Host–Guest Complexation. 24. Synthesis of Multiheteromacrocycles Containing Intramolecularly Interacting Units or New Steric Barriers[1]

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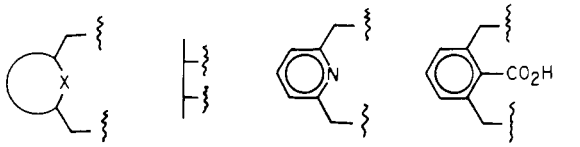
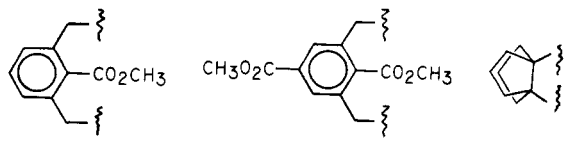
Abstract: Six new multiheteromacrocyclic hosts containing pyridine-2,6-dimethylyl (P), 2-carboxy-1,3-xylyl (A), 2-carbomethoxy-1,3-xylyl (M), 2,5-bis(carbomethoxy)-1,3-xylyl (T), 1,5-bicyclo[3.3.0]octyl (B), dimethylene (E), or oxygen (O) units are reported. Treatment of 2,6-bis((2-hydroxyethoxy)methyl)pyridine ($P(OEOH)_2$) with methyl 2,6-bis(bromomethyl)benzoate (MBr_2) in $(CH_2)_4O$–NaH gave $M(OEO)_2P$ (43%), hydrolysis of which gave $A(OEO)_2P$, whose pyridine nitrogen and carboxylic hydrogen form a strong transannular hydrogen bond (pK_a and crystal structure). The reaction of MBr_2 with diethylene glycol (HOEOEOH) in $(CH_2)_4O$–NaH gave $M(OEOEO)_2M$ (21%), which was hydrolyzed to $A(OEOEO)_2A$, whose transannularly located carboxyl groups form a planar eight-membered ring containing linear hydroxyl-to-carbonyl hydrogen bonds (crystal structure and pK_a's). Similarly, $T(OEOEO)_2T$ was formed from $T(Br)_2$ and HOEOEOH (18%). Treatment of $B(OH)_2$ with $(TsOEOEO)_2E$ in $(CH_2)_4O$–NaH gave $B(OEOEO)_2E$ (25%), whose ability to complex *tert*-butylammonium thiocyanate in chloroform saturated with water was found to be only slightly less than that of $E(OEOEO)_2E$.

Earlier publications in this series describe the introduction of a wide variety of structural units that allow the perimeter of macrocyclic polyether hosts to be shaped so they will exhibit structural recognition toward selected guests in complex formation.[2] These units fall roughly into two categories: (a) α,α'-dimethylene heterocycles or 1,3-dimethylene carbocycles bearing functional-group binding sites at the 2-position (**1**); (b) rigid or



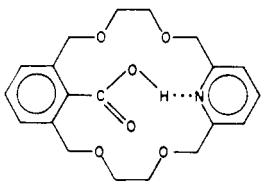
1 2 P unit A unit



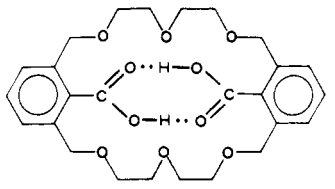
M unit T unit B unit

conformationally confined structures with semiconvergent sites for attaching the ends of oligoethyleneglycol chains (**2**). Examples from class a include the pyridine-2,6-dimethylyl,[3-5] 2-carboxy-1,3-xylyl,[6] 2-methoxy-1,3-xylyl,[7] furan-2,5-dimethylyl,[3,8,9] and tetrahydrofuranyl-2,5-dimethylyl units.[3,8] Class b is exemplified by the 1,1′-binaphthyl-2,2′-diyl,[3,10] 1,1′-bitetralyl-2,2′-diyl,[11] 1,1′-bicyclohexyl-2,2′-diyl,[12] and [2.2]paracyclophanyl[3,13] structural units.

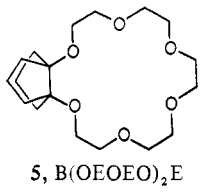
Here we report the incorporation into macrocyclic polyethers of "class a" units P, A, M, and T and of "class b" unit B. The structures of the hosts are designated with line formulas in the text that employ these abbreviations and the symbols E for CH_2CH_2 and O for oxygen. Of the six hosts prepared, **3**, **4**, and **5** are the most important.



3, $A(OEO)_2P$



4, $A(OEOEO)_2A$



5, $B(OEOEO)_2E$

These compounds were studied for several reasons. (1) In the design of host–guest complexes, we have used Corey–Pauling–Koltun (CPK) molecular models extensively as guides in designing complementary relationships between host and guest.[2] Compounds **3** and **4** represent "intramolecular complexes" that in CPK molecular models provide perfect alignment of potentially complexing functional groups. Since CPK molecular parts are based on crystal structures of simple organic compounds, it is important to test

(1) The authors thank the National Science Foundation for a grant (CHE 72-04616A 04) used in support of this work.

(2) For reviews, see: (a) Cram, D. J.; Trueblood, K. N. *Top. Curr. Chem.* **1981**, *98*, 43–106. (b) Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1978**, *11*, 8–14.

(3) Timko, J. M.; Helgeson, R. C.; Newcomb, M.; Gokel, G. W.; Cram, D. J. *J. Am. Chem. Soc.* **1974**, *96*, 7097–7099.

(4) (a) Newcomb, M.; Gokel, G. W.; Cram, D. J. *J. Am. Chem. Soc.* **1974**, *96*, 6810–6811. (b) Newcomb, M.; Timko, J. M.; Walba, D. M.; Cram, D. J. *Ibid.* **1977**, *99*, 6392–6398.

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(6) (a) Newcomb, M.; Cram, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 1257–1259. (b) Newcomb, M.; Moore, S. S.; Cram, D. J. *Ibid.* **1977**, *99*, 6405–6410.

(7) Koenig, K. E.; Lein, G. M.; Stückler, P.; Kaneda, T.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3553–3566.

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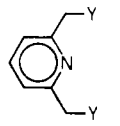
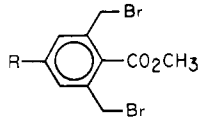
the hypothesis that CPK molecular parts in turn can be assembled into designed complexes whose crystal structures will validate or discount the design procedure. Compounds **3** and **4** were prepared mainly for crystal structure determination. (2) Few hosts containing steric barriers for shaping purposes have been prepared that are nonchiral and whose symmetry properties are such that the same perching complex is produced irrespective of which face of the host is bound. Host **5** contains such a steric barrier in the form of unit B. Host **5** was prepared to test the effect on binding properties of incorporating this unit into an 18-crown-6 host. (3) We wished to develop additional synthetic methods applicable to hosts containing multiple functional groups and steric barriers.

Results

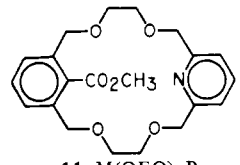
Syntheses. The key intermediate in the syntheses of the pyridyl-containing hosts was **8**. Treatment of **6**[4b] with NaH–C-



6, Y = OH
7, Y = $OCH_2CO_2CH_3$
8, Y = OCH_2CH_2OH



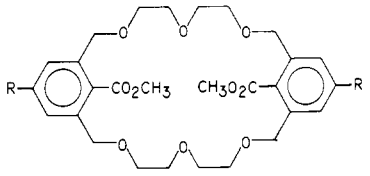
9, R = H
10, R = CO_2CH_3



11, $M(OEO)_2P$

$H_3O_2CCH_2Br$ afforded diester **7** (72%), which was converted to diol **8** (77%) with $NaBH_4$. The disodium salt of **8** was prepared in situ in $(CH_2)_4O$ with NaH and condensed with ester dibromide **9**[6b] under medium dilution conditions to furnish the cyclic ester–pyridine host **11** in 43% yield. Hydrolysis of **11** provided **3** (98%). Although amino acid **3** formed a crystalline complex when treated with $(CH_3)_3CNH_2$, it was not suitable for crystal structure determination.

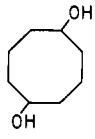
Hosts containing two convergent diester groups were synthesized by the reaction of dibromide **9** or **10**[14] with the disodium salts of diethylene glycol at medium dilution in $(CH_2)_4O$. Macrocycles **12** and **13** were obtained in 21% and 18% yields, respectively.



12, (R = H) or $M(OEOEO)_2M$
13, (R = CO_2CH_3) or $T(OEOEO)_2T$

Hydrolysis of diester **12** with KOH in hot 95% ethanol gave **4** (70%). No x-ray structure quality crystals of salt complexes of **4** were successfully prepared.

Diol **16**[15] was the desired synthon for preparation of hosts containing the bicyclo[3.3.0]octyl structural unit, B. This diol



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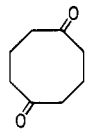

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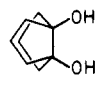

16 or $B(OH)_2$

was prepared in two steps from *cis*-1,5-cyclooctanediol (**14**).[16] Prolonged oxidation of **14** with pyridinium chlorochromate[17] in CH_2Cl_2 afforded cyclooctane-1,5-dione (**15**, 51%). This method was found superior to that reported[18] involving Jones reagent.[19]

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Table I. Comparison of pK_a Values of $A(OEO)_2P$ (**3**) with Those of Model Compounds in H_2O at 22 °C

compound	pK_a[a]	compound	pK_a[a]
$A(OEO)_2P$ (**3**)	5.8	$A(OCH_3)_2$ (**18**)	3.3
$A(OEO)_2PH^+$	3.6	$^+HP(OEOE)_2O$ (**19**)	4.8
$A(OEOE)_2O$ (**17**)	4.8	$^+HP(OCH_3)_2$ (**20**)	4.9

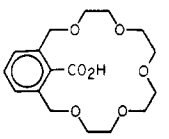
[a] Calculated as pH at half-titration.

Table II. Association Constants and Free Energies of Association in $CDCl_3$ Saturated with D_2O for Hosts with $(CH_3)_3CNH_3^+SCN^-$

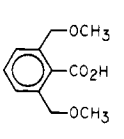
	$K_a \times 10^{-3}$, mol^{-1}		$-\Delta G°$, kcal mol^{-1}	
host	0 °C	24 °C	0 °C	24 °C
$B(OEOEO)_2E$ (**5**)	16 000	860	9.0	8.1
$E(OEOEO)_2E$	32 800	3000	9.4	8.8
$C_6H_4(OEOEO)_2E$	10 500	615	8.8	7.9

Reductive coupling of **15** with zinc amalgam[20] gave *cis*-diol **16**[15] (41%). The utility of this synthon for macrocyclic polyether synthesis was demonstrated by its conversion to host **5** (25%) by reaction with NaH–$TsO(EO)_5Ts$ in $(CH_2)_4O$ under medium dilution conditions.

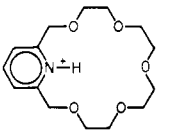
Properties. It was interesting to compare the acidities of $A(OEO)_2P$ (**3**) and $A(OEOEO)_2A$ (**4**) with those of related hosts $A(OEOE)_2O$ (**17**)[4b] and $^+HP(OEOE)_2O$ (**19**)[6b] and their open-



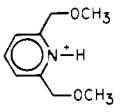
17, $A(OEOE)_2O$



18, $A(OCH_3)_2$



19, $^+HP(OEOE)_2O$



20, $^+HP(OCH_3)_2$

chain model compounds, $A(OCH_3)_2$ (**18**)[4b] and $^+HP(OCH_3)_2$ (**20**).[6b] The pK_a's of protonated **3** and of **3** were determined in water at 22 °C by titration with LiOH and HCl solutions. Table I reports the results and the pK_a's of **17**–**20**.[4b,6b] Unfortunately, the insolubility of $A(OEOEO)_2A$ (**4**) in water required that pK_a determinations be carried out in a 65:35 (v/v) mixture of $(CH_3)_2SO$ and H_2O. Under these conditions, $pK_1 = 6.30$ and $pK_2 = 8.00$, and the pK_a of the open-chain model compound $A(OCH_3)_2$ (**18**)[4b] was 6.65.

In order to compare the binding ability of $B(OEOEO)_2E$ (**5**) with other hosts, the association constant (K_a) was determined for **5** with $(CH_3)_3CNH_3^+SCN^-$ in $CDCl_3$ (saturated with D_2O) at 0 and 24 °C by the $CDCl_3$–D_2O extraction method.[8b] At 24 °C, 13% of the host was distributed into the aqueous layer, and at 0 °C, 9%. The k_a values were corrected for this distribution, as described for 18-crown-6 ($E(OEOEO)_2E$), of which 15% and 12% were found at equilibrium in D_2O at 24 C and 0 °C, respectively.[8b] Table II records the K_a values and derived free-energies of association ($-\Delta G°$) at the two temperatures for $B(OEOEO)_2E$ (**5**), $E(OEOEO)_2E$,[8b] and benzo-18-crown-6 ($C_6H_4(OEOEO)_2E$), which partitions negligibly into the aqueous phase.[8b]

Discussion

Structure. The single-crystal X-ray structures of acid pyrido host $A(OEO)_2P$ (**3**), shown in **21**,[21] and diacid host $A(OEOEO)_2A$ (**4**), shown in **22**,[22] turned out as predicted from CPK molecular

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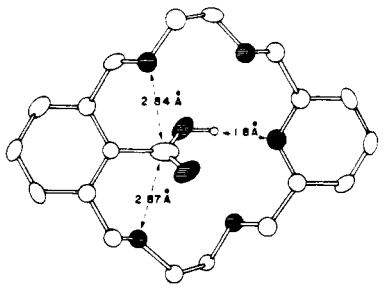
(22) Goldberg, I. *Acta Crystallogr., Sect. B* **1981**, *B37*, 102–107.



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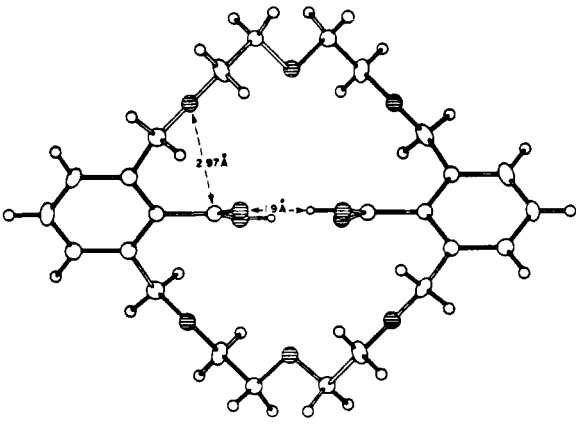

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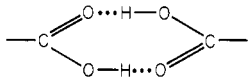
model examination. The length of the OCH_2CH_2O bridges in **21** in their gauche conformations is such as to place the carboxyl proton within comfortable hydrogen-bonding distance to the pyridine nitrogen (1.8 Å). Likewise, the length of the $OCH_2CH_2OCH_2CH_2O$ bridges in **22** in their OCH_2CH_2O gauche conformations places the two carboxyl groups within comfortable hydrogen-bonding distances from one another (C=O···H—O hydrogen-bond distances are 1.9 Å) to form a planar eight-membered hydrogen heterocyclic ring. Unlike ordinary 18-membered crown ethers or cryptands, neither **21** nor **22** contain any anti OCH_2CH_2O arrangements that place inward-turning CH_2 groups close to transannularly located oxygens to fill potential cavities. Actually, almost all of the potential cavity of **21** is filled with the pyridine-complexed carboxyl. The middle of **22** contains the carboxyl-complexed carboxyl



Thus, **21** and **22** are intramolecular complexes. Of additional interest are the distances between the benzyl oxygens and the carbonyl carbons. In the smaller and tighter cycle (**21**), one distance is 2.84 Å and the other 2.87 Å,[21] shorter than the usual van der Waals distance of ≈3.1 Å. In the larger and less rigid cycle **22**, the four distances are all about 2.97 Å.[22] Weak π–σ attractive forces previously studied in other systems[23] are probably present in **21**, but are more prominent in the less rigid cycle **22**. The planes of the two aryl groups in **21** are nearly parallel, but are displaced by about 1.2 Å to provide more effective hydrogen bonding.[21] In **22** the aryl planes are twisted in opposite directions relative to the plane of the carboxylic acid dimer to give a dihedral angle between the aryl planes of 103°.[22]

In molecular models, one conformation of tetraester T-$(OEOEO)_2$T (**13**) is somewhat cylindrical, with two ester groups protruding from the top and two from the bottom of the "aryl cylindrical walls." The ester groups represent potential points of attachment of rigidifying bridges for the generation of hosts with cavities of substantial size. Thus, **13** is a possible synthon for construction of more elaborate hosts with guest-encapsulating potential.

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Structure and Acidity. Comparisons of the pK_a values of Table I provide evidence that in aqueous solution, $A(OEO)_2P$ (**3**) possesses the same intramolecularly hydrogen-bonded structure as it does in the crystalline state. The pK_a of $A(OEO)_2P$ is 5.8, 1 unit weaker than $A(OEOE)_2O$ (pK_a = 4.8), which in turn is 1.5 units weaker than its open-chain model, $A(OCH_3)_2$ (pK_a = 3.3).[4b,6b] The pyridyl nitrogen of $A(OEO)_2P$ should be a more stable hydrogen-bonding site than the similarly located oxygen of $A(OEOE)_2O$, whose CO_2H···O intramolecular hydrogen bond appears responsible for the 1.5 pK_a unit difference between $A(OEOE)_2O$ and $A(OCH_3)_2$.[4b] The pK_a value of protonated cycle $^+HP(OEOE)_2O$ (4.8) and that of its open-chain model $^+HP(OCH_3)_2$ (4.9) are almost the same,[4b,6b] which suggests that both the protonated and nonprotonated forms of these compounds fit into the water structure with compensating differences. The protonated amino acid $A(OEO)_2PH^+$, with a pK_a of 3.6, is a stronger acid than $^+HP(OEOE)_2O$ or $^+HP(OCH_3)_2$ by over 1 unit, which is attributed again to the cost of breaking the CO_2H···N hydrogen bond in forming the conjugate acid. Possibly, $A(OEO)_2PH^+$ possesses a structure containing the new hydrogen bond, C=O···HN^+, which compensates somewhat for the loss of the stronger CO_2H···N hydrogen bond.

Comparison of the pK_a's of diacids $A(OEOEO)_2A$ (6.30 and 8.00) with that of open-chain model compound $A(OCH_3)_2$ (6.65) suggests that at least in the $(CH_3)_2SO$–H_2O solvent employed, the two carboxyl group of $A(OEOEO)_2A$ do not strongly hydrogen bond one another. Possibly the number of conformations that must be frozen out in this 24-membered ring system to organize the $-CO_2H:::HO_2C-$ ring system is too great a price to pay for the energy return from the intramolecular hydrogen bonds.

Structure and Binding. Substitution of the [3.3.0]octyl structural unit B for a CH_2CH_2 or *o*-C_6H_4 unit in 18-crown-6 hosts has only a small effect on the binding free energies of these hosts toward $(CH_3)_3CNH_3^+SCN^-$ as guest. Thus, at 0 °C, $-\Delta G°$ values in kcal mol^{-1} for the three hosts are $E(OEOEO)_2E$, 9.4; $B(OEOEO)_2E$, 9.0; and C_6H_4 $(OEOEO)_2E$, 8.8. Molecular models of the tripod complex $(CH_3)_3CNH_3^+$·$B(OEOEO)_2E$ indicate that if (as is observed in crystal structures of six other complexes)[2a] the C–N bond is normal to the best plane of the six oxygens and the CH_3–C–N–H dihedral bond angles are about 60°, one methyl of the $(CH_3)_3C$ group just reaches the methylenes of the B unit. Thus the B group offers little steric inhibition in complexation to a methyl in this position but probably would offer more to larger groups, particularly if this unit were incorporated into a more rigid host. The oxygens of the $B(O)_2$ unit are as rigidly eclipsed as those of the *o*-$C_6H_4(O)_2$ unit and are probably more basic because they are attached to saturated carbons. This B unit promises to be useful in tailoring the steric environment of the binding sites of rigid hosts.

Experimental Section

General. All temperatures are uncorrected. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl, whereas CH_2Cl_2 was fractionally distilled from CaH_2. All reactions requiring anhydrous conditions were carried out under argon or nitrogen. Gel permeation chromatography was performed at flow rates of 3.3–4.00 mL/min and at pressures of 400–900 psi by using the following column/solvent systems: (A) $^3/_8$ in. × 18 ft column of 200/400 Bio Beads SX-8 (Bio-Rad Lab)/THF; (B) $^3/_8$ in. × 20 ft column of 100-Å Styragel (Waters Assoc., Inc.)/CH_2Cl_2; (C) $^3/_8$ in. × 20 ft column of 60-Å Styragel (Waters)/CH_2Cl_2. Melting points were measured on a Thomas-Hoover apparatus. ^1H NMR spectra were recorded on a Varian T-60 (60 MHz) or a Bruker WP-200 (200 MHz) spectrometer. Infrared (IR) spectra were taken on a Beckman IR-5 or a Perkin-Elmer 297 spectrophotometer. Mass spectra were recorded on an AEI MS-9 mass spectrometer at 70 eV. Association constants between host **5** and *tert*-butylammonium thiocyanate were determined according to the procedure for "scale A".[8b]

2,6-Bis[((carbomethoxy)methoxy)methyl]pyridine (7). A mixture of 6.0 g (0.043 mol) of 2,6-bis(hydroxymethyl)pyridine (**6**),[4b] 10 g (0.21 mol) of 50% NaH in mineral oil, 40 g (0.26 mol) of methyl bromoacetate, and 250 mL of THF was heated under reflux for 8 h. The reaction mixture was filtered and concentrated in vacuo, and the residue was partitioned between CH_2Cl_2 and dilute aqueous HCl. Evaporation of the organic phase and chromatography of the residue on 220 g of silica gel

with 95:5 CH_2Cl_2/acetone (v/v) gave 8.7 g (72%) of diester **7** as a glass; ^1H NMR (60 MHz, $CDCl_3$) δ 3.7 (s, CH_3, 6 H), 4.2 (s, CH_2CO_2R, 4 H), 4.7 (s, Ar CH_2, 4 H), 7.2–7.8 (m, Ar H, 3 H). An analytical sample was obtained by VPC on 15% SE-30 (60/80 firebrick, 260 °C). Anal. Calcd for $C_{13}H_{17}NO_6$: C, 55.12; H, 6.05. Found: C, 55.06; H, 5.95.

2,6-Bis((2-hydroxyethoxy)methyl)pyridine (8). A mixture of 2.4 g (8.5 mmol) of diester **7**, 1.0 g (26 mmol) of $NaBH_4$ and 100 mL of absolute ethanol was stirred at ambient temperature for 10 h. Ethanol was removed by distillation, and the residue was dissolved in water. The resulting solution was continuously extracted with CH_2Cl_2 to give 1.5 g (77%) of diol **8** as a glass: ^1H NMR (60 MHz, $CDCl_3$) δ 3.7 (s, CH_2CH_2, 8 H), 4.6 (s, Ar CH_2, 4 H), 4.7 (br s, OH, 2 H), 7.2–7.8 (m, Ar H, 3 H). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.02; H, 7.52; N, 6.25.[24]

Methyl 3,6,14,17-Tetraoxa-23-azatricyclo[17.3.1.1^{8,12}]tetracosa-1-(23),8,10,12(24),19,21-hexaene-24-carboxylate (11). A suspension of 2.5 g (50 mmol) of 50% NaH in mineral oil in 250 mL of THF was stirred at reflux temperature as a solution of 6.9 g (21 mmol) of methyl 2,6-bis(bromomethyl)benzoate (**9**[7b] and 4.8 g (21 mmol) of diol **8** in 250 mL of THF was added dropwise over 5 h. The reaction mixture was stirred for 20 h at 25 °C, quenched by the addition of several drops of water, and filtered. Concentration of the filtrate in vacuo gave a residue, which was partitioned between CH_2Cl_2 and water. Evaporation of the organic phase and gel permeation chromatography of the residue (column A) gave 3.5 g (43%) of amino ester **11** as a glass, which was pure according to its ^1H NMR spectrum: (60 MHz, $CDCl_3$) δ 3.4 (s, CH_3, 3 H), 3.3–3.8 (m, CH_2CH_2, 8 H), 4.4–4.5 (m, Ar CH_2, 8 H), 7.0–7.8 (m, Ar H, 6 H); MS, *m/e* 387 (M^+). Anal. Calcd for $C_{21}H_{25}NO_6$: C, 65.10; H, 6.50. Found: C, 65.02; H, 6.47.

3,6,14,17-Tetraoxa-23-azatricyclo[17.3.1.1^{8,12}]tetracosa-1-(23),8,10,12(24),19,21-hexaene-24-carboxylic Acid (3). A solution of 2.2 g (5.7 mmol) of ester **11** in 50 mL of 95% aqueous ethanol was stirred at reflex temperature for 12 h. Solvent distillation gave a residue that was partitioned between CH_2Cl_2 and water. The aqueous solution was neutralized with aqueous HCl and extracted with four portions of CH_2Cl_2. The combined CH_2Cl_2 solutions were concentrated in vacuo to afford 2.1 g (98%) of amino acid **3**, which was pure according to its ^1H NMR spectrum. Recrystallization of **3** from CH_2Cl_2/pentane gave a sample with the following properties: mp 172–181 °C dec; ^1H NMR (60 MHz, $CDCl_3$) δ 3.8 (s, CH_2CH_2, 8 H), 4.7 (s, $ArCH_2$, 8 H), 7.1–7.8 (m, ArH, 6 H); MS, *m/e* 373 (M^+). Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21. Found: C, 64.23; H, 6.22.

Dimethyl 3,6,9,17,20,23-Hexaoxatricyclo[23.3.1.1^{11,15}]triaconta-1-(29),11,13,15(30),25,27-hexaene-29,30-dicarboxylate (12). A suspension of 3.43 g (0.143 mol) of NaH in THF was stirred at reflux temperature as a solution of 3.29 g (31 mmol) of diethylene glycol in 100 mL of THF was added. After 2 h, the reaction mixture was cooled to ambient temperature, and a solution of 10 g (31 mmol) of methyl 2,6-bis(bromomethyl)benzoate (**9**)[6b] in 100 mL of THF was added dropwise. The reaction mixture was stirred for 3 days and then quenched by the slow addition of 10 mL of water and filtered through Celite. The filtrate was concentrated to 300 mL in vacuo and treated with a large excess of diazomethane in ether. After 1 h, the excess diazomethane was quenched by addition of acetic acid, and solvents were evaporated in vacuo. The crude product was dissolved in ethyl acetate and filtered through silica gel to remove residual sodium bromide. Evaporation of the solvent and gel permeation chromatography (column B) afforded a semicrystalline residue that was recrystallized from CH_2Cl_2/cyclohexane to give 1.7 g (21%) of host **12**: mp 84–86 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 3.55 (s, CH_2CH_2, 16 H), 3.66 (s, CH_3, 6 H), 4.53 (s, $ArCH_2$, 8 H), 7.30 (m, ArH, 6 H); IR ($CHCl_3$) 1720 cm^{-1}; MS *m/e* 532 (M^+). Anal. Calcd for $C_{28}H_{36}O_{10}$: C, 63.17; H, 6.81. Found: C, 63.21; H, 6.85.

Dimethyl 2,6-Bis(bromomethyl)-1,4-benzenedicarboxylate (10).[14] A mixture of 19 g (86 mmol) of dimethyl 2,6-dimethyl-1,4-benzenedicarboxylate, 300 mL of CCl_4, 32 g (180 mmol) of *N*-bromosuccinimide, and 0.1 g of benzoyl peroxide was stirred at reflux for 3 h. The resulting mixture was cooled, diluted with CH_2Cl_2, washed with water, and dried. Removal of solvent gave an oil, which was then crystallized from cyclohexane to give 12.7 g (38%) of **10**: mp 123–125 °C: ^1H NMR δ 7.98 (s, 2 H), 4.60 (s, 4 H), 4.00 (s, 3 H), 3.92 (s, 3 H); MS, *m/e* 378 (M^+), 380, 382. Anal. Calcd for $C_{12}H_{12}Br_2O_4$: C, 37.92; H, 3.18. Found: C, 37.97; H, 3.20.

Tetramethyl 3,6,9,17,20,23-Hexaoxatricyclo[23.3.1.1^{11,15}]triaconta-1-(29),11,13,15(30),25,27-hexaene-13,27,29,30-tetracarboxylate (13). Reaction of 7.82 g (20.5 mmol) of dimethyl 2,6-bis(bromomethyl)terephthalate (**10**)[14] with NaH and diethylene glycol by the method described above afforded 1.2 g (18%) of host **13**, which was recrystallized from ether/pentane: mp 86–88 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 3.61 (s, CH_2CH_2, 16 H), 3.72 (s, CO_2CH_3, 6 H), 3.91 (s, Ar CH_3, 6 H), 4.58 (s, Ar CH_2, 8 H), 7.95 (s, Ar H, 4 H); IR ($CHCl_3$) 1730, 1715 cm^{-1}; MS, *m/e* 648 (M^+). Anal. Calcd for $C_{32}H_{40}O_{14}$: C, 59.25; H, 6.22. Found: C, 59.31; H, 6.30.

3,6,9,17,20,23-Hexaoxatricyclo[23.3.1.1^{11,15}]triaconta-1(29),11,13,15-(30),25,27-hexaene-29,30-dicarboxylic Acid (4). A mixture of 166 mg of diester **12**, 200 mg of KOH, and 30 mL of 95% aqueous ethanol was heated at reflux temperature for 12 h. The solvent was removed in vacuo, and 30 mL of 5% aqueous HCl was added to the residue. The resulting mixture was stirred for 1 h and then extracted with CH_2Cl_2. Concentration of the CH_2Cl_2 extract in vacuo followed by gel permeation chromatography (column B) afforded 110 mg (70%) of diacid **4**, which was recrystallized from CH_2Cl_2/ether to give colorless plates: mp 213–214 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 3.70 (s, CH_2CH_2, 16 H), 4.70 (s, Ar CH_2, 8 H), 7.35 (m, Ar H, 6 H); IR ($CHCl_3$) 3400–2500, 1710 cm^{-1}; MS, *m/e* 486 ($M^+ - H_2O$). Anal. Calcd for $C_{26}H_{32}O_{10}$: C, 61.90; H, 6.39. Found: C, 61.82; H, 6.37. Its single-crystal X-ray structure[22] completes its characterization.

2,5,8,11,14,17-Hexaoxatricyclo[16.3.3.0]tetracosane (5). A mixture of 0.50 g (21 mmol) of NaH, 0.71 g (5.0 mmol) of bicyclo[3.3.0]octane-1,5-diol (**16**),[15] and 150 mL of THF was stirred at ambient temperature for 30 min and then at reflux temperature for 30 min. Heating was continued as a solution of 2.7 g (4.9 mmol) of pentaethylene glycol ditosylate[6b,25] in 150 mL of THF was added dropwise over 22 h. The reaction mixture was stirred under reflux for 14 h and then quenched by addition of a few drops of water and filtered through Celite, washing with 100 mL of THF. The combined filtrates wee concentrated in vacuo, and the residue was dissolved in 100 mL of CH_2Cl_2. The resulting solution was extracted with 1.2 N aqueous HCl, dried ($MgSO_4$), and evaporated, affording 0.75 g of yellow oil. Gel permeation chromatography (column C) gave 0.15 g (21% of recovered diol **16** and 0.44 g (25%) of host **5**, which was further purified by gel permeation chromatography on column B (to give a glass): ^1H NMR (200 MHz, $CDCl_3$) δ 1.3–2.1 (m, C–C–H_2–C, 12 H), 3.68 (s, O–CH_2–C, 20 H); IR (neat) 2940, 2870, 1640, 1460, 1357, 1300, 1252, 1130 (br), 990, 950, 840 cm^{-1}; MS, *m/e* 344 (M^+). Anal. Calcd for $C_{18}H_{32}O_6$: C, 62.77; H, 9.36. Found: C, 62.96; H, 9.35.

Determination of pK_a Values. The pK_a's for dissociation of protonated **3** and **3** itself were determined by titration as described in ref 4b. The pK_a values for solutions of **4** and **18** in 65:35 (v/v) Me_2SO/water were obtained by graphical analysis of plots of pH vs. volume of 0.0965 N NaOH solution added at 25 °C. The pH values were measured with a glass electrode and an Orion 901 pH meter.

Registry No. 3, 68047-34-7; **4**, 76604-77-8; **5**, 82545-28-6; **6**, 1195-59-1; **7**, 76388-52-8; **8**, 76388-58-4; **9**, 56263-51-5; **10**, 59346-23-5; **11**, 82545-29-7; **12**, 82545-30-0; **13**, 82545-31-1; **16**, 32139-04-1; **17**, 55440-83-0; **18**, 64726-35-8; **19**, 64726-19-8; **20**, 64726-20-1; A-$(OEO)_2P^+H$, 82545-32-2; E$(OEOEO)_2$E, 17455-13-9; C_6H_4-$(OEOEO)_2$E, 71736-10-2; methyl bromoacetate, 96-32-2; diethylene glycol, 111-46-6; dimethyl 2,6-dimethyl-1,4-benzenedicarboxylate, 18958-18-4; pentaethylene glycol ditosylate, 41024-91-3.

(24) We warmly thank S. S. Moore for obtaining analyses on this compound.

(25) Kyba, E. P.; Helgeson, R. C.; Madan, K.; Gokel, G. W.; Tarnowski, T. L.; Moore, S. S.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 2564–2571.