.05 g (1.0 mmol) of a 50% dispersion of sodium hydride in oil (washed first with dry THF) were mixed with 100 mL of dry freshly distilled THF. The mixture was refluxed for 5 h and allowed to cool to 25 °C. Then 0.06 mL of CH_3I was added. The solution was stirred for 4 h, and 0.1 mL more CH_3I was added. The mixture was stirred for 16 h, and another 0.1 mL of CH_3I was added to the solution, which was brought to reflux. Eight hours later the solution was cooled and mixed with EtOH containing 1 mL of 6 M hydrochloric acid. The solvent was evaporated under reduced pressure. The residue was eluted twice with EtOAc–EtOH–CH_2Cl_2 (10:10:80) on a thick layer silica gel plate. A center band was extracted with CH_2Cl_2. Product solidified following evaporation of the solvent to give 0.104 g of **22** (66%): mp 192–194 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 2.05–2.25 (m, -CH_2-C, 4 H), 3.017 (s, NCH_3, 2 × 3 H), 3.268 (s, inner OCH_3, 2 × 3 H), 3.35–3.45 (m, N-CH_2, 4 H), 3.569 (s, outer OCH_3, 2 × 3 H), 3.56–3.70 (m, NCH_2, 4 H), 7.08–7.30 (m, ArH, 12 H); IR ($CHCl_3$) 3000, 1630, 1318, 1008, 920 cm^{-1}; MS (16 eV, 210 °C) m/e M^+ 650. Anal. Calcd for $C_{38}H_{42}N_4O_6$: C and H.

8,9,33,34-Tetrahydro-38,39,40,41-tetramethoxy-7*H*,36*H*-6,10:31,35-dimethano-11,15:16,20:21,25:26,30-tetrametheno-5*H*,32*H*-benzo[*g*][1,5,10,14]tetraazacyclotetratriacosin-37,42-dione (19). In a dry argon atmosphere were suspended 0.154 g of NaH (washed free of oil with dry THF) and 0.3317 g (0.533 mmol) of finely ground bisurea **21** in 500 mL of freshly distilled THF. The mixture was refluxed for 4 h and cooled to −77 °C, and 0.1408 g (0.533 mmol) of 1,2-bis(bromomethyl)benzene in 80 mL dry THF was added under an inert atmosphere by cannula. The temperature was held at −77 °C for 2 h. The reaction mixture was allowed to warm to 25 °C over a 16 h period. After a total of 26 h, the mixture was neutralized with a small portion of hydrochloric acid and concentrated under reduced pressure. The residue was partitioned between 200 mL of CH_2Cl_2 and 200 mL of brine. The organic layer was dried ($MgSO_4$). Gel permeation chromatography (column A, R_v = 178 mL) afforded an oil, which was decomplexed by washing the oil dissolved in 20 mL of CH_2Cl_2 with six 20-mL portions of deionized water. Ethanol was added to the organic layer and the solution was concentrated to 10 mL. The crystals, dried in vacuo, gave 0.1588 g (40.3%) of cycle **19**, 285 °C (darkens): mp 315–316 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 1.90–2.20 (m, C-CH_2-C, 4 H), 3.041 (s, inner OCH_3, 6 H), 3.10–3.20 (m, NCH_2, 4 H), 3.35–3.65 (m, NCH_2, 4 H), 3.686 (s, outer OCH_3, 6 H), 4.532 and 4.947 (AB, $ArCH_2N$, 4 H, J = 15.9), 7.09–7.42 (m, ArH, 16 H); MS (16 eV, 200 °C) m/e M^+ 724. Anal. Calcd for $C_{44}H_{44}N_4O_6$: C and H.

38,42,43,44-Tetramethoxy-18,22,28,32-tetraazaoctacyclo[32.3.1.$1^{2,6}$.$1^{7,11}$.$1^{12,16}$.$1^{18,22}$.$1^{23,27}$.$1^{28,32}$]tetratetraconta-1(38),2,4,6(44),7,9,11(43),12,14,16(42),23,25,27(40),34,36-pentadecaene-39,41-dione (20). To a suspension of 0.10 g of NaH (washed free of oil with dry THF) in 500 mL of dry THF stirred under dry conditions under argon was added 0.2749 g (1.00 mmol) of 1,3-bis(hexahydro-2-oxo-1-pyrimidinyl)benzene (**39**) (see next section). The mixture was refluxed for 4 h and cooled to −77 °C, and 0.6144 g (1.00 mmol) of dibromide **34** in 80 mL of dry THF was added under dry argon by cannula. After 2 h at −77 °C, the reaction mixture was allowed to warm to 25 °C over a 16 h period. After a 26 h period, the mixture was neutralized with a small amount of hydrochloric acid and concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 and brine, and the organic layer was washed with deionized water, dried, and evaporated. The residue in 20 mL of CH_2Cl_2 was subjected to gel permeation chromatography (column B, R_v = 146). The residue from this band was eluted from a thick layer silica gel plate (R_f = 0.3) with EtOH–Et_2O–CH_2Cl_2 (5:52:70). The oil obtained from the plate was crystallized from ethyl acetate. The solid, dried in vacuo, gave 0.082 g (11.3%) of host **20**: mp 250–251 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 1.80–2.25 (m, C-CH_2-C, 4 H), 3.03–3.18 (m, NCH_2, 4 H), 3.290 (s, inner OCH_3, 6 H), 3.440 (s, outer OCH_3, 6 H), 3.49–3.60 (m, NCH_2 4 H), 3.577 and 6.016 (AB, $ArCH_2N$, 4 H, J = 14.8), 6.85–7.38 (m, ArH, 16 H); MS (70 eV, 230 °C) m/e M^+ 724. Anal. Calcd for $C_{44}H_{44}N_4O_6$: C and H.

1,3-Bis(hexahydro-2-oxo-1-pyrimidyl)benzene (39). A solution of 1.0 g (9.3 mmol) of 1,3-diaminobenzene and 3 mL (3.4 g, 28.6 mmol) of 3-chloropropylisocyanate in 150 mL of CH_2Cl_2 was stirred at room temperature for 48 h. The mixture was concentrated under reduced pressure, and the residue that separated was collected, washed with ether, and dried under vacuum to give 3.15 g (98%) of crude open-chain dichloro bis(urea). This compound (2.5 g, 7.2 mmol) was suspended in 300 mL of dry *t*-BuOH, KOBu-*t* (4.50 g, 40 mmol) was added, and the mixture was stirred at 25 °C for 15 h. The mixture was acidified with dilute hydrochloric acid to pH 5, and the product that separated was collected and dried under vacuum to give 1.22 g of crude **39**. The mother liquor was evaporated, and the residue was distributed between CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4) and evaporated to yield an additional 0.65 g of **39**, total yield 96%: mp 256 °C; ^1H NMR (60 MHz, $(CD_3)_2SO$) δ 1.75 (m, 4 H, $NCH_2CH_2CH_2N$), 3.10 and 3.45 (2 × t, 2 × 4 H, $NCH_2CH_2CH_2N$), 6.40 (bs, 2 H, NH), 6.80–7.20 (m, 4 H, ArH). This material was used to prepare **20** (see previous section) without further purification or characterization.[10]

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