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Host–Guest Complexation. 18. Effects on Cation Binding of Convergent Ligand Sites Appended to Macrocyclic Polyethers

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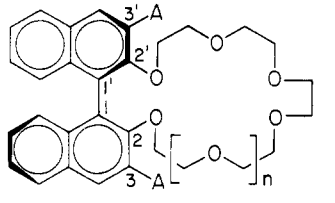
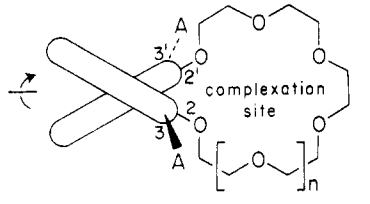
Abstract: Syntheses are reported for 16 new macrocyclic polyether ligand systems which contain potentially convergent side chains containing additional binding sites. The free energies of association of these systems in $CDCl_3$ at 25 °C with Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and t-$BuNH_3^+$ picrates were determined. The structures of these hosts are indicated by the following abbreviations: E is CH_2CH_2; D is 1,1′-dinaphthyl attached to two macroring oxygens at its 2,2′ positions and to two substituents at its 3,3′ positions; T is 1,1′-bitetralyl attached to two macroring oxygens at its 2,2′ positions and to two substituents in its 3,3′ positions; Ur is the cyclic urea unit, $N(CH_2)_3(CO)NCH_3$; Py is α-pyridyl; Bz is $C_6H_5CH_2$. The hosts prepared and examined were $(CH_3)_2$D(OEOEO)$_2$E (**3**), $(OCH)_2$D(OEOEO)$_2$E (**5**), $(CH_3O_2C)_2$D(OEOEO)$_2$E (**6**), $(HO_2C)_2$-D(OEOEO)$_2$E (**7**), $(CH_3CO)_2$D(OEOEO)$_2$E (**9**), $(UrCH_2)_2$D(OEOEO)$_2$E (**11**), $[(EtO)_2OPCH_2]_2$D(OEOEO)$_2$E (**12**), $[(EtO)_2OPCH_2]_2$D(OEOEOE)$_2$O (**13**), $(PySCH_2)_2$D(OEOEO)$_2$E (**14**), $(PyCH_2OCH_2)_2$D(OEOEO)$_2$E (**15**), $[(EtO)_2$-$OPCH_2]_2$T(OEOE)$_2$O (**20**), *cis*-$(BzOCH_2)_2$E(OEOEO)$_2$E (**22**), *trans*-$(BzOCH_2)_2$E(OEOEO)$_2$E (**23**), *cis*-$(o$-$ClC_6H_4)_2$-E(OEOEO)$_2$E (**24**), *trans*-$(o$-$ClC_6H_4)_2$E(OEOEO)$_2$E (**25**), and E(OEOEOCH$_2$)$_2$E(OEOEO)$_2$E (**26**). Noncyclic model compounds were also prepared: $(CH_3)_2$D(OEOEOCH$_3$)$_2$ (**1**) and $[(EtO)_2OPCH_2]_2$D(OCH$_3$)$_2$ (**17**). The free energies of association ($-\Delta G°$) of these compounds with various picrate salts were compared with one another and with those of known hosts, D(OEOEO)$_2$D (**2**), 2,3-naphtho-18-crown-6 (**21**), and dicyclohexyl-18-crown-6. The highest $-\Delta G°$ value (kcal/mol) observed involved $[(EtO)_2OPCH_2]_2$D(OEOEO)$_2$E (**12**) and Na^+ (12.4), and the lowest, $(CH_3)_2$D(OEOEOCH$_3$)$_2$ (**1**) and t-$BuNH_3^+$ (3.38), as complexing partners. The $-\Delta G°_{av}$ of association (kcal/mol) with Li^+, Na^+, K^+, Rb^+, Cs^+, and NH_4^+ picrates allowed the hosts to be ranked as general ligand systems. Values of $-\Delta(\Delta G°)_{max}$ (the difference in free energies of the best and poorest bound of these six picrate salts) allowed the ligand systems to be graded with regard to ion selectivity. Values of $-\Delta(\Delta G)^{NH_4^+}_{t\text{-}BuNH_3^+}$ allowed the ligand systems to be judged with regard to their capacity for structural recognition of NH_4^+ vs. t-$BuNH_3^+$ ions. With respect to all three parameters, the $[(EtO)_2OPCH_2]_2$D(OEOEO)$_2$E (**12**) system ranked the highest. The location, binding, and steric properties of the two P → O oxygens in this ligand system appear responsible for its superior properties.

Previous papers in this series dealt with the synthesis and complexing properties of neutral host compounds toward metal, ammonium, and alkylammonium picrate salts in $CHCl_3$.[2] Binding sites incorporated directly into the macroring systems include ethyleneoxy, m-xylyl,[2a] 2,6-substituted anisyl,[2d] 2,6-substituted phenylcarbomethoxy,[2b] 2,6-substituted phenylcarboxy,[2b] 2,6-substituted pyridine, 2,6-substituted pyridine oxide, ortho,ortho′-substituted arylphosphoryl, and N,N'-tetrasubstituted urea units.[2e] Two types of negatively charged macrocycles have been designed and prepared for complexation of cations. In one type, acetylacetonide units incorporated in the ring systems were examined.[3a] In a second study, carboxylate groups terminating side chains grafted to the macroring were designed and investigated.[3b]

This paper reports the design, syntheses, and complexing properties of 16 new macrocyclic polyethers in which additional convergent binding sites were appended to the macroring system. To provide for convergence of the extra binding sites, three strategies were employed. The first employed the rigid 1,1′-binaphthyl unit bonded to oxygens of the macroring system in its 2,2′ positions. The 3,3′ positions were substituted with side chains (A in formulas I and II). The planes of the two naphthalene rings in CPK molecular models are roughly perpendicular and tangential to the best plane of the macroring,



I



II

as indicated in formulas I and II. In proper conformations, the termini of appropriate A side chains can locate on an axis that passes through the center of the macroring. Thus, additional binding sites may be strategically positioned on either side of the central binding cavity. In all systems reported here, the two side chains are identical, so the systems possess a C_2 axis. Al-

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though the enantiomer of the *R* configuration is depicted both in I and its projection formula II, the compounds prepared were racemates.

In the second type of system, cis and trans isomers of 18-crown-6 substituted in their 2,3 positions with like groups were prepared and examined. In models of the compounds prepared, side chains trans to one another in the proper conformation can place additional binding sites on either side of the central hole. The substances thus possess C_2 axes. In the cis isomers, only substituents of one side chain at a time can be so located. Thus a comparison of the binding properties of diastereomeric pairs appeared interesting.

The third type of host prepared and studied was an 18-crown-6 with a cis-fused 20-crown-6 macroring, the two rings of which shared a CHCH group. In the all-gauche conformation of the OCH_2CH_2O units, the two macrorings form a set of "jaws" conformationally flexible enough in molecular models to close on a guest ion.[4]

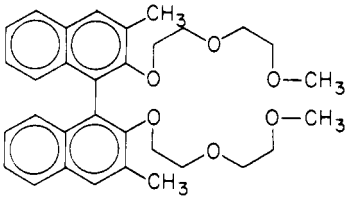
The general objective of these studies is to identify the varieties of complementary host–guest relationships in complexation. The specific goals are manifold: to identify the best ligands for the various types of cations; to determine the effects of different molecular organizations of binding sites on binding abilities; to develop feasibility in synthesis of systems that place ligands in positions relative to one another so that they might act cooperatively without extensive conformational reorganization; to determine the usefulness of molecular models in predicting complementary vs. noncomplementary host–guest relationships.

Results

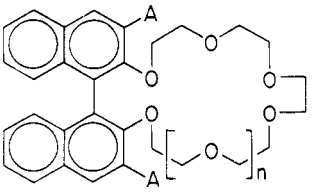
Syntheses. Compounds **1–3** were required as standard hosts that did not contain appended side chain ligand sites. Compound **1** was prepared (64%) by the reaction of KOH-$CH_3OCH_2CH_2OCH_2CH_2OTs$[5] with 2,2′-dihydroxy-3,3′-dimethyl-1,1′-binaphthyl.[6] The reaction of KOH-pentaethylene glycol ditosylate[2b] with the same diol gave **3** (44%). Compound **2** was available from an earlier study.[5]

Macrocyclic diol[3b] **4** served as the starting material for cycles **5–12, 14,** and **15.** Oxidation of **4** with activated MnO_2[7] gave dialdehyde **5** (88%), which with MnO_2,[7] NaCN, CH_3OH, and AcOH gave diester **6** (75%). Conventional hydrolysis of **6** gave diacid **7** (94%). Dialdehyde **5** with $HONH_3Cl$, NaO_2CH, and HO_2CH[9] gave nitrile **8** (84%), which when treated with CH_3Li gave diacetyl compound **9** (35%). Treatment of diol **4** with $SOCl_2$–C_6H_6 gave dichloride **10** (92%). With NaH and *N*-methyl-*N,N′*-trimethyleneurea,[10] **10** gave the macrocycle with the two urea side chains, **11** (70%). Dichloride **10** when heated with $(EtO)_3P$ gave the macrocycle with two appended alkylphosphinate ester side chains, **12** (90%). A similar sequence of conversions of bisalcohol[3b] to bischloride[3b] to bisalkylphosphinate ester **13** (97%) was employed in the higher oligomeric series whose macrocycles contained seven oxygens. Dichloride **10** when treated with NaOH–2-mercaptopyridine gave **14** (36%), which contained two side chains terminated by the α-thiapyridine group. When treated with 2-hydroxymethylpyridine, dichloride **10** gave macrocycle **15** (66%), whose side chains are terminated with two pyridine groups.

For purposes of differentiating between the binding contributions of the macroring system and the phosphinate ester side chains, compound **17** was needed. In **17,** the macrocycle is absent, but the side chains are present. Accordingly, 2,2′-dihydroxy-3,3′-bis(hydroxymethyl)-1,1′-binaphthyl[6] was methylated with CH_3I–K_2CO_3 to give diol **16** (90%). Treatment of **16** with $SOCl_2$–C_6H_6 produced the corresponding bis(chloromethyl) compound (89%), which when heated with $(EtO)_3P$ gave **17** (80%).



1, $(CH_3)_2D(OEOEOCH_3)_2$



2, n = 1, A = H, $D(OEOEO)_2E$

3, n = 1, A = CH_3, $(CH_3)_2D(OEOEO)_2E$

4, n = 1, A = CH_2OH

5, n = 1, A = CHO, $(OCH)_2D(OEOEO)_2E$

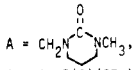
6, n = 1, A = CO_2CH_3, $(CH_3O_2C)_2D(OEOEO)_2E$

7, n = 1, A = CO_2H, $(HO_2C)_2D(OEOEO)_2E$

8, n = 1, A = CN

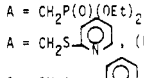
9, n = 1, A = $COCH_3$, $(CH_3CO)_2D(OEOEO)_2E$

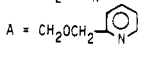
10, n = 1, A = CH_2Cl

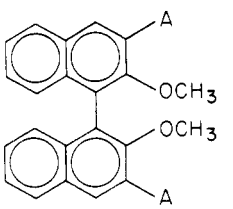
11, n = 1, A =  , $(UrCH_2)_2D(OEOEO)_2E$

12, n = 1, A = $CH_2P(O)(OEt)_2$, $[(EtO)_2OPCH_2]_2D(OEOEO)_2E$

13, n = 2, A = $CH_2P(O)(OEt)_2$, $[(EtO)_2OPCH_2]_2D(OEOEOE)_2O$

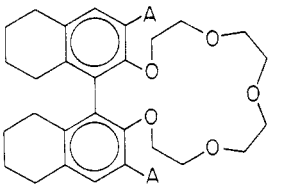
14, n = 1, A =  , $(PySCH_2)_2D(OEOEO)_2E$

15, n = 1, A =  , $(PyCH_2OCH_2)_2D(OEOEO)_2E$



16, A = CH_2OH

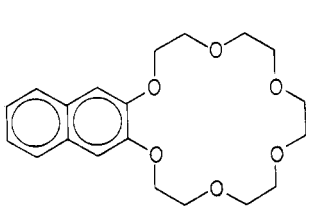
17, A = $CH_2P(O)(OEt)_2$, $[(EtO)_2OPCH_2]_2D(OCH_3)_2$



18, A = H

19, A = CH_2Cl

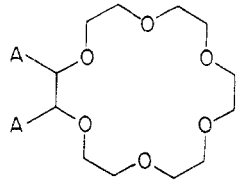
20, A = $P(O)(OEt)_2$, $[(EtO)_2OPCH_2]_2T(OEOE)_2O$



21, $Nap(OEOEO)_2E$

A comparison of the complexing properties of 17-, 20- and 23-membered macrocyclic ethers containing the $CH_2P(O)(OEt)_2$ side chains appeared desirable. The syntheses of examples (**12** and **13**) of the latter two compound types are described above. The lower oligomer of diol **4** ($n = 0$ in general formula) had been obtained only in very poor yields,[3b] so a synthesis of **20,** which contains the similarly shaped 1,1′-bitetralyl in place of the 1,1′-binaphthyl unit, was devised. Attempts to chloromethylate the available binaphthyl-17-crown-5[5] led to products in which both the 3 and 6 positions of the dinaphthyl nucleus were substituted. To avoid this problem, binaphthyl-17-crown-5 was reduced with H_2–Pt to **18** (95%), chloromethylation of which with AcOH–paraformaldehyde–HCl gave dichloride **19** (67%), which with $(EtO)_3P$ gave **20** (84%). Cycle **21,** also wanted for comparison purposes, was available from another study.[5]

An inspection of CPK molecular models of diastereomeric compounds **22** and **23** indicated that in the trans isomer the two

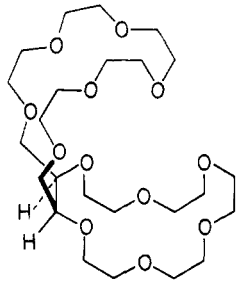


22, cis, A = $CH_2OCH_2C_6H_5$, cis-$(BzOCH_2)_2E(OEOEO)_2E$
23, trans, A = $CH_2OCH_2C_6H_5$, trans-$(BzOCH_2)_2E(OEOEO)_2E$
24, cis, o-ClC_6H_4, cis-$(o\text{-}ClC_6H_4)_2E(OEOEO)_2E$
25, trans, o-ClC_6H_4, trans-$(o\text{-}ClC_6H_4)_2E(OEOEO)_2E$

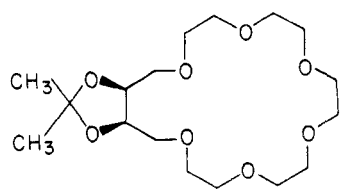
ether oxygens of the side chains could in proper conformations participate simultaneously in binding metal cations located in the hole. In models of the cis isomer, only one side-chain oxygen at a time can do this without generating one anti arrangement of the oxygens of the macroring. The two diastereomers were synthesized from (*R,S*)- and (*S,S*)-tartaric acids as the initial starting materials. Treatment of each acid with $CH_3C(OCH_3)_2CH_3$, CH_3OH, and TsOH gave the diastereomeric dimethyl tartrate 2,3-acetonides[11] (85–95%), which were reduced with $LiAlH_4$ to the corresponding diastereomeric 1,2,3,4-butanetetrol 2,3-acetonides[12] (63–79%). The terminal hydroxyl groups of these compounds were benzylated with NaH–$C_6H_5CH_2Br$ (94% for each diastereomer), and the resulting ketals hydrolyzed (93% for each diastereomer) to the corresponding *R,S* and *S,S* isomers of $C_6H_5CH_2O\text{-}CH_2CH(OH)CH(OH)CH_2OCH_2C_6H_5$. The *R,S* diol with NaH–THF–pentaethylene glycol ditosylate[2b] gave cis macrocycle **22** (33%), whereas the *S,S* diol with NaH–DMF–pentaethylene glycol ditosylate[2b] gave trans macrocycle **23** (35%). After this work was completed, others announced the preparation of 18-crown-6 systems, two of whose ethylene glycol units were replaced with units synthesized from (*S,S*)-tartaric acid.[13]

Hosts **24** and **25** are diastereomeric 18-crown-6 systems in which two *o*-chlorophenyl groups are substituted for vicinal hydrogens of one ethylene group. In molecular models of the (all-gauche) trans isomer, appropriate conformations of the two aryl groups place one chloride on one side and the second chlorine on the opposite side of the hole of the macroring at the same time. In the cis isomer, only one Cl can occupy that convergent position without developing an anti conformation for one of the oxygens of the OCHArCHArO group. The macrocycles were prepared from the *dl*- and *meso-o,o′*-dichlorohydrobenzoins as starting materials, which in turn were prepared by reduction of *o,o′*-dichlorobenzoin[14] with $NaBH_4$. The diastereomers were separated. As expected,[15] the meso isomer was present as the major component. The racemate was identified by its total enantiomeric resolution through the strychnine salt of its acid phthalate.[16] Treatment of the racemic diol with THF–KOH–pentaethylene glycol ditosylate[2b] gave the trans isomer, **25** (68%), while with THF–NaH–pentaethylene glycol ditosylate the meso diol gave cis isomer **24** (35%).

The synthesis of the "jaws-like" host **26** involved treatment of *meso*-1,2,3,4-butanetetrol 2,3-acetonide with NaH–DMF–pentaethylene glycol ditosylate[2b] to give macrocycle **27** (35%). When treated with acid, **27** gave **28** (95%), ring



26, $E(OEOEOCH_2)_2E(OEOEO)_2E$



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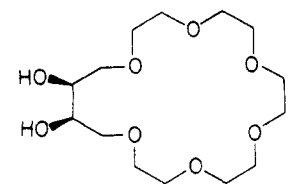


28

closure of which with NaH–DMF–pentaethylene glycol ditosylate[2b] gave **26** (35%).

In the purification of many of the hosts, gel permeation chromatography was used to separate the various cyclic oligomers formed in the ring-closing reactions. The retention times of cyclic oligomers differed markedly from one another, whereas cycles of similar molecular dimensions gave similar retention volumes. Mass spectral molecular ions, coupled with retention volume correlations, established the molecular weights of the desired compounds.

Association Constants and Free Energies of Association between Ligand Systems and Metal, Ammonium, and Alkylammonium Picrates. Association constants (K_a, defined in eq 1) for hosts (H) and guest picrate salts were determined in $CDCl_3$ at 24–26 °C. The previously described extraction technique was used in which Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and t-$BuNH_3^+$ picrates in H_2O were extracted with $CDCl_3$ both in the presence and absence of host.[2d,e] The extraction constants (K_e) defined in eq 2 and the distribution constants (K_d) defined in eq 3 were determined from the absorbances at 380 nm in the UV spectra of the H_2O and $CDCl_3$ layers at equilibrium. The molar ratio of picrate ion to host in the organic layer is indicated by the symbol R. Values of K_a were calculated from K_e and K_d and eq 4, and $-\Delta G°$ values from K_a values and eq 5. Table I records the data.

$$[M^+Pic^-]_{CDCl_3} + [H]_{CDCl_3} \overset{K_a}{\rightleftharpoons} [M^+ \cdot H \cdot Pic^-]_{CDCl_3} \quad (1)$$

$$[M^+]_{H_2O} + [Pic^-]_{H_2O} + [H]_{CDCl_3} \overset{K_e}{\rightleftharpoons} [M^+ \cdot H \cdot Pic^-]_{CDCl_3} \quad (2)$$

$$[M^+]_{H_2O} + [Pic^-]_{H_2O} \overset{K_d}{\rightleftharpoons} [M^+Pic^-]_{CDCl_3} \quad (3)$$

$$K_a = K_e/K_d \quad (4)$$

$$\Delta G° = -RT \ln K_a \quad (5)$$

The values for the parameters are reported to more figures than are significant until comparisons are made. Values for K_a have precisions that vary with R_{CDCl_3} between about ±14 and ±47%, and values for $-\Delta G°$ between about 1.4 and 2.6%. This easily applied, low-precision method provides reasonable estimates of association free energies useful for correlating the effects of structural changes in host and guest on binding properties in $CDCl_3$.

For general comparison purposes, Table I also reports $-\Delta G°_{av}$ values for each host binding in $CDCl_3$ the Li^+, Na^+, K^+, Rb^+, Cs^+, and NH_4^+ picrate$^-$ salts. Also reported is the $-\Delta(\Delta G°)_{max}$ value for each host, which equals the difference between the $-\Delta G°$ for the most strongly bound minus $-\Delta G°$ for the least strongly bound of these six salts.

Discussion

Effects on Free Energies of Association of Changes in Structure of Ligand Systems Containing the Binaphthyl Unit. The $-\Delta G°_{av}$ values provide a general measure of each host's ability to complex spherical (M^+) or near-spherical (NH_4^+) cations of a wide range of ionic diameters. The $-\Delta(\Delta G°)_{max}$ values provide a general measure of the ability of each host to differentially complex ions of different diameters. Ligand systems $(CH_3)_2D(OEOEOCH_3)_2$ (**1**) and $(CH_3)_2$-$D(OEOEO)_2E$ (**3**) differ only in the sense that the former contains two hydrogens in place of a carbon–carbon bond which completes a ring system in the latter. The system whose ligand sites are organized by the macroring gives a $-\Delta G°_{av}$ value of 8.5 kcal/mol, which is 2.8 kcal/mol higher than that of its noncyclic analogue whose $-\Delta G°_{av}$ value is 5.7 kcal/mol. The difference in $-\Delta(\Delta G°)_{max}$ for the two systems is more striking. Macrocycle $(CH_3)_2D(OEOEO)_2E$ (**3**) differentiates maximally between the six ions by 4.5 kcal/mol, whereas its open-chain analogue, $(CH_3)_2D(OEOEOCH_3)_2$ (**1**), differentiates by only 0.5 kcal/mol. This organization of the ligand sites prior to complexation is important both to general and to differential complexation. Interestingly, these two ligand systems have about the same affinity for Li^+ ion, for which neither is organized ($-\Delta G° \sim 5.9$ kcal/mol). However, they differ by 4.5 kcal/mol in their affinities for K^+, for which the cycle is superbly organized during complexation.

The two methyl groups substituted in the 3,3′ positions of the naphthalene rings of $(CH_3)_2D(OEOEO)_2E$ (**3**) play an important role in determining both its general and differential binding ability. Thus $(CH_3)_2D(OEOEO)_2E$ (**3**) provides a $-\Delta G°_{av}$ value of 1.4 kcal/mol and a $-\Delta(\Delta G°)_{max}$ value of 0.7 kcal/mol higher than is observed for its nonmethylated analogue, $D(OEOEO)_2E$ (**2**). An examination of molecular models of the two systems suggests that the effect of the two methyl groups is to force a conformation on the $ArOCH_2$ groups in which the electron pairs of their inward-turned oxygens "line" part of the hole of the macrocycle. In $(CH_3)_2D(OEOEO)_2E$ (**3**) the CH_3 of the $ArOCH_2$ has no space available other than on the outside of the hole, whereas in $D(OEOEO)_2E$ (**2**) other conformations are available.

Other substituents in the 3 position in models appear to play the same steric role as the CH_3 group. Consistent with this visual observation of models is the experimental fact that for all $A_2D(OEOEO)_2E$ systems binding any particular one of the cations, Li^+, Na^+, or K^+, the $-\Delta G°$ value when A is hydrogen is lower than when A is any other group. Thus the binding of those ions small enough to "nest" in the hole of the macrocycle is helped by this enforced convergence of the electron pairs of oxygens. The ions, NH_4^+ and Cs^+, are large and they "perch" on the cavity, and their binding is accordingly less sensitive to the electron pairs converging on the center of the hole.

Most of the A groups of the $A_2D(OEOEO)_2E$ hosts are polar and contain functional groups potentially capable of providing additional binding sites for a cationic guest. The question arises as to how much of the increased binding is due to the conformational effect on the macroring oxygens, and how much to the presence of additional binding sites. For these hosts, the A groups provide the following decreasing order of values of $-\Delta G°_{av}$ (kcal/mol): $CH_2PO(OEt)_2$ (10.0); CH_2SPy (8.7); CO_2CH_3 (8.7); CH_2OCH_2Py (8.7); CH_2Ur (8.7); CH_3 (8.5); $COCH_3$ (7.8); H (7.1). Interestingly, the A groups provide a somewhat similar decreasing order of values for $-\Delta(\Delta G°)_{max}$ (kcal/mol): $CH_2PO(OEt)_2$ (5.4); CH_3 (4.5); CH_2SPy (4.3); CH_2OCH_2Py (4.2); CH_2Ur (4.1); H (3.8); $COCH_3$ (2.3). Thus only when A = $CH_2PO(OEt)_2$ is the binding and discriminating ability of these hosts markedly better than when A = CH_3. The enhancement attributable to substituting two $PO(OEt)_2$ for the two hydrogens of the CH_3 groups amounts to 1.5 kcal/mol in $-\Delta G°_{av}$ and to 0.9 kcal in $-(\Delta(\Delta G°)_{max}$. With the exception of $COCH_3$, the other polar groups have net effects on $-G°_{av}$ values not far from those of the nonpolar CH_3 group. Although these latter polar groups may, and probably do, provide additional binding sites to the guest cations, what is gained by such contacts is possibly lost in freezing out rotational degrees of freedom in the complexation process.

Comparisons of the $-\Delta G°_{av}$ and $-\Delta(\Delta G°)_{max}$ values for the hosts whose A groups are $COCH_3$ and CO_2CH_3 support this explanation. Of the polar groups represented, the ketone and ester oxygens provide the poorest ligands for metal ion binding both because of their electronic character and their inability to reach far enough to center their electron pairs on either side of the hole. The CO_2CH_3 group might act as a noncentered binding group in either of two conformations since either of its two oxygens might be used (with the C=O group preferred). The $COCH_3$ group can act as a binding site in only one conformation, and in that conformation its electron pairs are deconjugated from those of its attached naphthalene.

Molecular model examinations of $[(EtO_2)OPCH_2]_2$-$D(OEOEO)_2E$ (**12**) indicates that, with the four bulky and lipophilic EtO groups oriented away from the hole, the two P→O groups can fall on an axis which is normal to the best plane of the macroring and which passes through its center. Such a conformation provides a roughly spherical hole lined with 32 electrons associated with 8 oxygens. Although the electron pairs of the oxygens of $(UrCH_2)_2D(OEOEO)_2E$ (**11**) and of the nitrogens of $(PsSCH_2)_2D(OEOEO)_2E$ (**14**) and $(PyCH_2OCH_2)_2D(OEOEO)_2E$ (**15**) can also center on either side of the hole, more conformations have to be frozen out in these arrangements than in $[(EtO)_2OPCH_2]_2D(OEOEO)_2E$ (**12**).

The noncyclic model compound, $[(EtO)_2OPCH_2]_2$-$D(OCH_3)_2$ (**17**), possesses only those four binding sites that are attached to and organized by the binaphthyl group of the parent system. This model gave $-\Delta G°_{av}$ = 4.9 kcal/mol, which is about half of the 10 kcal/mol observed for the parent cycle which contains eight binding sites. The model was much less discriminating toward ions since it gave $-\Delta(\Delta G°)_{max}$ = 1.8 kcal/mol compared to the 5.4 kcal/mol of the parent cycle.

The oligomer containing an additional ethylenoxy unit in its ring, $[(EtO)_2OPCH_2]_2D(OEOEOE)_2O$ (**13**), was almost as powerful and discriminating a host as its smaller relative, **12**. It provided values for $-\Delta G°_{av}$ and $-\Delta(\Delta G°)_{max}$ of 9.8 and 4.8 kcal/mol, respectively. As expected, this higher oligomer with its larger ring system was a better binder for the larger metal ions, Rb^+ and Cs^+, by 2.4 and 1.4 kcal/mol, respectively, than **12**. However, the ideal organization of the six-oxygen macrocycle for binding three of the hydrogens of NH_4^+ in a tripod arrangement is lost in the higher oligomer whose $-\Delta G°$ value for that ion dropped by 2.5 kcal/mol compared to that of the parent host. The most striking difference between the two oligomers involved their binding of the smaller ion, Na^+.

Table I. Equilibrium and Free Energy Parameters for Association between Hosts and Metal or Ammonium Picrates in $CDCl_3$ at 25 °C

ligand system structure[a]	no.	M^+ of M^+ picrate$^-$	R_{CDCl_3}[b]	$K_a \times 10^{-3}$, M^{-1}	$-\Delta G°$, kcal/mol	$-\Delta G°_{av}$,[c] kcal/mol	$\Delta(\Delta G°)_{max}$,[d] kcal/mol
$(CH_3)_2D(OEOEOCH_3)_2$[e]	**1**[f]	Li	0.0060	19	5.84		
		Na	0.0057	14.8	5.69		
		K	0.0112	20.2	5.88	5.7	0.5
		Rb	0.0058	14.4	5.68		
		Cs	0.0053	11.0	5.52		
		NH_4	0.0081	9.1	5.41		
		CH_3NH_3	0.0098	3.1	4.77		
		t-$BuNH_3$	0.0163	0.3	3.38		
$D(OEOEO)_2E$	**2**[f]	Li	0.0010	3.2	4.79		
		Na	0.0360	100	6.82		
		K	0.330	1900	8.57	7.1	3.8
		Cs	0.100	260	7.39		
		NH_4	0.280	740	8.01		
$(CH_3)_2D(OEOEO)_2E$	**3**[g]	Li	0.0078	22.8	5.95		
		Na	0.273	1730	8.52		
		K	0.718	42 800	10.4	8.5	4.5
		Rb	0.437	4700	9.10		
		Cs	0.181	576	7.87		
		NH_4	0.464	3260	8.89		
		CH_3NH_3	0.451	170	7.14		
		t-$BuNH_3$	0.245	48.9	6.40		
$(OHC)_2D(OEOEO)_2E$	**5**[f]	Na	0.0952	328	7.53		
		K	0.460	5100	9.16		
		Rb	0.156	568	7.86		
		Cs	0.0565	124	6.95		
$(CH_3O_2C)_2D(OEOEO)_2E$	**6**[g]	Li	0.0116	106	6.23		
		Na	0.512	11 600	8.62		
		K	0.722	52 600	10.5	8.7	4.3
		Rb	0.463	6010	9.25		
		Cs	0.228	853	8.11		
		NH_4	0.352	1610	8.47		
		t-$BuNH_3$	0.488	70.3	6.61		
$(HO_2C)_2D(OEOEO)_2E$	**7**[f,h]	Li	0.0142	42.1	6.31		
		Na	0.292	2000	8.60		
		Rb	0.211	863	8.11		
		Cs	0.102	246	7.36		
		NH_4	0.128	210	7.27		
		CH_3NH_3	0.160	80.9	6.70		
		t-$BuNH_3$	0.217	8.25	5.35		
$(CH_3CO)_2D(OEOEO)_2E$	**9**[f]	Li	0.0051	17.1	5.78		
		Na	0.182	811	8.07		
		K	0.517	6870	9.34	7.8	2.3
		Rb	0.237	1070	8.23		
		Cs	0.080	181	7.18		
		NH_4	0.248	637	7.93		
		CH_3NH_3	0.097	39.6	6.28		
		t-$BuNH_3$	0.088	2.12	4.54		
$(UrCH_2)_2D(OEOEO)_2E$	**11**[g]	Li	0.0189	56.9	6.49		
		Na	0.424	5340	9.19		
		K	0.746	60 200	10.6	8.7	4.1
		Rb	0.444	5000	9.15		
		Cs	0.193	638	7.93		
		NH_4	0.459	3150	8.87		
		CH_3NH_3	0.218	136	7.01		
		t-$BuNH_3$	0.268	12.4	5.59		
$[(EtO)_2OPCH_2]_2D(OEOEO)E$	**12**[g]	Li	0.0423	136	7.01		
		Na	0.888	1 160 000	12.4		
		K	0.902	839 000	12.2	10.0	5.4
		Rb	0.615	19 500	9.95		
		Cs	0.368	2520	8.74		
		NH_4	0.606	10 800	9.60		
		CH_3NH_3	0.451	953	8.16		
		t-$BuNH_3$	0.248	10.6	5.50		
$[(EtO)_2OPCH_2]_2D(OEOEOE)_2O$	**13**[g]	Li	0.0800	320	7.52		
		Na	0.014	8300	9.45		
		K	0.370	580 000	12.0		
		Rb	0.53	1 100 000	12.3	9.8	4.8
		Cs	0.340	23 200	10.1		
		NH_4	0.27	170 000	7.14		
$(PySCH_2)_2D(OEOEO)_2E$	**14**[f]	Li	0.0135	44	6.34		
		Na	0.30	2300	8.69		
		K	0.70	47 000	10.5		
		Rb	0.46	6300	9.28	8.7	4.3
		Cs	0.25	1100	8.25		
		NH_4	0.50	4500	9.08		

Table I (*Continued*)

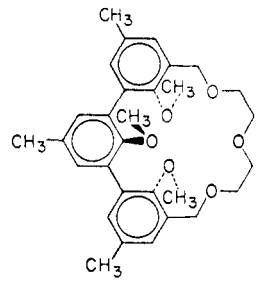
Ligand system structure[a]	no.	M^+ of M^+ picrate$^-$	R_{CDCl_3}[b]	$K_a \times 10^{-3}$, M^{-1}	$-\Delta G°$, kcal/mol	$-\Delta G°_{av}$,[c] kcal/mol	$-\Delta(\Delta G°)_{max}$,[a] kcal/mol
$(PyCH_2OCH_2)_2D(OEOEO)_2E$	**15**[g]	Li	0.015	50	6.42		
		Na	0.33	2800	8.80		
		K	0.725	61 000	10.6	8.7	4.2
		Rb	0.44	5600	9.21		
		Cs	0.215	820	8.08		
		NH_4	0.50	4500	9.08		
$[(EtO)_2OPCH_2]_2D(OCH_3)_2$	**17**[f]	Li	0.0019	6.1	5.17		
		Na	0.0067	17	5.78		
		K	0.0031	5.4	5.10	4.9	1.8
		Rb	0.0009	2	4.51		
		Cs	0.0005	0.9	4.03		
		NH_4	0.0021	2.4	4.62		
$[(EtO)_2OPCH_2]_2T(OEOE)_2O$	**20**[f]	Li	0.010	33	6.17		
		Na	0.023	620	7.91		
		K	0.0068	12	5.57	5.7	3.2
		Rb	0.002 05	4.5	4.99		
		Cs	0.0015	2.75	4.70		
		NH_4	0.0032	3.5	4.84		
$Nap(OEOEO)_2E$	**21**[g]	Li	0.007 04	22.5	5.94		
		Na	0.226	1220	8.30		
		K	0.740	85 900	10.8	8.7	4.8
		Rb	0.524	11 300	9.63		
		Cs	0.262	1250	8.31		
		NH_4	0.575	9850	9.53		
		CH_3NH_3	0.315	334	7.53		
		t-$BuNH_3$	0.534	105	6.85		
cis-$(BzOCH_2)_2E(OEOEO)_2E$	**22**[g]	Li	0.008 46	27.2	6.05		
		Na	0.128	480	7.75		
		K	0.671	34 300	10.3	8.4	4.2
		Rb	0.381	3560	8.94		
		Cs	0.164	529	7.81		
		NH_4	0.536	6650	9.31		
		CH_3NH_3	0.281	247	7.36		
		t-$BuNH_3$	0.313	18.3	5.82		
trans-$(BzOCH_2)_2E(OEOEO)_2E$	**23**[g]	Li	0.0132	43.1	6.33		
		Na	0.240	1430	8.40		
		K	0.769	227 000	11.4	9.1	5.1
		Rb	0.561	18 700	9.93		
		Cs	0.292	1650	8.49		
		NH_4	0.637	24 100	10.1		
		CH_3NH_3	0.419	832	8.08		
		t-$BuNH_3$	0.579	191	7.21		
cis-(*o*-$ClC_6H_4)_2E(OEOEO)_2E$	**24**[f]	Li	0.0121	39.5	6.28		
		Na	0.136	564	7.85		
		K	0.428	5980	9.25	8.0	3.0
		Rb	0.293	2250	8.67		
		Cs	0.0755	186	7.20		
		NH_4	0.320	1540	8.45		
		CH_3NH_3	0.104	50	6.42		
		t-$BuNH_3$	0.107	2.99	4.75		
trans-(*o*-$ClC_6H_4)_2E(OEOEO)_2E$	**25**[g]	Li	0.0176	58.0	6.50		
		Na	0.182	813	8.07		
		K	0.807	158 000	11.2	9.1	4.7
		Rb	0.608	20 400	9.98		
		Cs	0.316	1810	8.54		
		NH_4	0.683	24 000	10.1		
		CH_3NH_3	0.400	599	7.89		
		t-$BuNH_3$	0.449	48.2	6.39		
$E(OEOEOCH_2)_2E(OEOEO)_2E$	**26**[g,i]	Li	0.0246	82.9	6.72		
		Na	0.211	1050	8.22		
		K	0.698	41 900	10.4	8.7	3.7
		Rb	0.461	6320	9.29		
		Cs	0.236	987	8.19		
		NH_4	0.570	8450	9.46		
		CH_3NH_3	0.341	392	7.64		
		t-$BuNH_3$	0.380	29.5	6.10		

[a] D = 1,1′-binaphthyl substituted in the 2,2′ positions with O's and in the 3,3′ positions by side chains; E = CH_2CH_2; Ur = $N(CH_2)_3CONCH_3$; Py = α-pyridyl; T = 1,1′-bitetralyl substituted in the 2,2′ positions with O's and in the 3,3′ positions by side chains; Nap = 2,3-naphthalene; Bz = $C_6H_5CH_2$. [b] Ratio of picrate to host in $CDCl_3$ phase at equilibrium obtained by direct measurement, or calculated by difference from measurements made on aqueous phase. [c] Average $-\Delta G°$ values of each host binding Li^+, Na^+, K^+, Rb^+, Cs^+, and NH_4^+ picrates. [d] $\Delta(\Delta G°)_{max}$ for each host equals the highest $-\Delta G°$ value minus the lowest $-\Delta G°$ value among the Li^+, Na^+, K^+, Rb^+, Cs^+, or NH_4^+ picrate possible partners. [e] We thank Dr. L. Kaplan for these measurements. [f] Based on *A* values obtained by UV measurements on $CDCl_3$ layer. [g] Except for Li^+ picrate$^-$, based on *A* values calculated from UV measurements on H_2O layer. [h] K^+ picrate was not determined because the K^+ salt of the host precipitated. No correction was made for the small amount of host distributed in the aqueous phase at equilibrium. [i] Corrected for 1.1% solubility of host **26** in 0.015 M K^+ picrate$^-$ in H_2O.

For this ion, the smaller oligomer had a $-\Delta G°$ which was 4.9 kcal/mol higher than that of the larger oligomer. Apparently $[(EtO)_2OPCH_2]_2D(OEOEO)_2E$ (**12**) has a near ideal arrangement for binding Na^+, since its $-\Delta G°$ value exceeds that of all other systems reported here by at least 4 kcal/mol. This suggests that the P→O binding sites are substantially involved with Na^+, and correlates with the fact that $[(EtO)_2POCH_2]_2D(OCH_3)_2$ (**17**) binds Na^+ better than any other ion with a $-\Delta G°$ of 5.8 kcal/mol. Unexpectedly, $[(EtO)_2OPCH_2]_2D(OEOEOE)_2O$ (**13**) binds Li^+ about 0.5 kcal better than its smaller oligomer, $[(EtO)_2OPCH_2]_2D(OEOEO)_2E$ (**12**). Because of the small ionic diameter of Li^+ (~1.4 Å), it can accommodate fewer contact oxygen binding sites. Possibly the more flexible, larger oligomer generates more appropriate arrangements than the more rigidly organized lower oligomer.

Host $[(EtO)_2OPCH_2]_2T(OEOE)_2O$ (**20**) is a molecular substitute for its less accessible $[(EtO)_2OPCH_2]_2D(OEOE)_2O$ analogue. In molecular models and in complexation of RNH_3PF_6 salts, substitution of a 1,1′-bitetralyl for a 1,1′-binaphthyl unit in a host produced similar results.[17] The $-\Delta G°$ values of $[(EtO)_2OPCH_2]_2T(OEOE)_2O$ (**20**) provided a $-\Delta G°_{av}$ value of 5.7 kcal/mol, only 0.8 kcal/mol more than that of the noncyclic model, $[(EtO)_2OPCH_2]_2D(OCH_3)$ (**17**). Although $[(EtO)_2OPCH_2]_2T(OEOE)_2O$ (**20**) shows a small bias for binding the smaller ions, the magnitude of the bias is surprisingly small. Its molecular model suggests that it should be an ideal complexer of Na^+, which it is far from being. The system's distinguishing feature is that it is the only cycle studied thus far in $CDCl_3$ that binds Li^+ better than K^+, although the difference is only 0.6 kcal/mol.

It is interesting to compare the best host of this study with the best hosts of other studies, namely, dicyclohexyl-18-crown-6 and the noncrown host, **29**.[2d] The respective $-\Delta G°_{av}$



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and $-\Delta(\Delta G°)_{max}$ values (kcal/mol) for the three systems are as follows: **29,** 10.2 and 5.3; $[(EtO)_2OPCH_2]_2D(OEOEO)_2E$, 10.0 and 5.4; dicyclohexyl-18-crown-6, 9.3 and 4.1. Thus **29** and $[(EtO)_2OPCH_2]_2D(OEOEO)_2E$ (**12**), both of which have been designed with the help of molecular models, are the best and most differentiating hosts that have been examined in our test system.

Effects on Free Energies of Association of Changes in Structures of Ligand Systems Containing the 18-Crown-6 Macrocycle. The five substituted 18-crown-6 systems examined exhibited the following decreasing orders of $-\Delta G°_{av}$ and $-\Delta(\Delta G°)_{max}$ (kcal/mol), respectively: *trans*-$(BzOCH_2)_2E(OEOEO)_2E$ (9.1) (5.1); *trans*-$(o\text{-}ClC_6H_4)_2E(OEOEO)_2E$ (9.1) (4.7); $Nap(OEOEO)_2E$ (8.7) (4.8); *cis*-$(BzOCH_2)_2E(OEOEO)_2E$ (8.4) (4.2); *cis*-$(o\text{-}ClC_6H_4)_2E(OEOEO)_2E$ (8.0) (3.0). Both the order itself and the small magnitudes of differences suggest that the substituent effects are largely conformational in character. Molecular model examinations of the systems suggest that trans substitution does not disturb the preferred gauche O to O relationship of the substituted O-C-C-O unit.[18] Of course, naphtho substitution eclipses the oxygens of this unit, whereas cis substitution pushes the unit toward an anti relationship for the two oxygens. Since convergence of unshared electron pairs on the center of the hole should enhance binding, the conformational effect on binding is likely to be gauche > eclipsed > anti. This conformational order translates into the configurational order, trans-vicinal > naphtho > cis-vicinal, which corresponds to the order observed.

Commercial dicyclohexyl-18-crown-6 is composed largely of the cis,cis,syn and cis,cis,anti isomers. It provides calibration as to the effects of enforced gauche relationships of two O-C-C-O units on binding ability toward the six picrate salts. This macrocycle gave a $-\Delta G°_{av}$ value of 9.3 kcal/mol, close to the 9.1 kcal/mol observed for both *trans*-$(BzOCH_2)_2E(OEOEO)_2E$ (**23**) and *trans*-$(o\text{-}ClC_6H_4)_2E(OEOEO)_2E$ (**25**). All three systems best bind K^+, with $-\Delta G°$ values (kcal/mol) as follows: *trans*-$(BzOCH_2)_2E(OEOEO)_2E$, 11.4; dicyclohexyl-18-crown-6, 11.3; *trans*-$(o\text{-}ClC_6H_4)_2E(OEOEO)_2E$, 11.2. The near identity of these free-energy values provides a standard for comparing all-gauche 18-crown-6 systems with other hosts. Unfortunately, the solubility in water of 18-crown-6 and of its metal ion complexes precludes determination of its association constants in our test system.

No special binding effects arising out of its "jaws"-like structure are visible in the respective $-\Delta G°_{av}$ and $-\Delta(\Delta G°)_{max}$ values of 8.7 and 3.7 kcal/mol observed for $E(OEOEOCH_2)_2E(OEOEO)_2E$ (**26**). These values are close to those observed for *cis*-$(BzOCH_2)_2E(OEOEO)_2E$ (**22**), which are 8.4 and 4.2 kcal/mol, respectively. These two systems best bind K^+ with $-\Delta G°$ values of 10.4 and 10.3 kcal/mol, respectively. Thus the bicyclic system behaves like a cis-disubstituted 18-crown-6 in which only the better organized of the two ring systems is involved in binding. Although molecular models suggest that with the large Cs^+ ion the larger ring of $E(OEOEOCH_2)_2E(OEOEO)_2E$ (**26**) is beautifully structured to provide four additional binding sites, such an effect if it exists is disappointingly small. Thus for Cs^+ $E(OEOEOCH_2)_2E(OEOEO)_2E$ (**26**) gives $-\Delta G°$ of 8.2, whereas for *cis*-$(BzOCH_2)_2E(OEOEO)_2E$ (**22**) the value is 7.8 kcal/mol. Probably both rings of the bicyclic system are engaged in binding Cs^+, but too many conformations must be frozen out during complexation to provide much net free energy of association. This result illustrates how misleading molecular model examination can be in designing complementary host–guest relationships. Enforced conformational organization of contact sites appears to be a necessary condition for large additive effects on $-\Delta G°$ of association.

Correlations between Structures of Hosts and Their Abilities to Complex Ammonium and Alkylammonium Ions. The $-\Delta G°$ values for association were determined for nine of the new ligand systems complexing NH_4^+, $CH_3NH_3^+$, and *t*-$BuNH_3^+$ picrates (Table I). Table II reports the values for each host of $-\Delta(\Delta G°)^{NH_4^+}_{CH_3NH_3^+}$, $-\Delta(\Delta G°)^{CH_3NH_3^+}_{t\text{-}BuNH_3^+}$, and $-\Delta G°_{CH_3NH_3^+}$.

In complexing $CH_3NH_3^+$, the hosts rank in the following decreasing order of their $-(\Delta G°)$ values (kcal/mol): dicyclohexyl-18-crown-6 (9.4); $[(EtO)_2OPCH_2]_2D(OEOEO)_2E$ (8.2); *trans*-$(BzOCH_2)_2E(OEOEO)_2E$ (8.1); *trans*-$(o\text{-}ClC_6H_4)_2E(OEOEO)_2E$ (7.9); $E(OEOEOCH_2)_2E(OEOEO)_2E$ (7.6); $Nap(OEOEO)_2E$ (7.5); *cis*-$(BzOCH_2)_2E(OEOEO)_2E$ (7.4); $(CH_3)_2D(OEOEO)_2E$ (7.1); $(HO_2C)_2D(OEOEO)_2E$ (6.7); *cis*-$(o\text{-}ClC_6H_4)_2E(OEOEO)_2E$ (6.4); $(CH_3CO)_2D(OEOEO)_2E$ (6.3); $(CH_3)_2D(OEOEOCH_3)_2$ (4.8). This order again emphasizes the importance to binding of an all-gauche, regular arrangement of oxygens in the macrocycles. Among the top four binders, three are 18-crown-6 systems in which that arrangement is the most probable. At the bottom of the scale is found the noncyclic compound, $(CH_3)_2D(OEOEOCH_3)_2$ (**1**).

Interestingly, $[(EtO)_2OPCH_2]_2D(OEOEO)_2E$ (**12**) is second in rank. Thus its macroring oxygens appear similarly well organized for complexation of $CH_3NH_3^+$. Since its

Table II. Differences in Free Energies of Association of Hosts with NH_4^+, $CH_3NH_3^+$, and *t*-$BuNH_3^+$ Picrates$^-$ in $CDCl_3$ at 25 °C

ligand system	$-(\Delta G°)_{CH_3NH_3^+}$, kcal/mol	$-\Delta(\Delta G°)^{NH_4^+}_{CH_3NH_3^+}$, kcal/mol	$-\Delta(\Delta G°)^{CH_3NH_3^+}_{t\text{-}BuNH_3^+}$, kcal/mol
$(CH_3)_2D(OEOEOCH_3)_2$ (**1**)	4.8	0.6	1.4
$(CH_3)_2D(OEOEO)_2E$ (**3**)	7.1	1.8	0.7
$(HO_2C)_2D(OEOEO)_2E$ (**7**)	6.7	0.6	1.3
$(CH_3CO)_2D(OEOEO)_2E$ (**9**)	6.3	1.6	1.8
$[(EtO)_2OPCH_2]_2D(OEOEO)_2E$ (**12**)	8.2	1.4	2.7
$Nap(OEOEO)_2E$ (**21**)	7.5	2.0	0.6
cis-$(BzOCH_2)_2E(OEOEO)_2E$ (**22**)	7.4	1.9	1.6
trans-$(BzOCH_2)_2E(OEOEO)_2E$ (**23**)	8.1	2.0	0.9
cis-$(o\text{-}ClC_6H_4)_2E(OEOEO)_2E$ (**24**)	6.4	2.1	1.6
trans-$(o\text{-}ClC_6H_4)_2E(OEOEO)_2E$ (**25**)	7.9	2.2	1.5
$E(OEOEOCH_2)_2E(OEOEO)_2E$ (**26**)	7.6	1.9	1.5
dicyclohexyl-18-crown-6	9.4	1.2	2.5

$-\Delta G°_{CH_3NH_3^+}$ value exceeds that of $(CH_3)_2D(OEOEO)_2E$ (**3**) by 1.1 kcal/mol, one of the P→O oxygens of the side chain also must be involved in binding. A molecular model of the complex between $CH_3NH_3^+$ and $[(EtO)_2OPCH_2]_2$-$D(OEOEO)_2E$ (**12**) provides a structure in which the $CH_3NH_3^+$ is bound to the six ring oxygens by three $NH^+\cdots O$ hydrogen bonds in a tripod arrangement and by three $N^+\cdots O$ contact sites. This places the axis of the CH_3–N bond perpendicular to the best plane of six ring oxygens and roughly parallel to the plane of the tangential naphthalene ring. To provide room for the CH_3 group of the guest, the $CH_2PO(OEt)_2$ group on the methyl side of the macroring must occupy a conformation that turns the two hydrogens of the CH_2 group toward the methyl group and turns the bulky $PO(OEt)_2$ away from the methyl. On the side of the macroring opposite the methyl, the P→O oxygen beautifully contacts the N^+ by protruding slightly into the hole of the macroring. The model of this complex is very compact. Thus many degrees of conformational freedom must be frozen out during formation of the complexes. Apparently the $P\rightarrow O\cdots N^+$ interaction is enough to pay this cost and add 1.1 kcal to the binding as well.

The ranking of hosts in decreasing order of $-\Delta(\Delta G°)^{NH_4^+}_{CH_3NH_3^+}$ values (kcal/mol) is as follows: *trans*-$(o$-$ClC_6H_4)_2E(OEOEO)_2E$ (2.2); *cis*-$(o\text{-}ClC_6H_4)_2$-$E(OEOEO)_2E$ (2.1); $Nap(OEOEO)_2E$ (2.0); *trans*-$(BzOCH_2)_2E(OEOEO)_2E$ (2.0); *cis*-$(BzOCH_2)_2$-$E(OEOEO)_2E$ (1.9); $E(OEOEOCH_2)_2E(OEOEO)_2E$ (1.9); $(CH_3)_2D(OEOEO)_2E$ (1.8); $(CH_3CO)_2D(OEOEO)_2E$ (1.6); $[(EtO)_2OPCH_2]_2D(OEOEO)_2E$ (1.4); dicyclohexyl-18-crown-6 (1.2); $(HO_2C)_2D(OEOEO)_2E$ (0.6); $(CH_3)_2$-$D(OEOEOCH_3)_2$ (0.6). If three of the hydrogens of NH_4^+ in the complexes hydrogen bond oxygens, the fourth is available to hydrogen bond the picrate counterion in a contact ion pair. When $CH_3NH_3^+$ is complexed by three hydrogen bonds to oxygen, the ion pair must be more separated. This difference accounts for the fact that NH_4^+ is always better bound than $CH_3NH_3^+$.

The above ranking of hosts in $-\Delta(\Delta G°)^{NH_4^+}_{CH_3NH_3^+}$ values undoubtedly reflects many factors, only two of which will be discussed. Since $CDCl_3$ is a weakly polar medium, the degree of charge separation in the complex is bound to affect this parameter rather seriously. With the exception of dicyclohexyl-18-crown-6, the position of the host in the rank correlates roughly with the polarity of the groups close to the positive charge. Thus chlorophenyl, naphthyl, and benzyl groups are less polar than $CDCl_3$ as media for charge separation, and hosts containing these groups are high in the order. Groups such as $COCH_3$, CO_2H, and $PO(OEt)_2$ are more polar than $CDCl_3$, and hosts containing these groups are found relatively low in the order. The second factor involves positive charge delocalization in the complex. The strongly complexing hosts such as dicyclohexyl-18-crown-6 and $[(EtO)_2OPCH_2]_2$-$D(OEOEO)_2E$ (**12**) undoubtedly disperse the positive charge better than the more weakly binding hosts. The more dispersed the charge, the smaller should be the cost in free energy of charge separation.

In molecular models of these complexes of $CH_3NH_3^+$, no serious steric repulsions are visible between the CH_3 group of the guest and the substituents of the host. The much greater spacial requirement of *t*-Bu as compared to the CH_3 are reflected in the values of $-\Delta(\Delta G°)^{CH_3NH_3^+}_{t\text{-}BuNH_3^+}$. Ranking of the hosts in terms of decreasing values of this parameter (kcal/mol) provides the following order: $[(EtO)_2OPCH_2]_2D(OEOEO)_2E$ (2.7); dicyclohexyl-18-crown-6 (2.5); $(CH_3CO)_2$-$D(OEOEO)_2E$ (1.8); *cis*-$(BzOCH_2)_2E(OEOEO)_2E$ (1.6); *cis*-$(o\text{-}ClC_6H_4)_2E(OEOEO)_2E$ (1.6); *trans*-$(o\text{-}ClC_6H_4)_2$-$E(OEOEO)_2E$ (1.5); $E(OEOEOCH_2)_2E(OEOEO)_2E$ (1.5); $(CH_3)_2D(OEOEOCH_3)_2$ (1.4); $(HO_2C)_2D(OEOEO)_2E$ (1.3); *trans*-$(BzOCH_2)_2E(OEOEO)_2E$ (0.9); $(CH_3)_2$-$D(OEOEO)_2E$ (0.7); $Nap(OEOEO)_2E$ (0.6). Fortunately, X-ray structures of the complexes between $(CH_3)_3CNH_3ClO_4$ and hosts $(CH_3)_2D(OEOEO)_2E$,[19] $Nap(OEOEO)_2E$,[20] and 18-crown-6[20] have been completed and correspond pretty much to what was expected from examination of CPK molecular models.

The relatively large $-\Delta(\Delta G°)^{CH_3NH_3^+}_{t\text{-}BuNH_3^+}$ value of 2.7 kcal/mol for $[(EtO)_2OPCH_2]_2D(OEOEO)_2E$ (**12**) compared to the much smaller value of 0.7 for $(CH_3)_2D(OEOEO)_2E$ (**3**) correlates with the differences in steric compression observed in models of the four complexes involved. In models of the complexes of $CH_3NH_3^+$ and $(CH_3)_3CNH_3^+$ with $(CH_3)_2$-$D(OEOEO)_2E$ (**3**), little compression is visible. Both in models of the latter complex and in its X-ray structure, two guest CH_3 groups abut the face of a 2-methylnaphthyl group of the host. The system accommodates potential compression by the best plane of the macroring tilting away from being normal to the plane of the 2-methylnaphthyl group. This tilt is resisted somewhat by the $CH_2PO(OEt)_2$ group on the face of the macroring opposite the *t*-Bu in the complex of *t*-$BuNH_3^+$ with $[(EtO)_2OPCH_2]_2D(OEOEO)_2E$ (**12**).

The relatively large $-\Delta(\Delta G°)^{CH_3NH_3^+}_{t\text{-}BuNH_3^+}$ value of 2.5 kcal/mol for dicyclohexyl-18-crown-6 compared to the much smaller value of 0.9 kcal/mol for *trans*-$(BzOCH_2)_2E(OEOEO)_2E$ (**23**) also correlates with expectations based on molecular model examination. In models of the complexes of $CH_3NH_3^+$ and of $(CH_3)_3CNH_3^+$ with *trans*-$(BzOCH_2)_2E(OEOEO)_2E$ (**23**), little compression is visible. However, the cis-fused cyclohexane rings in models of either *cis,cis,syn-* or *cis,cis,-anti*-dicyclohexyl-18-crown-6 are compressed by the CH_3 groups of the $(CH_3)_3CNH_3^+$ guest in two out of the three isomeric complexes. In models of the complex of *cis,cis,syn*-dicyclohexyl-18-crown-6 in which the *t*-Bu group is anti to the two cyclohexane rings, no such compression is visible. How-

ever, the two cyclohexane rings fused syn to one another in such a complex provide considerable steric inhibition of contact ion pairing by the picrate ion.

The low steric requirements for complexation of t-$BuNH_3^+$ with $Nap(OEOEO)_2E$ (**21**) is obvious in molecular models, and $-\Delta(\Delta G°)^{CH_3NH_3^+}_{t\text{-}BuNH_3^+}$ is only 0.6 kcal/mol. The other systems provide values for this parameter interpretable in terms of the same types of structural features discussed above. The only exception involves the noncyclic host, $(CH_3)_2$-$D(OEOEOCH_3)_2$ (**1**), whose value of 1.4 kcal/mol is surprisingly high, particularly in view of the fact that $-\Delta G°_{CH_3NH_3^+}$ for this host is only 4.8 kcal/mol. Possibly the RNH_3^+ complexes of this relatively unorganized host are held together by only two NH···O hydrogen bonds and several N^+···O contact binding sites. Such structures leave the third NH^+ free to hydrogen bond and form a contact ion pair with the picrate ion. This latter effect may be much more sterically inhibited by the t-Bu than by a methyl group.

The magnitudes of the $-\Delta(\Delta G°)^{CH_3NH_3^+}_{t\text{-}BuNH_3^+}$ values provide a measure of the structural recognition based on steric effects between potential complexing partners. The maximum value observed thus far for any of the hosts is 2.7 kcal/mol, and is observed for $[(EtO)_2POCH_2)]_2D(OEOEO)_2E$ (**12**). The steric character of this parameter suggests that the maximum amount of *chiral recognition*[17] based on steric effects that might be realized in these types of systems is of the same magnitude. The parameter $-\Delta(\Delta G°)^{NH_4^+}_{t\text{-}BuNH_3^+}$ reflects both steric and electronic effects.

The largest value observed thus far for any host is 4.1 kcal, and is found for $[(EtO)_2OPCH_2]_2D(OEOEO)_2E$ (**12**). This value is about 42% of that for $-\Delta G°_{NH_4^+}$ binding this host. In other words, substitution of a t-Bu for a hydrogen of NH_4^+ reduces its free energy binding potential by about 42%.

Experimental Section

General. All solvents were reagent grade. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use. Dimethylformamide (DMF) was distilled at 30 mm from 3 Å molecular sieves, and was stored over the same agent. Diethyl ether was distilled from lithium aluminum hydride ($LiAlH_4$) immediately prior to use, and CH_2Cl_2 was fractionally distilled. Melting points were measured on a Thomas-Hoover apparatus, and are uncorrected. Mass spectra were taken on an AEI MS-9 machine at 70 eV. Infrared spectra were taken on a Perkin-Elmer Model 297 spectrometer, and ^1H NMR spectra were taken on either a Varian HA-100 or a Varian T-60 spectrometer, with chemical shifts given in δ (ppm) from internal $(CH_3)_4Si$. Ultraviolet measurements were made at 24–26 °C with a Beckman DU spectrometer equipped with a Gilford Model 252 modernization system. Gel permeation chromatographic columns were used as follows: column A, $\frac{3}{8}$ in. (o.d.) by 20 ft of Styragel 100 Å beads (Waters Associates Inc.), 37–75 μm particle size, exclusion limit 1500 mol wt in CH_2Cl_2 at a flow rate of about 4 min^{-1} and a pressure of 400–600 psi; column B, same as A except THF was solvent. Optical rotations were taken with a Perkin-Elmer 141 polarimeter in a 1-dm thermostated cell.

2,2′-Bis(1,4,7-trioxaoctyl)-3,3′-dimethyl-1,1′-binaphthyl (1). A mixture of 2.0 g (6.4 mmol) of 2,2′-dihydroxy-3,3′-dimethyl-1,1-binaphthyl,[6] 3.6 g (13.1 mmol) of 3,6-dioxaheptyl tosylate,[5] 0.73 g (13 mmol) of KOH pellets (85%), and 200 mL of THF was stirred under N_2 at reflux for 48 h. The mixture was cooled and shaken with 400 mL each of water and CH_2Cl_2. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to give a residue that was chromatographed on 100 g of alumina-CH_2Cl_2. The column was washed with 2 L of CH_2Cl_2. The product was eluted with 4 L of 5% Et_2O in CH_2Cl_2 (v) to give 2.1 g (64%) of **1** as an oil, film dried at 0.1 mm for 24 h at 50 °C; M^+ *m/e* 518; ^1H NMR (60 MHz, $CDCl_3$) δ 2.52 (s, $ArCH_3$, 6 H), 3.22 (s, OCH_3, 6 H), 3.38 (m, OCH_2O, 16 H), 7.22 (m, ArH, 6 H), 7.76 (m, ArH^5, 2 H), 7.78 (s, ArH^4, 2H). Anal. ($C_{32}H_{38}O_6$) C,H.

2,3:4,5-Bis[1,2-(3-methylnaphtho)]-1,6,9,12,15,18-hexaoxacyclo-eicosa-2,4-diene (3). Procedure A. To a solution stirred under N_2 of 4.0 g (12.7 mmol) of 3,3′-dimethyl-2,2′-dihydroxy-1,1′-binaphthyl[6] and 7.0 g (12.8 mmol) of pentaethylene glycol ditosylate[2b] dissolved in 600 mL of THF was added 1.5 g (26.8 mmol) of KOH (85%) in 6 mL of H_2O. The mixture was refluxed for 48 h, cooled, and shaken with 500 mL each of CH_2Cl_2 and water. The layers were separated, and the organic layer was washed with water, dried, and evaporated under reduced pressure. The residue was chromatographed on 150 g of alumina-CH_2Cl_2. The column was washed with 2 L of CH_2Cl_2, and the product was eluted with 3 L of 5% Et_2O in CH_2Cl_2 (v), evaporation of which gave 2.9 g (44%) of **3** after recrystallization from Et_2O-CH_2Cl_2: mp 130–131 °C; M^+ *m/e* 516; ^1H NMR (60 MHz, $CDCl_3$), δ 2.53 (s, CH_3, 6 H), 3.48 (m, OCH_2CH_2O, 20 H), 7.08 (m, ArH, 6 H), 7.66 (m, ArH^5, 2 H) 7.70 (s, ArH^4, 2 H). Anal. ($C_{32}H_{36}O_6$) C, H.

2,3:4,5-Bis[1,2-(3-aldehydonaphtho)]-1,6,9,12,15,18-hexaoxacy-cloeicosa-2,4-diene (5). A solution of 1.3 g (1.88 mmol) of 2,3:4,5-bis[1,2-(3-hydroxymethylnaphtho)]-1,6,9,12,15,18-hexaoxacy-cloeicosa-2,4-diene (**4**)[3b] in 50 mL of CH_2Cl_2 was stirred with 2.02 g (23.2 mmol) of activated MnO_2[7] for 77 h at 25 °C under N_2. The mixture was filtered through a Celite pad which was washed with CH_2Cl_2. The filtrates were evaporated to give 1.02 g of **5**, mp 164–166 °C, which was recrystallized from CH_2Cl_2-Et_2O to give 0.89 g (88%) of **5**: mp 165–167 °C; M^+ *m/e* 544; ^1H NMR ($CDCl_3$, 60 MHz) δ 3.1–3.8 (m, OCH_2O, 16 H), 3.92 (broad t, J = 5 Hz, $ArOCH_2$, 4 H), 7.0–7.7 (m, ArH, 6 H), 7.9–8.25 (m, ArH, 2 H), 10.67 (s, CHO, 2 H); IR spectrum ($CDCl_3$) 1682 cm^{-1} (C=O). Anal. ($C_{32}H_{32}O_8$) C, H.

2,3:4,5-Bis[1,2-(3-carbomethoxynaphtho)]-1,6,9,12,15,18-hex-aoxacycloeicosa-2,4-diene (6). A mixture of 2.694 g (4.952 mmol) of dialdehyde **5**, 10.0 g (0.115 mol) of activated MnO_2,[7] 1.60 g (32.6 mmol) of NaCN, and anhydrous CH_3OH (200 mL) was stirred under an N_2 atmosphere at 0 °C as a solution of glacial acetic acid (0.9 mL) in 50 mL of anhydrous CH_3OH was added dropwise over a 10-min period.[8] The reaction mixture was stirred at 25 °C for 14 h and filtered through a Celite pad, and the solids were washed with CH_2Cl_2. The filtrates were evaporated, the residue was distributed between CH_2Cl_2 (50 mL) and H_2O (60 mL), and the aqueous phase was extracted with two 50-mL portions of CH_2Cl_2. The combined organic phases were dried (Na_2SO_4), and solvent was removed to yield a white foam (3.0 g), which was passed through a chromatographic column of 125 g of MCB 80–325 mesh chromatographic grade basic alumina in 98/2 (v/v) CH_2Cl_2/EtOH. The first 200 mL of eluate was evaporated and the residue was triturated with Et_2O to yield 2.4 g of crystalline material, recrystallization of which gave 2.20 g (75%) of **6**: mp 119–120 °C; M^+ *m/e* 604; IR ($CHCl_3$) 1717 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 60 MHz) δ 2.9–4.2 (m, OCH_2CH_2O, 20 H), 4.01 (s, CH_3O, 6 H), 7.00–7.70 (m, ArH, 6 H), 7.87–8.13 (m, ArH, 2 H), 8.52 (s, $ArH^{4,4'}$, 2 H). Anal. ($C_{34}H_{36}O_{10}$) C, H. This compound is sensitive to hydrolysis on silica gel or basic alumina chromatography. Neutral activity 3 (Brockman) is recommended.

2,3:4,5-Bis[1,2-(3-carboxynaphtho)]-1,6,9,12,15,18-hexaoxacyclo-eicosa-2,4-diene (7). Diester **6** (360 mg, 0.600 mmol) was added to a solution of 310 mg (7.75 mmol) of NaOH in 1 mL of H_2O–13 mL of 95% EtOH, and the solution was stirred under N_2 at 25 °C for 6 h. The solvent was evaporated under reduced pressure, and the residue shaken with 30 mL of CH_2Cl_2 and 40 mL of H_2O. The aqueous phase was separated and acidified to pH 1 by dropwise addition of 6 N HCl. The cloudy mixture was extracted with three 30-mL portions of CH_2Cl_2, the combined extracts were dried (Na_2SO_4), and solvent was evaporated to give a white foam (348 mg). This material was subjected to gel permeation chromatography on column A to give product with retention volume of 173 mL of CH_2Cl_2, which after solvent evaporation gave 322 mg (94%) of diacid **7**, which crystallized when triturated with Et_2O: mp 201–205 °C; M^+ *m/e* 576; IR ($CHCl_3$) 1715 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 60 MHz) δ 3.0–4.2 (m, OCH_2CH_2O, 20 H), 7.00–7.70 (m, ArH, 6 H), 7.90–8.20 (m, ArH, 2 H), 8.9 (broad s, ArH^4, 2 H), 8.9–9.57 (broad s, CO_2H, 2 H). Anal. ($C_{32}H_{32}O_{10}$) C, H.

2,3:4,5-Bis[1,2-(3-cyanonaphtho)]-1,6,9,12,15,18-hexaoxacyclo-eicosa-2,4-diene (8). A mixture of 1.8 g (3.3 mmol) of dialdehyde **5**, 2.6 g (38.2 mmol) of NaO_2CH, and 1.4 g (20.3 mmol) of $HONH_3Cl$ in 30 mL of formic acid[9] was stirred under N_2 and heated to 110 °C for 2 h. The solution was cooled and shaken with 400 mL each of $CHCl_3$ and water. The organic layer was washed with water (500 mL) and a 10% NaHCO solution in water (500 ml) and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was chromatographed on 60 g of alumina-CH_2Cl_2, and the product

was eluted with 2 L of 10% Et_2O in CH_2Cl_2 (v) to give 1.5 g (84%) of **8** after recrystallization from Et_2O–CH_2Cl_2: mp 148–149 °C; M^+ *m/e* 538; ^1H NMR (60 MHz, $CDCl_3$) δ 3.72 (m, OCH_2CH_2O, 20 H), 7.36 (m, ArH, 6 H), 7.97 (m, ArH^5, 2 H), 8.45 (s, ArH^4, 2 H). Anal. ($C_{32}H_{30}N_2O_6$) C, H.

2,3:4,5-Bis[1,2-(3-acetylnaphtho)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (9). To a solution of 0.40 g (0.74 mmol) of dinitrile **8** in 100 mL of THF stirred under N_2 at −78 °C was added 10 mL of CH_3Li in Et_2O (1.6 M). The mixture was stirred for 30 min, and 10 mL of CH_3OH was cautiously added dropwise followed by 50 mL of 6 N hydrochloric acid. The mixture was stirred at 25 °C for 12 h and shaken with 200 mL of $CHCl_3$ and 400 mL of H_2O. The organic layer was washed with 500 mL of H_2O and 300 mL of 10% $NaHCO_3$ aqueous solution and dried ($MgSO_4$). The solvent was evaporated under reduced pressure, and the residue was chromatographed on 40 g of silica gel–CH_2Cl_2. The column was washed with 500 mL of CH_2Cl_2 and 1 L of 10% THF in CH_2Cl_2. The product was eluted with 1-L portions (v) of CH_2Cl_2–THF (4:1, 1:1, and 1:3) to give after recrystallization from CH_2Cl_2–THF 150 mg (35%) of diketone **9**: mp 154–155 °C; M^+ *m/e* 572; ^1H NMR (60 MHz, $CDCl_3$) δ 2.79 (s, CH_3, 6 H), 3.59 (m, OCH_2CH_2O, 20 H), 7.34 (m, ArH, 6 H), 8.00 (m, ArH^5, 2 H), 8.24 (s, ArH^4, 2 H). Anal. ($C_{34}H_{36}O_8$) C, H.

2,3:4,5-Bis[1,2-(3-chloromethylnaphtho)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (10). Procedure B. This procedure is superior to that reported previously.[3b] To a mixture of macrocyclic diol **4**[3b] (2.40 g, 4.37 mmol) and 50 mL of anhydrous C_6H_6 stirred at 25 °C under N_2 was added dropwise (5 min) a solution of 4.51 g (38 mmol) $SOCl_2$ (distilled from triphenyl phosphite) in 5 mL of anhydrous benzene. The reaction mixture was stirred for 15 min at 25 °C and was heated to reflux for 30 min. Solvent was evaporated under reduced pressure, and the residue was dissolved in 125 mL of Et_2O. The solution was successively washed with 5% aqueous $NaHCO_3$ (three 50-mL portions) and saturated NaCl (two 50-mL portions). The organic phase was dried ($MgSO_4$), and the solvent was evaporated to give a white solid, which was recrystallized from CH_2Cl–Et_2O to yield **10:** 2.4 g (92%); mp 109–110.5 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 2.9–3.9 (m, OCH_2CH_2O, 20 H), 4.86 (ν_a) and 5.17 (ν_b) (AB, J = 12 Hz, CH_2Cl, 4 H), 6.96–7.60 (m, ArH, 6 H), 7.75–8.00 (m, ArH, 2 H), 8.12 (broad s, ArH, 2 H). The analysis of this compound has been previously reported.[3b]

2,3:4,5-Bis[1,2-[3-(2-oxo-1,3-diaza-3-methylcyclohexylmethyl)-naphtho]]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (11). From 5.0 g (50 mmol) of 2(1*H*)-tetrahydropyrinidone (Eastman), 2.40 g of NaH (50% mineral dispersion, 50 mmol), 250 mL of dry dimethoxyethane, and 7.10 g (50 mmol) of methyl iodide was prepared 0.60 g (~10%) of *N*-methyl-*N,N'*-trimethyleneurea, mp 90.5–92.5 °C (lit.[10] 86–89 °C). A mixture of 0.24 g (2.1 mmol) of this material, 0.101 g of NaH (2.096 mmol, as a 50% dispersion), and 25 mL of THF was refluxed under N_2 until H_2 evolution ceased. The reaction mixture was cooled to 25 °C, and bis(chloromethyl) macrocycle **10** (0.300 g, 0.515 mmol) was added. The reaction mixture was stirred at 25 °C for 36 h, the solvent was evaporated under reduced pressure, and the residue was shaken with CH_2Cl_2 (40 mL), H_2O (30 mL), and 1 N HCl (20 mL). The organic phase was dried (Na_2SO_4), and solvent was evaporated under reduced pressure to give a light yellow foam. This material was chromatographed on 50 g of MCB 80–325 mesh basic alumina. Elution of product with 1% EtOH in CH_2Cl_2 (v) came between 140 and 240 mL. This material was further purified by gel permeation chromatography on column A, compound **11** having a retention volume of 161 mL of CH_2Cl_2. This product was isolated as a white foam, 268 mg (70%): M^+ *m/e* 740; ^1H NMR (60 MHz, $CDCl_3$) δ 1.77–2.30 (m, $CH_2CH_2CH_2$, 4 H), 3.05 (s, NCH_3, 6 H), 3.0–4.2 (m, OCH_2CH_2O and NCH_2, 28 H), 4.95 (broad s, $ArCH_2N$, 4 H), 7.00–7.53 (m, ArH, 6 H), 7.77–8.07 (m, ArH, 4 H); IR ($CHCl_3$) 1620 cm^{-1} (C=O). Anal. ($C_{42}H_{52}N_4O_8$) C, H.

2,3:4,5-Bis[1,2-(3-diethoxyoxophosphinylmethyl)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (12). Procedure C. A mixture of 1.7 g (2.9 mmol) of bis(chloromethyl) macrocycle **10** and 10 mL of triethyl phosphite was heated under N_2 with stirring at 165 °C for 2 h. The excess triethyl phosphite was evaporated at 100 °C (30 mm) to produce a residue of colorless oil, which was subjected to gel permeation chromatography on column A to give a retention volume for **12** of 168 mL of CH_2Cl_2. The product was isolated as a glass which was film dried at 40 °C (0.01 mm) for 24 h to give 2.06 g (90%): M^+ *m/e* 788; ^1H NMR (60 MHz, $CDCl_3$) δ 1.30 (m, CH_3, 12 H), 3.51 (m, OCH_2CH_2O, $ArCH_2$, 24 H), 4.08 (m, $POCH_2$, 8 H), 7.18 (m, ArH, 6 H), 7.80 (m, ArH^5, 2 H), 8.10 (d, ArH^4, J = 3.8 Hz, 2 H). Anal. ($C_{40}H_{54}O_{12}P_2$) C, H.

2,3:4,5-Bis[1,2-(3-diethoxyoxophosphinylmethylnaphtho)]-1,6,9,12,15,18,21-heptaoxacyclotricosa-2,4-diene (13). By procedure B, 3.0 g (5.1 mmol) of 2,3:4,5-bis[1,2-(3-hydroxymethylnaphtho)]-1,6,9,12,15,18,21-heptaoxacyclotricosa-2,4-diene[3b] dissolved in 300 mL of C_6H_6 and 10 g (84 mmol) of $SOCl_2$ was converted in 88% yield to 2,3:4,5-bis[1,2-(3-chloromethylnaphtho)]-1,6,9,12,15,18,21-heptaoxacyclotricosa-2,4-diene, isolated as a glass; M^+ *m/e* 628 (^{35}Cl); ^1H NMR (60 MHz, $CDCl_3$) δ 3.52 (m, OCH_2CH_2O, 24 H), 4.98 (AB q, $ArCH_2$, 4 H), 7.21 (m, ArH, 6 H), 7.81 (m, ArH^5, 2 H), 8.05 (s, ArH^4, 2 H). By procedure C, 1.4 g (2.2 mmol) of this dichloride and 8 mL of triethyl phosphite was converted to diphosphinate **13,** which on gel permeation on column A gave a retention volume of 161 mL of CH_2Cl_2. The substance was isolated as a glass and film dried at 40 °C under 0.01 mm for 24 h to give 1.80 g (97%) of **13**: M^+ *m/e* 832; ^1H NMR (60 MHz, $CDCl_3$) δ 1.29 (m, CH_3, 12 H), 3.59 (m, $ArCH_2$, OCH_2CH_2O, 28 H), 4.11 (m, $POCH_2$, 8 H), 7.16 (m, ArH, 6 H), 7.86 (m, ArH^5, 2 H), 8.13 (d, ArH^4, J = 3.8 Hz, 2 H). Anal. ($C_{42}H_{58}O_{13}P_2$) C, H.

2,3:4,5-Bis{1,2-[3-(α-pyridylthiamethyl)naphtho]}-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (14). A solution of 291 mg (7.27 mmol) of NaOH in 1 mL of water was added to a solution of 808 mg (7.2 mmol) of 2-mercaptopyridine dissolved in 8 mL of DMF. Dichloride **10** (1.0 g, 1.7 mmol) dissolved in 10 mL of DMF was added. The mixture was stirred for 3 h at ambient temperature, the solvent was evaporated at 1 mm of pressure, and the residue was shaken with CH_2Cl_2 and H_2O (100 mL each). The organic layer was washed with 50 mL of 15% aqueous NaOH, dried ($MgSO_4$), and evaporated under reduced pressure, and the residue was chromatographed on 40 g of silica gel. The column was washed with 200 mL of CH_2Cl_2, and the product was eluted with 2% EtOH in CH_2Cl_2 (v). Compound **14** was isolated as an amorphous wax after being dried for 24 h at 165 °C (0.1 mm), wt 450 mg (36%): M^+ *m/e* 734; ^1H NMR (60 MHz, $CDCl_3$) δ 3.0–4.0 (m, OCH_2CH_2O, 20 H), 5.12 (s, $ArCH_2$, 4 H), 6.8–8.0 (m, ArH, 16 H), 8.07 (s, ArH, 2 H). Anal. ($C_{42}H_{42}N_2O_6S$) C, H.

2,3:4,5-Bis{1,2-[3-(3α-pyridyl-2-oxapropyl)naphtho]}-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (15). Freshly distilled 2-hydroxymethylpyridine (1.09 g, 10 mmol, Aldrich) in 25 mL of THF was added dropwise to a suspension of NaH (480 mg, 10 mmol, suspension in mineral oil) stirred under N_2 in 5 mL of THF. After the evolution of H_2 ceased (15 min), 1.5 g (2.6 mmol) of dichloride **10** in 15 mL of THF was added, and the resulting mixture was refluxed for 12 h under N_2. The solvent was removed under reduced pressure, and the residue was shaken with a mixture of 100 mL of CH_2Cl_2 and 100 mL of H_2O. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure, and the residue was chromatographed on 65 g of alumina. Elution of the product with 2% EtOH in CH_2Cl_2 (v) gave 1.55 g of material which was submitted to column C gel permeation chromatography: retention volume 170 mL of THF; wt 1.25 g (66%); M^+ *m/e* 730; ^1H NMR (60 MHz, $CDCl_3$) δ 3.0–4.0 (m, OCH_2CH_2O, 20 H), 4.87 (s, $ArCH_2$, 4 H), 5.01 (s, $ArCH_2$, 4 H), 7.0–7.8 (m, ArH, 8 H), 7.6–8.0 (m, ArH, 6 H), 8.13 (s, ArH, 2 H), 8.5–8.7 (m, ArH, 2 H). Anal. ($C_{44}H_{46}O_8N_2$) C, H.

2,2'-Dimethoxy-3,3'-bis(hydroxymethyl)-1,1'-binaphthyl (16). To a solution of 25 g (72.3 mmol) of 2,2'-dihydroxy-3,3'-bis(hydroxymethyl)-1,1'-binaphthyl in 800 mL of acetone at 60 °C stirred under N_2 was added 25 g (181 mmol) of K_2CO_3 followed by 50 g (352 mmol) of CH_3I. The mixture was refluxed for 36 h, evaporated to 200-mL volume, cooled, and shaken with 500 mL each of CH_2Cl_2 and H_2O. The aqueous layer was extracted with two 100-mL portions of CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$), evaporated to 150 mL volume, and diluted with 200 mL of benzene. The product crystallized at 25 °C to give 24.3 g (90%) of **16**: mp 178–179 °C; M^+ *m/e* 374; ^1H NMR (60 MHz, $CDCl_3$) δ 2.29 (m, OH, 2 H), 3.38 (s, OCH_3, 6 H), 4.91 (m, $ArCH_2$, 4 H), 7.21 (m, ArH, 6 H); 7.80 (m, ArH, 2 H), 7.88 (s, ArH^4, 2 H). Anal. ($C_{24}H_{22}O_4$) C, H.

2,2'-Dimethoxy-3,3'-bis(diethoxyoxyphosphinylmethyl)-1,1'-binaphthyl (17). By procedure B, 10.0 g (26.7 mmol) of diol **16,** 20 g (168 mmol) of $SOCl_2$, and 400 mL of benzene provided 9.8 g (89%) of 2,2'-dimethoxy-3,3'-bis(chloromethyl)-1,1'-binaphthyl: mp 142–143 °C (from CH_2Cl_2–cyclohexane); M^+ *m/e* 410 (^{35}Cl); ^1H NMR (60 MHz, $CDCl_3$) δ 3.33 (s, OCH_3, 6 H), 4.95 (AB q, $ArCH_2$, 4 H), 7.33 (m, ArH, 6 H), 7.90 (m, ArH, 2 H), 8.07 (s, ArH^4, 2 H). Anal. ($C_{24}H_{20}Cl_2O_2$) C, H.

By procedure C, 2.0 g (4.9 mmol) of the above dichloride and 8 mL of triethyl phosphite gave 2.4 g (80%) of **17** as an oil: M^+ *m/e* 614; ^1H NMR (60 MHz, $CDCl_3$) δ 1.30 (m, CH_3, 12 H), 3.32 (s, OCH_3, 6 H), 3.73 (m, $ArCH_2$, 4 H), 4.14 (m, OCH_2, 8 H), 7.25 (m, ArH, 6 H), 7.91 (m, ArH^5, 2 H), 8.12 (d, ArH^4, J = 3.8 Hz, 2 H). Anal. ($C_{32}H_{40}O_8P_2$) C, H.

2,3:4,5-Bis[1,2-(5,6,7,8-tetrahydronaphtho)]-1,6,9,12,15-pentaoxacycloheptadeca-2,4-diene (18). To a hot solution of 10 g (22.5 mmol) of 2,3:4,5-bis(1,2-naphtho)-1,6,9,12,15-pentaoxacycloheptadeca-2,4-diene[5] dissolved in 1 L of glacial acetic acid was added 1 g of PtO_2, and the mixture was shaken in an atmosphere of H_2 for 7 days at 25 °C. The mixture was filtered and the filtrate was shaken with 1 L of CH_2Cl_2 and 2 L of H_2O. The organic layer was washed with three 1-L portions of H_2O and two 1-L portions of 10% aqueous $NaHCO_3$ solution. The solution was dried ($MgSO_4$) and evaporated under reduced pressure, and the residue was chromatographed on 50 g of alumina-CH_2Cl_2. The product was eluted with 3 L of CH_2Cl_2 to give 9.7 g (95%) of **18** as an oil, which was film dried at 50 °C for 25 h at 0.01 mm: M^+ *m/e* 452; ^1H NMR (60 MHz, $CDCl_3$) δ 1.63 (m, CCH_2CH_2C, 8 H), 2.14 (m, $ArCH_2$, 4 H), 2.70 (m, $ArCH_2$, 4 H), 3.68 (m, OCH_2, 16 H) 6.83 (AB q, ArH, 4 H). Anal. ($C_{28}H_{36}O_5$) C, H.

2,3:4,5-Bis[1,2-(3-chloromethyl-5,6,7,8-tetrahydronaphtho)]-1,6,9,12,15-pentaoxacycloheptadeca-2,4-diene (19). To a solution of 9.0 g (19.9 mmol) of macrocycle **18** dissolved in 500 mL of CH_3CO_2H-$CHCl_3$ (4:1, v) at 55 °C were added 18 g (0.60 mol) of formaldehyde and 98 g of concentrated hydrochloric acid. The mixture was stirred at 65 °C for 3 h, cooled, and shaken with 300 mL of $CHCl_3$ and 1 L of H_2O. The organic layer was washed with three 1-L portions of H_2O and two 1-L portions of 10% $NaHCO_3$ aqueous solution and dried ($MgSO_4$). The solution was evaporated under reduced pressure, and the residue was chromatographed on 150 g of silica gel-CH_2Cl_2. The column was washed with 2 L of CH_2Cl_2 and the product eluted with 5% Et_2O in CH_2Cl_2 (v) to give, after film drying for 24 h at 25 °C and 0.01 mm, 7.3 g (67%) of **19** as a glass: M^+ *m/e* 548 (^{35}Cl); ^1H NMR (60 MHz, $CDCl_3$) δ 1.68 (m, CCH_2CH_2C, 8 H), 2.18 (m, $ArCH_2$, 4 H), 2.77 (m, $ArCH_2$, 4 H), 3.60 (m, OCH_2, 16 H), 4.85 (AB q, $ArCH_2Cl$, 4 H), 7.10 (s, ArH, 2 H). Anal. ($C_{30}H_{38}Cl_2O_5$) C, H.

2,3:4,5-Bis[1,2-(3-diethoxyoxophosphinylmethyl-5,6,7,8-tetrahydronaphtho)]-1,6,9,12,15-pentaoxacycloheptadeca-2,4-diene (20). By procedure C, 2.0 g (3.6 mmol) of dichloride **19** and 10 mL of triethyl phosphite was converted to **20**, which was purified by gel permeation chromatography on column A, retention volume 174 mL of CH_2Cl_2. The compound was isolated as a glass, film dried at 40 °C for 24 h at 0.01 mm, 2.3 g (84%): M^+ *m/e* 752; ^1H NMR (60 MHz, $CDCl_3$) δ 1.29 (m, CH_3, 12 H), 1.68 (m, CCH_2CH_2C, 8 H), 2.17 (m, $ArCH_2$, 4 H), 2.78 (m, $ArCH_2$, 4 H), 3.74 (m, OCH_2, $ArCH_2$, 28 H), 7.13 (d, J = 3.8 Hz, ArH, 2 H). Anal. ($C_{38}H_{58}O_{11}P_2$) C, H.

***meso*-Dimethyl Tartrate 2,3-Acetonide. Procedure D.** A mixture of 25 g (0.15 mol) of *meso*-tartaric acid monohydrate, 40 mL (0.38 mol) of 2,2-dimethoxypropane, 10 mL of CH_3OH, and 0.2 g of *p*-toluenesulfonic acid was heated with stirring at 50 °C for 45 min. An additional 20 mL of 2,2-dimethoxypropane and 114 mL of cyclohexane were added. Over a 24-h period, 125 mL of distillate (bp ca. 45 °C) was collected by conducting a slow, fractional distillation through an 18-in. Vigreux column packed with 1/4-in. glass rings. The product was distilled to give 30.9 g (95%) of product: bp 101-103 °C (1.5 mm); M^+ −15, *m/e* 203; ^1H NMR (60 MHz, $CDCl_3$) δ 1.4 (s, CH_3, 3 H), 1.6 (s, CH_3, 3 H), 3.7 (s, OCH_3, 6 H), 5.8 (s, CH, 2 H). Anal. ($C_9H_{14}O_6$) C, H.

(*R,S*)-1,2,3,4-Butanetetrol 2,3-Acetonide. Procedure E. To a solution of 7.0 g (0.18 mol) of $LiAlH_4$ in 150 mL of anhydrous Et_2O was added dropwise with stirring under N_2 a solution of 30 g (0.14 mol) of *meso*-dimethyl tartrate 2,3-acetonide in 150 mL of anhydrous Et_2O. Gentle reflux was maintained. Addition took 1 h, after which the mixture was refluxed for 8 h and cooled to 25 °C. The excess $LiAlH_4$ was decomposed with 1:1:3 (v) mixture of H_2O-15% aqueous NaOH-H_2O, the mixture was filtered, and the salts were extracted for 24 h in a Soxhlet extractor with ether. The combined extract and filtrate were combined, the solvent was evaporated under reduced pressure, and the residue was distilled to give 17.7 g (79%) of product: bp 120 °C (2 mm); M^+ − 15, *m/e* 147; ^1H NMR (60 MHz, $CDCl_3$) δ 1.35 (s, CH_3, 3 H), 1.43 (s, CH_3, 3 H), 3.5-4.8 (m, CH_2, CH, OH, 8 H). This material was used in the next step without further purification or characterization.

(*R,S*)-1,8-Diphenyl-2,7-dioxa-4,5-octanediol 4,5-Acetonide. Procedure F. A solution of 5.0 (30.9 mmol) of (*R,S*)-1,2,3,4-butanetetrol 2,3-acetonide in 50 mL of THF was added dropwise to a mixture stirred under N_2 of NaH (3.3 g, 69 mmol) and 10 mL of THF. After the mixture had stirred for 30 min, benzyl bromide (21.0 g, 0.123 mol) was added in a solution of 50 mL of THF, and the solution was refluxed for 12 h. The mixture was filtered and the precipitate washed with THF. The filtrates were combined, the solvent was evaporated under reduced pressure, and the residue was chromatographed on silica gel with hexane-CH_2Cl_2 gradient mixtures to yield, after evaporation and drying at 50 °C (0.1 mm), 10 g (94%) of product as an oil suitable for use in the next step. An analytical sample was prepared by molecular distillation (120-140 °C, 0.1 mm): M^+ *m/e* 342; ^1H NMR (60 MHz, $CDCl_3$) δ 1.3 (s, CH_3, 3 H), 1.4 (s, CH_3, 3 H), 3.4-3.6 (m, $CHCH_2$, 4 H), 4.2-4.4 (m, CH, 2 H), 4.4, (s, $ArCH_2$, 4 H), 7.3 (s, ArH, 10 H). Anal. ($C_{21}H_{26}O_4$) C, H.

(*R,S*)-4,5-Dihydroxy-1,8-diphenyl-2,7-dioxaoctane. Procedure G. A mixture of 22.0 g (64 mmol) of (*R,S*)-1,8-diphenyl-2,7-dioxa-4,5-octanediol 4,5-acetonide was dissolved in a mixture of 250 mL of CH_3OH and 20 mL of 10% HCl and stirred for 12 h. The solvent was evaporated under reduced pressure at 25 °C or lower, and the residue was dissolved in CH_2Cl_2 (100 mL). The solution was dried ($MgSO_4$), the solvent was evaporated, and the residual oil was solidified. This material was sublimed at 150 °C (0.1 mm) to give 18.2 g (93%) of product used in the next step. An analytical sample was recrystallized from cyclohexane to give white prisms: mp 56-57.5 °C; M^+ *m/e* 302; ^1H NMR (60 MHz, $CDCl_3$) δ 2.8-3.0 (broad s, OH, 2 H), 3.5-4.0 (m, CH_2CH, 6 H), 4.5 (s, $ArCH_2$, 4 H), 7.3 (s, ArH, 10 H). Anal. ($C_{18}H_{22}O_4$) C, H.

(*R,S*)-2,3-Bis(benzyloxymethyl)-1,4,7,10,13,16-hexaoxacyclooctadecane (22). A mixture of 1.8 g (6.0 mmol) of (*R,S*)-4,5-dihydroxy-1,8-diphenyl-2,7-dioxaoctane, 140 mL of THF, and 0.6 g (15 mmol) of NaH was stirred under argon at reflux for 10 min. Pentaethylene glycol ditosylate[2b] (3.3 g, 6.0 mmol) was added in a solution of 100 mL of THF, and the resulting mixture was refluxed for 48 h. The excess NaH was carefully decomposed with 1 mL of H_2O, the solvent was evaporated under reduced pressure, and the residue was shaken with CH_2Cl_2 and water (200 mL each). The organic layer was dried ($MgSO_4$) and evaporated, and the residue was submitted to alumina dry column chromatography with 2% CH_3OH in CH_2Cl_2. The macrocycle was further purified by gel permeation chromatography on column A, retention volume 177 mL of CH_2Cl_2, to give after drying at 50 °C (0.01 mm) for 24 h product **22** as a colorless oil: 1.0 g (33%); M^+ *m/e* 504; ^1H NMR (60 MHz, $CDCl_3$) δ 3.4-4.0 (m, CH_2OCH_2, CH, 26 H), 4.5 (s, $ArCH_2$, 4 H), 7.3 (s, ArH, 10 H). Anal. ($C_{28}H_{40}O_8$) C, H.

(*S,S*)-(+)-Dimethyl Tartrate 2,3-Acetonide. Application of procedure D to 101 g (0.67 mol) of (+)-tartaric acid, 160 g (1.54 mol) of 2,2-dimethoxypropane, 40 mL of methanol, and 0.4 g of *p*-toluenesulfonic acid gave 126 g (85%) of product: bp 85 °C (0.15 mm) (lit.[11] 82-90 °C (0.02 mm)); ^1H NMR (60 MHz, $CDCl_3$) δ 1.48 (s, CH_3, 6 H), 3.78 (s, CH_3O, 6 H), 4.77 (m, CH, 2 H); $[\alpha]^{25}_{578}$ −58.2° (neat) (lit.[11] $[\alpha]^{25}_{D}$ −53.1° (neat)).

(*S,S*)-1,2,3,4-Butanetetrol 2,3-Acetonide. Application of procedure E to 124 g (0.57 mol) of (*S,S*)-(+)-dimethyl tartrate 2,3-acetonide, 28 g (0.74 mol) of $LiAlH_4$, and 1.2 L of anhydrous ether gave 58 g (63%) of product: bp 95 °C (0.15 mm) (lit.[12] 93 °C); M^+ *m/e* 162; ^1H NMR (60 MHz, $CDCl_3$) δ 1.42 (s, CH_3, 6 H), 2.7-2.9 (broad s, CH, 2 H), 3.7-3.9 (broad m, CH_2, 4 H), 4.0-4.2 (broad m, CH, 2 H); $[\alpha]^{25}_{546}$ +6.7°, $[\alpha]^{25}_{436}$ +13.3° (*c* 7.2, $CHCl_3$) (lit.[12] $[\alpha]^{25}_{D}$ +4.1° (*c* 5, $CHCl_3$)).

(*S,S*)-1,8-Diphenyl-2,7-dioxa-4,5-octanediol 4,5-Acetonide. Application of procedure F to 18 g (0.11 mol) of (*S,S*)-1,2,3,4-butanetetrol 2,3-acetonide, 19 g of NaH (0.32 mol), 250 mL of THF, and 76 g (0.44 mol) of benzyl bromide gave crude product from which the excess benzyl bromide was distilled at 30 °C (0.1 mm). The residue was chromatographed on 200 g of silica gel, and product was eluted with CH_2Cl_2 to give 36 g (94%) of product used in the next step. A small sample was subjected to molecular distillation at 120-140 °C (0.01 mm); M^+ *m/e* 342; ^1H NMR (60 MHz, $CDCl_3$) δ 1.40 (s, CH_3, 6 H), 3.5-3.7 (m, CH_2CH, 4 H), 3.9-4.1 (m, CH_2CH, 2 H), 4.50 (s, $ArCH_2$, 4 H), 7.20 (s, ArH, 10 H); $[\alpha]^{25}_{578}$ −6.5°, $[\alpha]^{25}_{546}$ −7.2°, $[\alpha]^{25}_{436}$ −10.1° (*c* 5.7, $CHCl_3$). Anal. ($C_{21}H_{26}O_4$) C, H.

(*S,S*)-4,5-Dihydroxy-1,8-diphenyl-2,7-dioxaoctane. Application of procedure G to 36.6 g (0.11 mol) of (*S,S*)-1,8-diphenyl-2,7-dioxa-4,5-octanediol 4,5-acetonide, 250 mL of methanol, and 50 mL

of 5% HCl in water gave product which was sublimed in 10-g batches at 130–150 °C (0.08 mm) to give 27 g (93%) of product: mp 55–57 °C; M^+ *m/e* 302; ^1H NMR (60 MHz, $CDCl_3$) δ 2.8 (broad s, OH, 2 H), 3.4–3.6 (m, CH_2CH, 4 H), 3.7–3.9 (m, $CHCH_2$, 2 H), 4.5 (s, $ArCH_2$, 4 H), 7.28 (s, ArH, 10 H); $[\alpha]_{578}^{25}$ −6.1°, $[\alpha]_{546}^{25}$ −6.9°, $[\alpha]_{436}^{25}$ −11.5° (*c* 5, $CHCl_3$). Anal. ($C_{18}H_{22}O_4$) C, H.

(*S,S*)-2,3-Bis(benzyloxymethyl)-1,4,7,10,13,16-hexaoxacyclooctadecane (23). To a suspension stirred under N_2 of NaH (2.52 g, 52.4 mmol) in 200 mL of DMF was added dropwise (30 min) 7.2 g (23.8 mmol) of (*S,S*)-4,5-dihydroxy-1,8-diphenyl-2,7-dioxaoctane dissolved in 240 mL of DMF. The solution was heated to 55 °C until H_2 evolution ceased (45 min). Pentaethylene glycol ditosylate[2b] (13.0 g, 23.8 mmol) in 120 mL of DMF was added, and the reaction mixture was stirred under N_2 at 65–75 °C for 36 h. The solvent was evaporated at 1 mm of pressure, and the residue was distributed between 200 mL each of H_2O and Et_2O. The water layer was extracted with 100 mL of Et_2O, the combined organic layers were dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was chromatographed on alumina with a gradient elution of Et_2O to 5% acetone in Et_2O (v). The product was submitted to gel permeation chromatography on column A, and was eluted with a retention volume of 165 mL of CH_2Cl_2 to yield after drying at 50 °C (1 mm) for 24 h 4.2 g (35%) of (*S,S*)-**23**; M^+ *m/e* 504; ^1H NMR (60 MHz, $CDCl_3$) δ 3.5–3.9 (m, CH_2OCH_2, CH_2OCH, 26 H), 4.5 (s, $ArCH_2$, 4 H), 7.3 (s, ArH, 10 H); $[\alpha]_{578}^{25}$ +2.77°; $[\alpha]_{436}^{25}$ +5.0° (*c* 6.8, $CHCl_3$). Anal. ($C_{28}H_{40}O_8$) C, H.

(*R,S*)-1,6,9,12,15,18-Hexaoxacycloeicosane-3,4-diol Acetonide (27). Procedure H. To a solution of 0.3164 g (1.95 mmol) of (*R,S*)-1,2,3,4-butanetetrol 2,3-acetonide in 20 mL of DMF stirred under N_2 was added 0.3 g (7.5 mmol) of a 50% suspension of NaH in mineral oil mixed with 10 mL of DMF. The solution was heated to 70 °C until H_2 evolution ceased. A solution of 1.06 g (1.95 mmol) of pentaethylene glycol ditosylate[2b] in 10 mL of DMF was added. The mixture was stirred under N_2 at 70 °C for 48 h and cooled, and 1 mL of water was added. The solvent was evaporated under vacuum. The residue was shaken with 200-mL portions of H_2O and CH_2Cl_2. The aqueous layer was washed with two 50-mL portions of CH_2Cl_2, the combined organic layers were dried ($MgSO_4$), and the solvent was evaporated under vacuum to give a yellow oil. This material was passed through an alumina dry column (14 by 1 in.) in CH_2Cl_2 for an initial purification, and was then submitted to gel permeation chromatography on column A. Macrocycle eluted with a retention volume of 185 mL of CH_2Cl_2. The solvent was evaporated under reduced pressure to give, after film drying at 50 °C (0.1 mm) for 24 h, 0.251 g (35%) of **27**: M^+ *m/e* 364; ^1H NMR (60 MHz, $CDCl_3$) δ 1.3 (s, CH_3, 3 H), 1.5 (s, CH_3, 3 H), 3.6 (m, CH_2OCH_2, 24 H), 4.1–4.4 (m, CH, 2 H). Anal. ($C_{17}H_{32}O_8$) C, H.

(*R,S*)-1,6,9,12,15,18-Hexaoxacycloeicosane-3,4-diol (28). A solution of 0.217 g (0.596 mmol) of macrocycle **27** in 50 mL of CH_3OH and 5 mL of 5% aqueous HCl was stirred at 25 °C for 10 h. The solvent was evaporated under vacuum until the solution became cloudy. Water (200 mL) was added, and the mixture was continuously extracted with $CHCl_3$ for 14 h. The $CHCl_3$ solution was dried ($MgSO_4$); the solvent was evaporated under reduced pressure and film dried at 30 °C (0.01 mm) for 20 h to give 0.178 g (95%) of diol **28** as an oil: M^+ *m/e* 324; ^1H NMR (60 MHz, $CDCl_3$) δ 3.2 (broad s, OH, 2 H), 3.7–3.8 (m, CH_2, CH, 26 H). Anal. ($C_{14}H_{28}O_8$) C, H. This material was very air sensitive, and had to be stored under argon or used immediately.

(*R,S*)-3,6,9,12,15,18,21,24,27,30,33,36-Dodecaoxabicyclo[18.16.0]hexatriacontane (26). By procedure H, 0.170 g (0.525 mmol) of (*R,S*)-1,6,9,12,15,18-hexaoxacycloeicosane-3,4-diol (**28**), 0.286 g (0.525 mmol) of pentaethylene glycol ditosylate,[2b] 0.10 g of NaH (2 mmol as a 50% dispersion in mineral oil), and 50 mL of DMF was converted at 70 °C (48 h) to crude product. This material was chromatographed in CH_2Cl_2 on a silica gel dry column. The appropriate eluate fractions were submitted to gel permeation chromatography on column A. The product gave a retention volume of 153 mL, and was film dried at 40 °C (0.01 mm) for 24 h to give **26** as an oil: 95.6 mg (35%); M^+ *m/e* 526; ^1H NMR (60 MHz, $CDCl_3$) δ 3.6 (m). Anal. ($C_{24}H_{46}O_{12}$) C, H.

***meso*- and *dl*-1,2-Bis(2-chlorophenyl)-1,2-ethanediol.** To a solution of 20 g (0.074 mol) of crude 1,2-bis(2-chlorophenyl)-2-hydroxyethanone[14] in 200 mL of 95% EtOH stirred at 0 °C was added 2.0 g (0.053 mol) of $NaBH_4$. After the reaction had subsided (cooling of the flask was required), 100 mL of water was added, and the mixture was heated at 100 °C for 1 h while ethanol evaporated. The mixture was cooled and extracted with ether, and the ether layer was washed with brine, dried (Na_2SO_4), and evaporated to give 21 g of an orange oil. A 4.0-g portion of this material was chromatographed on 100 g of silica gel in 10% ether–pentane. The column was washed with 1 L of 15% ether in pentane (v), and the product eluted with 500 mL of 50% ether in pentane (v) to give a yellow oil. This material was crystallized from ether–pentane to give 1.27 g (33%) of meso diol: mp 112.5–113.5 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 2.67 (s, OH, 2 H), 5.60 (s, CH, 2 H), 7.19 (m, ArH, 8 H). Anal. ($C_{14}H_{12}Cl_2O_2$) C, H.

The mother liquor was recrystallized from the same solvent to give additional meso isomer, as well as 0.30 g (8%) of *dl* diol: mp 105–106.5 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 2.67 (broad s, OH, 2 H), 5.17 (broad s, CH, 2 H), 7.19 (m, ArH, 8 H). Anal. ($C_{14}H_{12}Cl_2O_2$) C, H.

(*R,R*)(*S,S*)-2,3-Bis(2-chlorophenyl)-1,4,7,10,13,16-hexaoxacyclooctadecane (25). Procedure J. A mixture of 8.0 g (28 mmol) of *dl*-1,2-bis(2-chlorophenyl)-1,2-ethanediol, 400 mL of THF, and 4.2 g (63 mmol) of 85% KOH was stirred under N_2 at 25 °C for 30 min. A solution of 15.5 g (28 mmol) of pentaethylene glycol ditosylate[2b] in 200 mL of THF was added, and the resulting mixture was refluxed for 60 h. The mixture was cooled, the solvent was evaporated under reduced pressure, and the residue was shaken with 200 mL of water and 200 mL of CH_2Cl_2. The organic layer was dried ($MgSO_4$), the solvent was evaporated under reduced pressure, and the residue was chromatographed on 250 g of alumina with 10% ethyl acetate in CH_2Cl_2 (v) as eluting agent. The appropriate fractions were evaporated under reduced pressure and submitted to gel permeation chromatography on column A to give a retention volume of 183 mL of CH_2Cl_2. The eluate was evaporated and the residue crystallized to give 9.3 g (68%) of **25**. A small sample was recrystallized from ether–pentane to give mp 77–78.5 °C; M^+ *m/e* 484 (^{35}Cl); ^1H NMR (60 MHz, $CDCl_3$) δ 3.3–3.8 (m, OCH_2CH_2O, 20 H), 5.07 (s, ArCH, 2 H), 7.1–7.9 (m, ArH, 8 H). Anal. ($C_{24}H_{30}Cl_2O_6$) C, H.

(*R,S*)-2,3-Bis(2-chlorophenyl)-1,4,7,10,13,16-hexaoxacyclooctadecane (24). Procedure J was applied to 12.0 g (42.5 mmol) of *meso*-1,2-bis(2-chlorophenyl)-1,2-ethanediol, 300 mL of THF, 6.2 g (94 mmol) of 85% KOH dissolved in 15 mL of H_2O, and 23.2 g (45.5 mmol) of pentaethylene glycol ditosylate[2b] (18-h reflux). The product that was isolated from the chromatographic purification was crystallized from ether–pentane to give 7.2 g (35%) of **24**: mp 72–73 °C; M^+ *m/e* 484 (^{35}Cl); ^1H NMR (60 MHz, $CDCl_3$) δ 3.4–3.9 (m, OCH_2CH_2O, 20 H), 5.27 (s, ArCH, 2 H), 7.0–7.4 (m, ArH, 8 H). Anal. ($C_{24}H_{30}Cl_2O_6$) C, H.

Determination of Association Constants and Free Energies of Association between Ligand Systems and Metal Ammonium and Alkylammonium Picrates. Glassware used in K_a and K_d determinations was cleaned by first washing it thoroughly with water, acetone, and again water, and then immersing it in Chromerge for 24 h. The glassware was then washed with distilled water, immersed in a 15% aqueous $NaHCO_3$ bath for 1 h, washed thoroughly with distilled and deionized water, and dried at 100 °C for 24 h. Acidic or basic residues in the glassware gave erratic results. The method described previously was used.[2d,e] Reasonable agreement between K_a values calculated from absorbances of the $CDCl_3$ and of the H_2O layers was found where *R* values were between 0.1 and 0.5. As *R* values calculated from $CDCl_3$ layer measurements reached the 0.6–1.0 range, K_a values deviated upward from those calculated from H_2O layer measurements. The latter, however, agreed well with those determined by ^1H NMR measurements on the $CDCl_3$ layer. This deviation became increasingly greater when *R* values determined from UV absorbances of the $CDCl_3$ layer reached the range 0.8–1.0, generating K_a values up to 10^2 higher than those observed by the other two methods. When *R* values calculated from the UV aqueous layer measurements were below 0.1, they also became unreliable. Accordingly, *R*, K_a, and $-\Delta G°$ values reported in Table I were based on UV measurements made on the $CDCl_3$ layer as long as none of the *R* values for the individual ions exceeded 0.5. When *any* of those *R* values for a given host exceeded 0.5, the *R*, K_a, and $-\Delta G°$ values reported in Table I were based on UV measurements made on the H_2O layer, except for those involving Li^+ picrate. With this salt, the parameters were always based on $CDCl_3$ layer measurements because of the relatively low *R* values calculated from measurements made on either layer. From the nature of the equation involved in calculating low R_{CDCl_3} values from UV measurements made on the aqueous layer, small differences between

Table III. Comparison of Values of R_{CDCl_3}, K_a, and $-\Delta G°$ Calculated from Measurements Made for $CDCl_3$ and H_2O Layers with *trans*-$(BzOCH_2)_2E(OEOEO)_2E$ (**23**) as Host

	$CDCl_3$ phase measurements			H_2O phase measurements		
ion	R_{CDCl_3}	$K_a \times 10^{-3}$, M^{-1}	$-\Delta G°$ kcal/mol	R_{CDCl_3}	$K_a \times 10^{-3}$, M^{-1}	$-\Delta G°$, kcal/mol
Li^+	0.0132	43.1	6.33	0.0144	47.2	6.37
Na^+	0.200	1010	8.19	0.240	1430	8.40
K^+	0.756	178 000	11.3	0.769	227 000	11.4
Rb^+	0.609	30 400	10.2	0.561	18 700	9.93
Cs^+	0.315	2010	8.59	0.290	1650	8.49
NH_4^+	0.620	19 700	9.95	0.637	24 100	10.1
$CH_3NH_3^+$	0.425	875	8.10	0.419	832	8.08
t-$BuNH_3^+$	0.552	147	7.02	0.579	191	7.21

Table IV

phase	aliquot, μL	V_f, mL	A	R
$CDCl_3$	s, 10	5	2.14	0.844
$CDCl_3$	s, 10	10	1.081	0.853
$CDCl_3$	s, 5	10	8.544	0.858
$CDCl_3$	s, 5	25	0.211	0.832
H_2O	s, 10	5	0.153	0.736
H_2O	m, 5	5	0.148	0.745

large numbers are involved and the errors become large (see below). Table III provides the values of the R, K_a, and $\Delta G°$ values calculated from the two layers with *trans*-$(BzOCH_2)_2E(OEOEO)_2E$ (**23**) as host for eight picrate salts.

A maximum random error analysis was made that included all of the physical measurements that went into determinations of K_a values.[21] The analysis was based on the precisions of the apparatus used and the equations

$$K_a = \frac{R^*}{K_d(1 - R^*)\{[G_i^*] - R^*[H_i^*](V^*/V)\}^2} \quad (6)$$

$$K_d = \frac{[G^*]}{[G]^2} = \frac{[G^*]}{[\sim G_i]^2} = \frac{AD^d}{\epsilon l[G_i]^2} \quad (7)$$

$$R^* = ([G_i^*]/[H_i^*])_{equil} = AD^*/\epsilon l[H_i^*] \quad (8)$$

$$R_a^* = \frac{\{[G_i] - AD/(\epsilon l)\}(V/V^*)}{[H_i^*]} \quad (9)$$

In these equations, the starred letters refer to the $CDCl_3$ layer and the nonstarred to the D_2O layer. The definitions are as follows: K_a and K_d are defined by eq 1 and 3; the subscripts i refer to initial concentrations, and when absent, the concentrations are those at equilibrium; G is guest, H is host, V is volume; R^* is the ratio, $[G^*]/[H_i^*]$, at equilibrium obtained from measurements made on the $CDCl_3$ layer; R_a^* equals the ratio, $[G^*]/H_i^*]$, in the $CDCl_3$ layer calculated from measurements *made on the aqueous layer* at equilibrium; A is the observed absorbance of the picrate ion in CH_3CN; ϵ is the extinction coefficient of the picrate ion at 380 nm in CH_3CN; D^d is the factor by which the aliquots taken from the $CHCl_3$ layer are diluted in CH_3CN for the K_d determination; D^* is the factor by which the aliquots taken from the $CDCl_3$ layer are diluted in the R^* determinations; D is the factor by which aliquots taken from the aqueous layer are diluted in CH_3CN for the R_a^* determination; l is the light path length for the UV cell.

The precisions for $[G_i]$ and $[H_i]$ of eq 6–9 were ±0.05 and ±0.4%, respectively. The precisions for V^*/V of eq 6 and 9 were ±1.7% for Li^+, Na^+, K^+, NH_4^+, $CH_3NH_3^+$, and t-$BuNH_3^+$ picrates and ±2.2% for Rb^+ and Cs^+ picrates. The precision for all ϵ values was determined by serial dilutions of standard picrate solutions of known concentration and determination of the absorbance of the resulting solutions. Potassium picrate provides an example: 12 standards ranging from 0 to 1.00×10^{-4} M were formed by serial dilution of a 5.00×10^{-4} M solution of K^+ picrate$^-$ in CH_3CN. A plot of absorbance vs. concentration gave ϵ 16 900 cm^{-1} M^{-1} with r = 1.0000. The standard deviation of the ϵ's of the 11 samples other than the blank was ±570 cm^{-1} M^{-1}, or ±3.4%. The ϵ values for Li^+, Na^+, K^+, Rb^+, and Cs^+ were all the same. The ϵ value for NH_4^+ picrate was 17 700 cm^{-1} M^{-1} ±3.4%, and for $CH_3NH_3^+$ and t-$BuNH_3^+$ picrates$^-$ were 17 400 cm^{-1} M^{-1} ±3.4%. The precision for D^d was ±0.5%, and for l was ±0.1%. The error in A was trivial compared to the others. The overall precision for K_d for all the guests was about ±4.2%. The precision for D^* was ±1.4%. Thus the precision for R^* was ±4.9%. The precision for D was ±0.9%. The precision of R_a^* varied with the magnitude of A. For example, with A = 0.499, 0.339, 0.236, and 0.122, the precisions for R_a^* were ±280, ±11, ±5.9, and ±3.6%, respectively. This analysis indicates that the highest precision for R_a^* occurred with A lower than 0.2.

The precision of K_a varied with R^* values, and, therefore, whether they were determined from the $CDCl_3$ or H_2O layer. For example, for R^* (±4.9%) of 7.04×10^{-3}, 0.308, and 0.720, the precisions for K_a became ±14, ±21, and 54%, respectively. The maximum precision for any K_a value was ±14%. Corresponding $-\Delta G°$ precisions (see eq 5) were ±1.4, ±1.6, and ±3.0% at 25 °C. When R_a^* values of 0.315 ± 11 and 0.740 ± 3.6% were used in eq 6 in place of R^* values, K_a values had precisions of 39 and 47%, respectively. Corresponding $-\Delta G°$ precisions were ±3.1 and ±2.6%. This apparent inverse relationship between the precisions in K_a and $-\Delta G°$ arises out of the fact that, when K_a is high valued, a large % K_a error translates to a small relative $-\Delta G°$ error owing to the correspondingly high magnitude of $-\Delta G°$.

Several control experiments were conducted. In the first, a 4.895×10^{-5} M solution of potassium picrate in CH_3CN was prepared, and absorbance measurements were made at 380 nm. A 10-μL sample of 0.075 M host $(CH_3O_2C)_2D(OEOEO)E$ (**6**) in $CDCl_3$ was then diluted to 5 mL with the same potassium picrate solution (corresponding to R = 0.326) and absorbance again was measured. The difference between the two measurements was 1.2%. Similarly, a 9.79×10^{-5} M potassium picrate solution was utilized for the same experiment with the same host (corresponding to R = 0.652). In this case the difference was 0.5%.

In a second control experiment, a 100-μL sample of a 0.075 M solution of host $(UrCH_2)_2D(OEOEO)_2E$ (**11**) in $CDCl_3$ was equilibrated in the usual way with 0.50 mL of a 0.0156 M aqueous potassium picrate solution. The phases were separated, and aliquots were removed with syringes (s) or micropipets (m) and diluted to their final volumes (V_f) with CH_3CN. Absorbance values (A) were measured at 380 nm with the results shown in Table IV.

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Host–Guest Complexation. 20. Chiral Recognition in Transport as a Molecular Basis for a Catalytic Resolving Machine[1,2]

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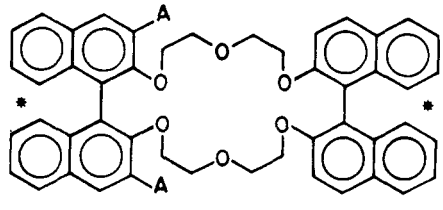
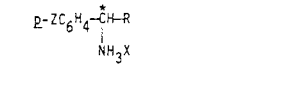
Abstract: Enantiomer differentiation (chiral recognition) occurred when designed, chiral hosts complexed and carried racemic amine salt guests from one aqueous solution through chloroform to a second aqueous solution where the guests were released. Optically pure hosts examined were 22-membered ring systems containing six roughly coplanar ether oxygens regularly spaced by attachment to one another through four ethylene (E) units. Two 1,1′-dinaphthyl (D) units of identical configuration, attached to oxygens at their 2,2′ positions, provided chiral barriers in the cycles. Besides the parent host, $D(OEOEO)_2D$ (**1**), two others were examined in which one of the dinaphthyl units was substituted in its 3,3′ positions to give $(CH_3)_2D(OEOEO)_2D$ (**2**) and $(ClCH_2)_2D(OEOEO)_2D$ (**3**). Chloroform solutions of these hosts (0.027 M), stirred at 24 °C in the bottom of a U-tube, contacted aqueous layers in the two arms. The solution in the α arm was 0.80 M in $LiPF_6$, 0.08 M in HCl, and 0.05–0.28 M in guest $*RNH_3Cl$ or $*RNH_3Br$ salt. The aqueous solution in the β arm was 0.10 M in HCl. Guests examined were $C_6H_5CH(CH_3)NH_3Br$ (**4**), $C_6H_5CH(CO_2CH_3)NH_3Cl$ (**5**), and p-$HOC_6H_4(CO_2CH_3)NH_3Cl$ (**6**). Rate constants for transport were measured for the faster moving A enantiomer (k_A*) and the slower moving B enantiomer (k_B*). Values of k_A*/k_B* varied from 1.45 (host **1** and guest **4**) to 10 (host **2** and guest **5**) and correlated roughly with D_A/D_B values, where D_A was the distribution coefficient of the more and D_B that of the less complexed enantiomer drawn from the aqueous into chloroform phases in one-plate extraction experiments. Hosts **2** and **3**, with their chiral barriers extended with CH_3 or $ClCH_2$ substituents, and the amino ester guests (**5** and **6**) gave the greatest chiral recognition in transport. The direction of the configurational bias in complexation corresponded to expectations based on scale molecular model examination of the diastereomeric complexes. A W-tube was designed for continuous and simultaneous removal of each enantiomer of racemic **5** from a central aqueous solution contacting two separate chloroform pools, one containing (*S,S*)-**2** and the second (*R,R*)-**2**. The enantiomeric guests were delivered to separate aqueous solutions, one in the left- and the other in the right-hand arm of the W-tube. Depending on experimental details, the *S,S* host delivered L-**5** to the left-hand aqueous pool in optical purities that ranged from 70 to 86%, and the *R,R* host delivered D-**5** to the right-hand aqueous pool in optical purities that ranged from 77 to 90%.

Biological transport of amino acids and their derivatives through lipophilic cell walls, up concentration gradients, is driven by linked H^+, Na^+, or K^+ transport down concentration gradients.[3] Metal cation transport, made possible by complexation with natural or synthetic host carriers through thin, synthetic membranes and organic bulk liquid membranes, has been studied extensively.[4] Lipophilic anions or cations in bulk toluene have been found to ion pair and transport amino acids and dipeptides from one aqueous solution to another.[5] The first example of chiral recognition in the differential transport (factors of 1.5 to >10) of enantiomeric guests through lipophilic media by complexation with chiral lipophilic hosts was reported in 1974.[2] The complexes were structured by hydrogen bonding of amine or amino ester salts to optically active macrocyclic ethers. A second example, communicated in 1975,[6] made use of optically active *N*-(1-naphthyl)methyl-α-phenylethylammonium ion paired differentially with the enantiomers of mandelic acid anion (factors of 1.22–1.42).[7]

The present paper[2] reports the results of experiments in which optically pure host compounds **1–3** selectively transport the enantiomers of guest salts **4–6** from one aqueous solution



1, A = H, or $D(OEOEO)_2D$
2, A = CH_3, or $(CH_3)_2D(OEOEO)_2D$
3, A = $ClCH_2$, or $(ClCH_2)_2D(OEOEO)_2D$



4, Z = H, R = CH_3
5, Z = H, R = CO_2CH_3
6, Z = HO, R = CO_2CH_3

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