Host–Guest Complexation. 17. Design, Syntheses, and Complexation of Macrocycles Containing Phosphoryl, Pyridine Oxide, and Urea Binding Sites[1,2]

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Phosphoryl (P=O), urea (N_2C=O), pyridine, and pyridine oxide (N → O) groups have been incorporated into the ring systems of macrocyclic polyethers. The association constants of the resulting eight new ligand systems toward Li^+, Na^+, K^+, Rb^+, Cs^+, and NH_4^+ picrates in $CHCl_3$ were surveyed, and the free energies of association were estimated. The P=O complexing sites were covalently bonded through two attached *o*-tolyl groups as in the unit $RP(O)(C_6H_4CH_2\text{-}o)_2$, in which different R groups were attached to phosphorus. The resulting unit, written as RPOD, was attached to two ether oxygens (O), which in turn were connected through CH_2CH_2 or E units to form macrocycles. Ligand systems $C_6H_5POD(OEOE)_2O$ (**9**), $C_6H_5POD(OEOEO)_2E$ (**10**), $o\text{-}HO_2CC_6H_4POD(OEOE)_2O$ (**11**), $o\text{-}CH_3O_2CC_6H_4POD(OEOE)_2O$ (**12**), $CH_3OPOD(OEOE)_2O$ (**13**), and $C_6H_5POD(OEO)_2PODC_6H_5$ (**14** and **15**, the syn and anti isomers) were synthesized and examined. The urea complexing site was cyclic, $CH_2(CH_2N)_2C$=O (abbreviated to UON), and was bonded through its two nitrogens to E units. The cycle prepared and examined was $UON(EOEOE)_2O$ (**16**). The pyridine and pyridine oxide complexing sites were bonded through CH_2 groups in their α,α' positions to comprise the units $\alpha\text{-}CH_2(C_5H_3N)CH_2\text{-}\alpha'$ and $\alpha\text{-}CH_2(C_5H_3NO)CH_2\text{-}\alpha'$, respectively, the latter of which was abbreviated as POM. The new cycle prepared and examined was $POM(OEOE)_2O$ (**18**). The patterns of $\Delta G°$ values of complexation of these ligand systems were compared to those of 2,3-naphtho-18-crown-6 (**19**), 2,6-pyrido-18-crown-6 (**20**), and 1,3-benzo-18-crown-5 (**21**). The results suggest that those ligand systems whose organization of binding sites before and after complexation are the most similar show the highest structural recognition toward the anions. Necessary requirements for high free energies of complexation are: (1) the hosts and guests must possess complimentary structural relationships; (2) the hosts must undergo complexation accompanied by a minimum amount of conformational reorganization.

A major objective in our studies of host–guest complexation has been to determine what structural features in potential partners provide the highest free energies of binding and the highest structural recognition. The hosts which were designed and synthesized were organic macrocycles composed of units that provide size, shape, and support structure for sets of convergent binding sites.[3] The guests were organic[4] or metal cations[5] with divergent binding sites. In some cases, the hosts contained carboxylate[4d,5c] or β-diketonide[5c] anions that balanced the charges of the guests. In the other systems, the counterions of the guests were external and played little role in structuring the complexes.[4]

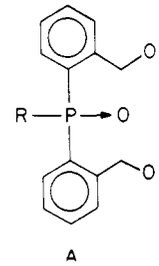
The phosphoryl group (P=O) has been shown to be a good ligand for alkali,[6,7] alkaline earth,[8] transition,[9] and actinide[10] metal salts. Studies of the hydrogen bond accepting abilities of a large number of organic functionalities toward alcohols,[11a] alkylamines,[11b] and alkylammonium salts[11c] indicated that the phosphoryl and urea functional groups are among the most strongly binding. For example, the log K^f values for eq 1 where R_2NH is 5-fluoroindole in CCl_4 at 25 °C vary with the structure of the hydrogen bond acceptor (B:) as follows: $(C_6H_5)_3P$=O, 2.05; $(CH_3O)_3P$=O, 1.49; $[(CH_3)_2N]_2C$=O, 1.43; $(C_2H_5)_2O$, 0.23.[11b] Pyridine oxide as B: should also be among the best binders, but it was not examined by these authors.[11b]

$$R_2NH + :B \overset{K^f}{\rightleftarrows} R_2NH \cdots :B \qquad (1)$$

Many heterocycles that contain the phosphoryl group have been reported.[12a] Only one was specifically prepared as a potential ligand system,[12b] but no reports of its binding abilities have appeared. During the course of our work, others reported the synthesis of several macrocycles incorporating urea units in macroring systems.[13a] The same authors reported the results of "yes–no" tests for the abilities of their compounds to complex alkali and alkaline-earth metal ions. They found qualitative evidence that in rings of the right size, complexation occurred.[13b] To our knowledge, pyridine oxide units have not been previously incorporated in macrocyclic ligand systems.

Results and Discussion

Design and Synthesis. According to Corey–Pauling–Koltun (CPK) molecular models of unit A, the three oxygen atoms can be located in positions so that lone pairs can act cooperatively as ligands for metal cations. When incorporated into macrocyclic structures such as **9** and **10**, the phosphoryl oxygen can occupy a position so that the oxygens describe the circumference of a circular cavity, as in the crown ethers.[14] In A, R can be a C_6H_5, an $o\text{-}C_6H_4CO_2H$, an $o\text{-}C_6H_4CO_2CH_3$, or a CH_3O group. With R = $o\text{-}C_6H_4CO_2H$ or $o\text{-}C_6H_4CO_2CH_3$, the acid or ester functions can occupy positions that converge on the cavity. The CH_3O group provides a masked phosphinic acid for potential internal valence control of the ligand system.



A

The syntheses of the desired hosts involved compounds **1**–**6** as key starting materials, from which **6**–**8** were prepared for cyclization. Accordingly, Grignard reagent $o\text{-}CH_3C_6H_4MgBr$ was treated with $C_6H_5POCl_2$ to give phosphine oxide **1** (78%), which with *N*-bromosuccinimide (NBS) gave dibromide **6** (51%). The same Grignard reagent reacted with $POCl_3$ to provide acid **2** (28%), which was converted to ester **3** (~100%) with CH_2N_2. Phosphinic ester **3** reacted with NBS to give dibromide **7** (47%). Acid **2** when mixed with PCl_5 gave the corresponding acid chloride (77%), which reacted readily with 2-(2-lithiophenyl)-4,4-dimethyloxazoline[15a] to provide phosphine oxide **4** (67%) whose oxazoline side chain is a masked carbomethoxyl group. In methanol–sulfuric acid, **4** underwent methanolysis[15b] to produce ester **5** (97%). This

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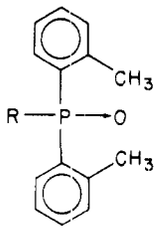
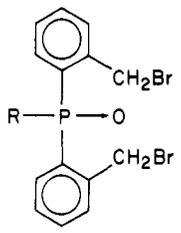
compound was brominated with NBS to provide dibromide **8** (40%).



1, R = C_6H_5
2, R = CH
3, R = OCH_3
4, R = o-C_6H_4-(C=O)-N
5, R = o-C_6H_4-CO_2CH_3

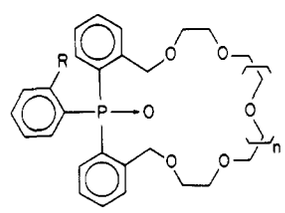


6, R = C_6H_5
7, R = OCH_3
8, R = o-C_6H_4-CO_2CH_3

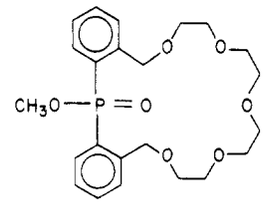
The macroring closures were carried out under high dilution conditions by slowly adding the appropriate ethylene glycol and dibromide as a mixture in THF to a stirred refluxing suspension of NaH in THF.[4c,5a] The insoluble NaH reacts with the glycol almost instantaneously to produce the sodium alkoxide, which in turn reacts rapidly with the dibromide. Under the reaction conditions, the reactants do not accumulate. By this procedure, dibromide **6** with tetraethylene glycol[4d] gave cycle **9** (69%) and pentaethylene glycol[4d] gave cycle **10** (67%). Likewise, dibromide **8** with tetraethylene glycol gave cycle **11** (18%). Apparently, the CO_2CH_3 group became hydrolyzed to the CO_2H group during its isolation. The ligand system probably acted as a collecting and orienting group for NaOH and thus potentiated the hydrolysis reaction rate. Ester **12** was obtained by treatment of acid **11** with CH_2N_2 (~100%). Similarly, dibromide **7** with tetraethylene glycol[4d] gave cycle **13** (23%), whose phosphinic ester group was also hydrolyzed during the ring closure and isolation but was reesterified with CH_2N_2. Dibromide **6**, when similarly treated with ethylene glycol, gave the isomeric cycles **14** (19%) and **15** (22%). Isomer **14** was soluble in organic solvents and possessed mp 200–203 °C; its mass spectrum exhibited the expected M^+ at *m/e* 728. Its solubility properties allowed it to be tested as a ligand system. Isomer **15** was insoluble in solvents suitable for ^1H NMR spectral examination. It possessed mp >320 °C, and its mass spectrum gave an M^+ at *m/e* 728 and no peaks of higher mass.

Apparently because of its high lattice energy, it was too insoluble for examination as a ligand system. The configurations of these isomers were not assigned. The syn isomer possesses two mirror planes and a C_2 axis, whereas the anti isomer has a center of symmetry, a mirror plane, and a C_2 axis. In the abbreviated line formulas written under the structural formulas, POD is the phosphine oxide ditolyl unit, O is oxygen and E is CH_2CH_2.

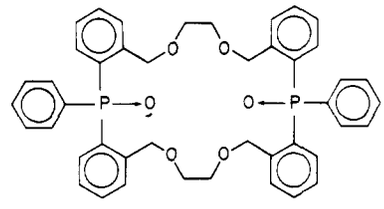
The cyclic trimethyleneurea unit was selected for incorporation into macrocyclic ligand systems for two reasons. The unit is relatively rigid, and CPK molecular models suggested that in **16** the carbonyl oxygen could be placed similarly to those of the oxygen of the phosphine oxide in macrocycle **9**. Macrocycles **16** and **17** were synthesized by treating a dry THF solution of 2(1*H*)-tetrahydropyridinone[16] with NaH and hexaethylene glycol ditosylate.[4d] Monomeric cycle was produced in 54% and dimeric cycle in 10% yield, although high dilution conditions were not used. The only ambiguity in the syntheses involved the possibility that not only N-alkylation but O-alkylation occurred in the cyclizations. The IR carbonyl stretching frequencies of both **16** and **17**, and the symmetry of **16** as revealed by its ^{13}C NMR spectrum, confirmed that **16** and **17** possessed the structures that are drawn. In the abbreviated line formula written underneath the structural formula, UON represents the urea unit.



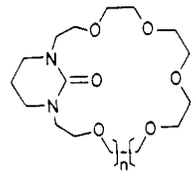
9, R = H, n = 1: $C_6H_5POD(OEOE)_2O$
10, R = H, n = 2: $C_6H_5POD(OEOEO)_2E$
11, R = CO_2H, n = 1: o-$HO_2CC_6H_4POD(OEOE)_2O$
12, R = CO_2CH_3, n = 1: o-$CH_3O_2CC_6H_4POD(OEOE)_2O$



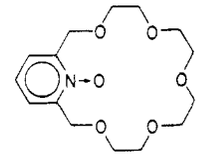
13: $CH_3OPOD(OEOE)_2O$



syn and anti-isomers
14, mp 200–203 °C: $C_6H_5POD(OEO)_2PODC_6H_5$
15, mp > 320 °C: $C_6H_5POD(OEO)_2PODC_6H_5$



16, n = 1: UON(EOEOE)$_2$
17, n = 2



18: POM(OEOE)$_2$O

In CPK molecular models, the oxygen of the pyridine oxide unit in **18** can occupy a position similar to that of the urea oxygen in **16** and that of the phosphine oxygen in **9**, except that the N → O oxygen penetrates much more deeply into the cavity. Macrocycle **18** was prepared by hydrogen peroxide oxidation of 2,6-pyrido-18-crown-6 (**19**), which was prepared in another study.[4c] The α-$CH_2(C_5H_3NO)CH_2$-α' unit is abbreviated to POM in the line formula for **18** written underneath the structural formula.

Binding of Ligand Systems to Alkali-Metal and Ammonium Ions. The association constants (K_a) of the ligand systems and the alkali metal and ammonium picrate salts were determined in $CDCl_3$ at 25 °C by the extraction technique.[5a] Equations 2–4 indicate the equilibria involved, in which H is the ligand system and M^+Pic^- is the salt. The extraction constants (K_e) and distribution constants (K_d) were experimentally determined, and the K_a values were calculated from K_e and K_d using eq 6.[5a–d] Ligand systems **9–14, 16, 18,** and **19** were examined,[4c,2] and Table I reports their K_a values. Values of the molar ratio of picrate ion to ligand system at equilibrium in the organic phase in the extraction[5a] (R) are also recorded. From the K_a values and eq 6, the free energies of complexation were calculated and are listed. For reference purposes, these

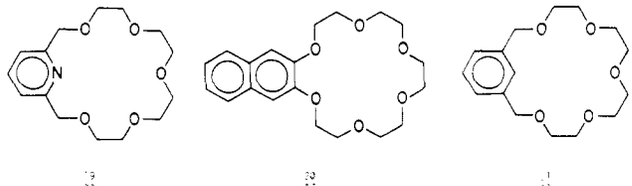


Table I. Association Constants (K_a) for Ligand Systems and Alkali Metal Picrates in $CDCl_3$ at 24–26 °C

ligand system line formula (no.)	M^+	R_{CDCl_3}[a]	$K_a \times 10^{-3}$, M^{-1}	$-\Delta G°$, kcal/mol	$-\Delta G°_{av}$,[b] kcal/mol	$-\Delta(\Delta G°)_{max}$,[c] kcal/mol
2,3-naptho-18-crown-6 (**20**)	Li	0.00704	22.5	5.94		
	Na	0.226	1220	8.31		
	K	0.740	85900	10.8	8.8	4.8
	Rb	0.524	11300	9.63		
	Cs	0.262	1250	8.33		
	NH_4	0.575	9850	9.55		
$C_6H_5POD(OEOE)_2O$ (**9**)	Li	0.008	25.6	6.01		
	Na	0.061	189	7.19		
	K	0.221	815	8.06	6.9	2.1
	Rb	0.058	109	6.87		
	Cs	0.017	32.3	5.95		
	NH_4	0.179	358	7.57		
o-$HO_2CC_6H_4POD(OEOE)_2O$ (**11**)	Li	0.022	75	6.64		
	Na	0.146	599	7.88		
	K	0.298	1500	8.42	7.5	1.8
	Rb	0.117	372	7.59		
	Cs	0.052	113	6.89		
	NH_4	0.154	281	7.42		
o-$CH_3O_2CC_6H_4POD(OEOE)_2O$ (**12**)	Li	0.012	38	6.24		
	Na	0.123	466	7.72		
	K	0.394	3100	8.85	7.6	2.6
	Rb	0.136	461	7.72		
	Cs	0.034	882	6.70		
	NH_4	0.329	1200	8.29		
$C_6H_5POD(OEOEO)_2E$ (**10**)	Li	0.013	41	6.29		
	Na	0.041	117	6.91		
	K	0.241	961	8.16	7.7	2.3
	Rb	0.223	1040	8.20		
	Cs	0.321	1900	8.56		
	NH_4	0.262	721	7.99		
$C_6H_5POD(OEO)_2PODC_6H_5$ (**14**)	Li	0.024	80	6.68		
	Na	0.036	103	6.83		
	K	0.026	50	6.41	6.2	1.6
	Rb	0.007	15	5.69		
	Cs	0.004	7.5	5.28		
	NH_4	0.027	32.5	6.15		
$CH_3OPOD(OEOE)_2O$ (**13**)	Li	0.003	10	5.45		
	Na	0.023	63.9	6.55		
	K	0.098	233	7.13	6.4	1.7
	Rb	0.027	64.6	6.55		
	Cs	0.009	18	5.80		
	NH_4	0.057	75.5	6.60		
$UON(EOEOE)_2O$[d] (**16**)	Li	0.021	71	6.62		
	Na	0.024	67	6.59		
	K	0.100	240	7.35	7.0	0.8
	Rb	0.078	220	7.30		
	Cs	0.0645	150	7.07		
	NH_4	0.130	210	7.27		
$POM(OEOE)_2O$[d] (**18**)	Li	0.022	70	6.62		
	Na	0.090	310	7.50		
	K	0.420	3800	8.98	7.8	2.4
	Rb	0.180	690	7.97		
	Cs	0.081	190	7.21		
	NH_4	0.310	1000	8.19		
2,6-pyrido-18-crown-6[d] (**19**)	Li	0.012	38	6.23		
	Na	0.219	1170	8.29		
	K	0.77	109000	11.0	9.2	4.7
	Rb	0.64	28800	10.19		
	Cs	0.32	1870	8.56		
	NH_4	0.76	61600	10.64		
1,3-benzo-18-crown-5 (**21**)	Li	0.00004	0.1	2.73		
	Na	0.00065	1.7	4.41		
	K	0.053	109	6.88	5.7	4.2
	Rb	0.027	66	6.58		
	Cs	0.025	51	6.43		
	NH_4	0.081	115	6.91		

[a] Ratio of mol of picrate to mol of host in the $CDCl_3$ phase at equilibrium with the water phase. [b] Average of $-\Delta G°$ values for the ligand system complexing the six ions. [c] $\Delta G°$ that is most negative minus $\Delta G°$ that is the least negative for each ligand complexing the six different ions. [d] Values uncorrected for small amounts of host or their complexes in the water phase at equilibrium. Corrections would raise values of R, K_a, and $-\Delta G°$ slightly.

parameters for 2,3-naphtho-18-crown-6[5b] (**20**) and 1,3-benzo-18-crown-5[4a] (**21**) are reported. Cycle **20** is a more practical standard than 18-crown-6 because the high solubility of the latter compound in water makes the technique inapplicable. A random error analysis was made that included all of the physical measurements that contributed to $-\Delta G°$ values.[5e] The precisions varied between ±1.4 and ±2.0%.

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

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

$$[M^+]_{H_2O} + [Pic^-]_{H_2O} \overset{K_d}{\rightleftharpoons} [M^+Pic^-]_{CDCl_3} \quad (4)$$

$$K_a = K_e/K_d \quad (5)$$

$$\Delta G° = -RT \ln K_a \quad (6)$$

Relationships between Structures and Free Energies of Complexation. Of the free energies of complexation in $CDCl_3$ at 25 °C for the 11 ligand systems and 6 ions, the highest $-\Delta G°$ value is for 2,6-pyrido-18-crown-6 binding K^+ (11.0 kcal/mol) and the lowest is for 1,3-benzo-18-crown-5 binding Li^+ (2.7 kcal/mol). Thus the difference in free energy of complexation between the best and poorest partner combination is 8.3 kcal/mol. For each individual ion, the differences in free energy of complexation in kcal/mol between the best and the poorest binding ligand system are as follows: Li^+, 4.0; Na^+, 3.9; K^+, 4.7; Rb^+, 4.5; Cs^+, 3.3; and NH_4^+, 4.5. Thus the maximum spread in $-\Delta G°$ values for the individual ions varies from 40 to 57% of the total maximum spread observed among all ions and all ligand systems. These comparisons indicate that the six ions all have approximately the same capacity for structural recognition by this group of ligand systems.

Each ligand system is generally characterized by the two free energy parameters, $-\Delta G°_{av}$ and $-\Delta(\Delta G°)_{max}$, listed in Table I. The $-\Delta G°_{av}$ measures the average binding ability of the ligand system toward the six ions. The $-\Delta(\Delta G°)_{max}$ measures the general ability of each system to differentiate between the ions in complexation. The $-\Delta G°_{av}$ values (kcal/mol) for the 11 ligand systems decrease in the order: 2,6-pyrido-18-crown-6 (9.2); 2,3-naphtho-18-crown-6 (8.8); $POM(OEOE)_2O$ (7.8); $C_6H_5POD(OEOEO)_2E$ (7.7); *o*-$CH_3O_2CC_6H_4POD(OEOE)_2O$ (7.6); *o*-$HO_2CC_6H_4POD(OEOE)_2O$, (7.5); $UON(EOEOE)_2O$ (7.0; $C_6H_5POD(OEOE)_2O$ (6.9); $CH_3OPOD(OEOE)_2O$ (6.4); $C_6H_5POD(OEO)_2PODC_6H_5$ (6.2); 1,3-benzo-18-crown-5 (5.7). The first three ligand systems in the above series (the best complexers) all contain highly organized 18-membered rings with 6 binding heteroatoms. The last system in the series contains the same highly organized 18-membered ring minus one of the binding heteroatoms. The other systems in CPK molecular models appear to be more conformationally flexible in the noncomplexed state. Although these latter systems can assume conformations in models which place the oxygens of the phosphoryl, urea, carboxyl, or carbomethoxyl groups in conformations favorable to binding, these conformations do not seem enforced by the equivalent of the gauche preferences characteristic of the OCH_2CH_2O linkage.[17] The superior binding potential of the crown ethers appears to be associated with the small amount of conformational reorganization they have to undergo during complexation. Although the P → O and urea C=O oxygens are probably better intrinsic binding sites than the ether oxygens, this superiority is probably lost because of the lack of an enforced favorable orientation prior to complexation.

The magnitudes of the $-\Delta(\Delta G°)_{max}$ values of Table I provide an index of the general capacity of the cycle for structural recognition. The magnitudes of the $-\Delta(\Delta G°)_{max}$ values (kcal/mol) for the 11 macrocycles decrease in the following order: 2,3-naphtho-18-crown-6 (4.8); 2,6-pyrido-18-crown-6 (4.7); 1,3-benzo-18-crown-5 (4.2); *o*-$CH_3O_2CC_6H_4POD(OEOE)_2O$ (2.6); $POM(OEOE)_2O$ (2.4); $C_6H_5POD(OEOEO)_2E$ (2.3); $C_6H_5POD(OEOE)_2O$ (2.1); *o*-$HO_2CC_6H_4POD(OEOE)_2O$ (1.8); $CH_3OPOD(OEOE)_2O$ (1.7); $C_6H_5POD(OEO)_2PODC_6H_5$ (1.6); and $UON(EOEOE)_2O$ (0.8). Interestingly, the first three of the ligand systems in the above order all contain 18-membered rings whose ether oxygens probably are approximately circularly arranged both before and after complexation, as in 18-crown-6, itself.[17] Except for $POM(OEOE)_2O$, the remaining systems have macrorings containing more atoms. However, their units probably are less conformationally organized prior to complexation and more adaptable to the variation in diameter of the metal ions when complexed. Molecular models (CPK) of these seven remaining systems indicate that although they *can assume conformations* that place six ring oxygens in positions that resemble those of 2,3-naphtho-18-crown-6, many other conformations also appear possible that might be more energetically favorable. Thus, an organization of oxygen binding sites that allows the oxygens to act cooperatively without reorganization upon complexation appears to be a prerequisite for high structural recognition.

High complexing power, as measured by $-\Delta G°_{av}$, does not correlate with high structural recognition as measured by $-\Delta(\Delta G°)_{max}$. Of the 11 systems studied, 2,6-pyrido-18-crown-6 and 2,3-naphtho-18-crown-6 gave the highest $-\Delta G°_{av}$ values, and 1,3-benzo-18-crown-5 gave the lowest $-\Delta G°_{av}$ value. Yet these three systems exhibited the highest $-\Delta(\Delta G°)_{max}$ values. Common to the molecular models of all three systems in their usual all-gauche conformations is a circular set of oxygens. However, one of the six oxygens present in 2,3-naphtho-18-crown-6 is missing in 1,3-benzo-18-crown-5.

All of the systems except $C_6H_5POD(OEOEO)_2E$, $POM(OEOE)_2O$, and $C_6H_5POD(OEO)_2PODC_6H_5$ were designed so that when the five or six binding oxygens were almost planar, the diameter of the cavity they described was about 2.7 Å. The approximate diameters of the metal ions (Å) are as follows: Li^+, 1.40; Na^+, 1.90; K^+, 2.66; Rb^+, 2.96; Cs^+, 3.38. All of the ligand systems except $C_6H_5POD(OEOEO)_2E$ and $C_6H_5POD(OEO)_2PODC_6H_5$ bind K^+ or Rb^+ the best. The diameters of K^+ and Cs^+ come closest to matching the measured hole diameters in CPK models of their eight best hosts. Interestingly, the hole diameter in CPK models of $C_6H_5POD(OEOEO)_2E$ with its seven oxygens as coplanar as possible is about 3.3 Å, which comes close to matching the 3.38-Å diameter of Cs^+. This ligand system binds Cs^+ better than it does any of the other ions. A CPK model of $C_6H_5POD(OEO)_2PODC_6H_5$ of either syn or anti configurations with their oxygens arranged as close to circular as possible provides a hole involving only five coplanar oxygens and a diameter of about 2.16 Å. This ligand system binds Na^+ (diameter, 1.90 Å) better than any other ion ($-\Delta G°$ = 6.8 kcal/mol). It binds Li^+ (diameter 1.40 Å) better than does any of the other macrocycles ($-G°$ = 6.7 kcal/mol) but is within probable error of several others. This system appears to be highly conformationally flexible, and in models of either isomer four oxygens can easily contact a sphere the diameter of Li^+ in a roughly tetrahedral arrangement.

The system containing the pyridine oxide unit, $POM(OEOE)_2O$, possesses a geometry unlike that of the other cycles. In CPK models, if the pyridine oxide unit is coplanar with the other five oxygens, the cavity is partially filled with the oxygen of the N → O group. The remaining hole is composed of four roughly coplanar oxygens and in the model is about 1.85 Å in diameter. If warped toward a tetrahedral confor-

mation, all four of these oxygens can contact a sphere the diameter of Li^+ ion at the same time. This system is the second best binder of Li^+ ($-\Delta G°$ = 6.6 kcal/mol). When the pyridine oxide ring of $POM(OEOE)_2O$ is bent out of the plane for the five ring oxygens in models, the out-of-plane oxygen can still contact a complexed ion such as K^+ at the same time that the other five oxygens do. Such a conformation explains why $POM(OEOE)_2O$ is a good complexer of K^+ ($-\Delta G°$ = 9.0 kcal/mol) but not as good as its parent, 2,6-pyrido-18-crown-6 ($-\Delta G°$ = 11.0 kcal/mol).

The relatively poor binding and indiscriminate character of the urea-containing system, $UON(EOEOE)_2O$, was not anticipated from CPK model examination. The $-\Delta G°$ values are in the 6–7-kcal range, and the $-\Delta(\Delta G°)_{max}$ value (Table I) for this macrocycle was only 0.8 kcal/mol. With an all-gauche conformation of ethylene groups, the six oxygens describe a cycle closely resembling that of 18-crown-6. If this conformation were the most stable, $UON(EOEOE)_2O$ should have $-\Delta G°$ values for K^+ and Rb^+ of 10 kcal/mol or more, and it should show much higher ion selectivity. Possibly, the two CH_2CH_2 groups attached to the two nitrogens possess anti conformations which are more stable than their gauche conformations, requiring the cycle to reorganize during complexation.

The ligand systems containing one phosphoryl group possess conformations in molecular models that place six oxygens in a circular arrangement closely resembling that of 18-crown-6. Unfortunately, many other conformations also exist, some of which are probably more stable than that required for complexation of ions such as K^+ and Rb^+. Thus the reorganization of $C_6H_5POD(OEOE)_2O$ required to bind K^+ and Rb^+ probably costs at least 2.5 kcal/mol.

Comparisons of $C_6H_5POD(OEOE)_2O$, o-HO_2C-$C_6H_4(OEOE)_2O$, o-$CH_3O_2CC_6H_5POD(OEOE)_2O$, and $CH_3OPOD(OEOE)_2O$ are instructive since they all possess the same macroring system. The CO_2H and CO_2CH_3 groups attached to the ortho position of the phenyl not involved in the macroring increase the $-\Delta G°_{av}$ value by about 0.6 kcal/mol. Molecular models indicate that in the proper conformation, one oxygen of these functional groups can serve as an extra ligand for a complexed metal ion. The effectiveness of these extra functional groups undoubtedly would have been much larger had not other favorable conformations been frozen out during complexing. Interestingly, the CO_2H group favored Li^+ binding more than the CO_2CH_3 group by about 0.5 kcal/mol, and the CO_2CH_3 group favored NH_4^+ binding by about 0.9 kcal/mol. Substitution of a CH_3O group, as in $CH_3OPOD(OEOE)_2O$, for the C_6H_5 group in $C_6H_5POD(OEOE)_2O$ depressed $-\Delta G°_{av}$ by about 0.6 kcal/mol. This effect correlates qualitatively with that observed for the hydrogen bonding of phosphine oxides vs. phosphinic esters,[11b] the former being the better hydrogen bonding functional group.

The NH_4^+ ion most resembled the K^+ in its pattern of host preferences. The $-\Delta G°$ values (kcal/mol) for NH_4^+ decreased in the following order: 2,6-pyrido-18-crown-6 (10.6); 2,3-naphtho-18-crown-6 (9.6); o-$CH_3O_2CC_6H_4POD(OEOE)_2O$ (8.3); $POM(OEOE)_2O$ (8.2); $C_6H_5POD(OEOEO)_2O$ (8.0); o-$HO_2CC_6H_4POD(OEOE)_2O$ (7.4); $UON(EOEOE)_2O$ (7.3); 1,3-benzo-18-crown-5 (6.9); $CH_3OPOD(OEOE)_2O$ (6.6); and $C_6H_5POD(OEO)_3PODC_6H_5$ (6.2). As with the other ions, the importance of proper organization of host to good binding and to high structural recognition is visible in this sequence.

Experimental Section

All Chemicals were reagent grade. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use. Dimethylformamide (DMF) was distilled from 4 Å molecular sieves and stored over 4 Å molecular sieves. Diethyl ether was distilled from $LiAlH_4$ immediately prior to use. All reactions were conducted in an inert atmosphere of argon or nitrogen; those involving trivalent phosphorus compounds were always conducted in an argon atmosphere. Melting points below 200 °C were measured on a Thomas-Hoover apparatus, those above 200 °C were measured on a Mel-Temp apparatus, and all are uncorrected. Mass spectra were recorded on an AEI Model MS-9 double-focusing spectrometer. The ^1H NMR spectra were recorded on a Varian T-60 spectrometer, with chemical shifts given in δ ppm from internal tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer Model 297 spectrophotometer. Ultraviolet measurements were made at 24–26 °C with a Beckman DU spectrophotometer. Gel permeation chromatograms were run on one of the following columns: column A, 3/8 in. (o.d.) × 20 ft column of Styragel 100 Å beads (Waters Assoc. Inc.) in THF (37–75 μm particle size, exclusion limit 1500 mol wt) at a flow rate of 4 mL m^{-1} and a pressure of 400–600 psi; column B, 3/8 in. (o.d.) × 20 ft column of Styragel 100 Å beads in CH_2Cl_2, at a flow rate and pressure identical with those of column A; column C, 3/8 in. (o.d.) × 20 ft column of BioBeads SX-12 (Bio-Rad Laboratories) in CH_2Cl_2 (mesh size 200–400, exclusion limit 400 mol wt) at a flow rate of 4 mL m^{-1} and a pressure of 750–900 psi.

Bis(*o*-tolyl)phenylphosphine Oxide (1). To a magnetically stirred suspension of 22.4 g (0.92 mol) of magnesium turnings in 300 mL of dry THF was added dropwise at a rate sufficient to maintain gentle reflux a solution of 15.0 g (0.88 mol) of 2-bromotoluene in 300 mL of dry THF. After the addition was complete, the reaction mixture was refluxed for 2 h and cooled to 25 °C, and to this dark brown reaction mixture was added dropwise a solution of 85.4 g (0.44 mol) of phenylphosphonic dichloride (Aldrich, freshly distilled) in 300 mL of dry THF. After the addition was complete, the reaction mixture was refluxed for 2 h, stirred at 25 °C for 12 h, and poured into an ice cold 10% aqueous ammonium chloride solution. The resulting white precipitate was collected and recrystallized from 95% EtOH to give 105.0 g (78%) of **1** as a white crystalline solid: mp 193–194 °C (lit.[18] mp 192–194 °C); ^1H NMR ($CDCl_3$) δ 6.8–7.8 (m, ArH, 13 H) and 2.5 (s, $ArCH_3$, 6 H).

Bis(2-bromomethylphenyl)phenylphosphine Oxide (6). To a solution of 30.0 g (0.098 mol) of **1** in 400 mL of CCl_4 (dried over CaH_2) was added 36.6 g (0.20 mol) of *N*-bromosuccinimide (NBS), and the stirred suspension was brought to reflux. A catalytic amount (ca. 0.2 g) of dibenzoyl peroxide was added and the reaction mixture was refluxed for 4 h. The reaction mixture was allowed to cool to 25 °C and was filtered. The filtrate was washed twice with 10% aqueous $NaHSO_3$ and once with brine and dried ($MgSO_4$); the solvent was removed in vacuo, leaving a clear oil which solidified upon standing. Three recrystallizations of the solid from cyclohexane gave 23.2 g (51%) of pure **6** as a white crystalline solid: mp 160–161 °C; ^1H NMR ($CDCl_3$) δ 6.8–8.2 (m, ArH, 13 H) and δ 5.1 (s, CH_2Br, 4 H); mass spectrum (70 eV) *m/e* 462 (M^+, ^{79}Br). Anal. Calcd for $C_{20}H_{17}Br_2OP$: C, 51.76; H, 3.69; P, 6.67. Found: C, 51.83; H, 3.78; P, 6.72.

1-Phenyl-2,3:19,20-dibenzo-5,8,11,14,17-pentaoxa-1-phosphacycloeicosa-2,19-diene 1-Oxide (9). Method A. To a refluxing, rapidly stirred suspension of 0.50 g (10.3 mmol) of NaH (50% oil dispersion) in 300 mL of dry THF was added dropwise over a period of 6 h a solution containing 2.2 g (4.7 mmol) of dibromide **6** and 0.95 g (4.9 mmol) of tetraethylene glycol[4d] in 200 mL of dry THF. After the addition was complete, the light yellow reaction mixture was refluxed for an additional 12 h. The solvent was removed in vacuo and the residue distributed between 300 mL of CH_2Cl_2 and 300 mL of H_2O. The aqueous layer was extracted with three 200-mL portions of CH_2Cl_2, the organic phases were combined, washed with brine, and dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was chromatographed on silica gel eluting first with CH_2Cl_2 (to remove mineral oil) and then with increasing ratios of THF–CH_2Cl_2, 1:4 to 1:2 (v:v), to give 1.8 g of crude **9**. Final purification was effected by either gel permeation chromatography (column A, retention volume 152 mL) or crystallization from Et_2O to give 1.5 g (65%) of pure **9** as clear plates: mp 75–76 °C; ^1H NMR ($CDCl_3$) δ 6.8–7.9 (m, ArH, 13 H), 5.0 (AB_q, J_{ab} = 12 Hz, $ArCH_2$, 4 H), and 3.6 (broad s, OCH_2CH_2, 16 H); mass spectrum (11 eV) *m/e* 496 (base, M^+). Anal. Calcd for $C_{28}H_{33}O_6P$: C, 67.73; H, 6.70; P, 6.24. Found: C, 67.65; H, 6.54; P, 6.27.

1-Phenyl-2,3:22,23-dibenzo-5,8,11,14,17,20-hexaoxa-1-phosphacyclotricosa-2,22-diene 1-Oxide (10). By method A (see above), from 0.25 g (4.7 mmol) of NaH, 500 mL of THF, 1.0 g (2.15 mmol) of dibromide **6**, and 0.51 g (2.15 mmol) of pentaethylene glycol,[4d] was obtained 1.4 g of products as an orange viscous oil. The crude material was filtered through 15 g of silica gel eluting first with CH_2Cl_2 to remove the mineral oil and then with acetone to give 1.0 g of the crude product as a light yellow oil. Final purification was effected either by gel permetation chromatography (column B, retention volume 168 mL) or by crystallization from Et_2O at −20 °C to yield 0.80 g (68%)

of pure **10** as white microcrystals: mp 64–66 °C; ^{1}H NMR ($CDCl_3$) δ 6.8–7.9 (m, ArH, 13 H), 4.9 (AB_q, J_{AB} = 13 Hz, $ArCH_2$, 4 H), and 3.4–3.7 (m, OCH_2CH_2, 20 H); mass spectrum (70 eV) *m/e* 540 (M^+). Anal. Calcd for $C_{30}H_{37}O_7P$: C, 66.65; H, 6.90; P, 5.73. Found: C, 66.71; H, 6.85; P, 5.66.

Bis[2-(2-hydroxyethoxymethylphenyl)]phenylphosphine Oxide. To 25 mL of ethylene glycol (freshly distilled from 4 Å molecular sieves) was added cautiously 0.22 g (4.5 mmol) of NaH (50% oil dispersion). After the vigorous evolution of hydrogen had subsided, the solution was stirred for an additional 15 min, and 1.0 g (2.15 mmol) of dibromide **6** was added as a solid. After the solution was stirred for 24 h at 55 °C, the reaction mixture was cooled to 25 °C and partitioned between CH_2Cl_2 and H_2O. The phases were separated, the organic phase was washed with five equal portions of H_2O and dried ($MgSO_4$), and the solvent was removed in vacuo, leaving 0.9 g of a viscous opaque white oil. This oil was washed with three 10-mL portions of pentane (to remove mineral oil) and dried at high vacuum to give 0.85 g (92%) of diol product, which by NMR and TLC (silica gel, acetone) appeared pure and was used directly in the next reaction. An analytical sample was prepared by silica gel chromatography (acetone) to give pure product: ^{1}H NMR ($CDCl_3$) δ 6.8–7.8 (m, ArH, 13 H), 4.8 (broad s, $ArCH_2$, 4 H), 4.27 (s, OH, 2 H), and 3.4 (broad s, OCH_2CH_2, 8 H); mass spectrum (70 eV) *m/e* 426 (M^+), 381 ($M - C_2H_5OH$); IR ($CHCl_3$) 3340 cm^{-1} (OH). Anal. Calcd for $C_{24}H_{27}O_4P$: C, 66.12; H, 6.23; P, 7.55. Found: C, 66.08; H, 6.16; P, 7.60.

***syn*- and *anti*-1,12-Diphenyl-2,3:10,11:13,14:21,22-tetrabenzo-5,8,16,19-tetraoxa-1,12-diphosphacyclodocosa-2,10,13,21-tetraene 1,12-Dioxide (14 and 15).** To a refluxing, rapidly stirred suspension of 0.21 g (4.5 mmol) of NaH (50% oil dispersion) in 300 mL of dry THF was added dropwise over a period of 10 h a solution containing 0.85 g (2.0 mmol) of the above diol and 0.92 g (2.0 mmol) of dibromide **6** in 250 mL of dry THF. After the addition was complete, the reaction mixture was refluxed for 3 h, and the THF was removed in vacuo. The residue was distributed between CH_2Cl_2 and H_2O, the phases were separated, and the aqueous phase was extracted with two portions of CH_2Cl_2. The combined organic phases were washed with brine and dried ($MgSO_4$), and the solvent was removed in vacuo leaving 1.25 g of a yellow powder. The crude product was then triturated with pentane (to remove residual mineral oil). About one-half of the material was readily soluble in boiling MeOH (isomer **14**), while the remaining solid could not be dissolved even in large volumes of boiling MeOH (isomer **15**). The insoluble material was filtered, and the MeOH was removed from the filtrate in vacuo to give a yellow powder. Gel permetation chromatography of this soluble component (column A, retention volume 162.6 mL) followed by crystallization from MeOH–Et_2O gave 0.28 g (19%) of **14** as a white crystalline solid: mp 200–203 °C; ^{1}H NMR ($CDCl_3$) δ 6.8–8.0 (m, ArH, 26 H), 4.8 (AB_q, J_{AB} = 14 Hz, $ArCH_2$, 8 H), and 3.56 (s, OCH_2, 8 H); mass spectrum (70 eV) *m/e* 728 (M^+). Anal. Calcd for $C_{44}H_{42}O_6P_2$: C, 72.52; H, 5.81; P, 8.50. Found: C, 72.25; H, 5.71; P, 8.40.

The insoluble material, isomer **15** (see above), was washed with several portions of boiling $CHCl_3$ to give 0.32 g (22%) of product **15** as an amorphous white powder, mp >320 °C. This material was insoluble in all common ^{1}H NMR solvents, so no spectrum could be recorded. The mass spectrum of **15** was essentially identical (molecular ion and major fragmentations) with that of its isomer, **14**. No peaks with *m/e* greater than 728 (M^+) were observed. Anal. Calcd for $C_{44}H_{42}O_6P_2$: C, 72.52; H, 5.81; P, 8.50. Found: C, 72.34; H, 5.73; P, 8.36.

2-(2′-Bromophenyl)-4,4-dimethyloxazoline. This compound was prepared by the literature procedure[15a] in a 65% overall yield from 2-bromobenzoic acid: bp 94–97 °C (0.05 mm); mp 39–40.5 °C (lit.[15a] mp 33–35.5 °C); ^{1}H NMR identical with that reported.[15a]

Bis(*o*-tolyl)phosphinic Acid (2). The method used is a modification of that reported for the preparation of diphenylphosphonic acid.[19] A solution of 37.5 g (0.23 mol) of 2-bromotoluene in 100 mL of anhydrous ether was added dropwise to 5.5 g (0.23 mol) of Mg powder suspended in 100 mL of anhydrous ether. After the addition was complete, the reaction mixture was refluxed for 2 h. The resulting mixture was cannulated through a plug of glass wool into a 500-mL addition funnel under N_2. The yellow-brown solution was diluted to a total volume of 500 mL with anhydrous Et_2O, and this solution was added dropwise to a gently refluxing, mechanically stirred solution of 32.2 g (0.21 mol) of phosphorus oxychloride (freshly distilled) in 500 mL of anhydrous Et_2O. Immediate formation of a white precipitate was observed upon impact of each drop. After the addition was complete (ca. 3.5 h), the reaction mixture was allowed to stand at 25 °C for 12 h. The Et_2O was decanted from the yellow powder, and 300 mL of ice water was added to the remaining solid. The resultant aqueous emulsion was extracted with two 300-mL portions of Et_2O. The organic extracts were combined, and the solvent was removed in vacuo. The solid residue was mixed with 10% aqueous NaOH and the insoluble material was filtered. Acidification of the filtrate with concentrated hydrochloric acid gave a white precipitate which was recrystallized from aqueous ethanol to give 7.5 g (28%) of **2** as a white crystalline solid: mp, 170.5–172 °C; ^{1}H NMR (CD_3CO_2D) δ 8.17–7.70 (m, ArH, 2 H), 7.68–7.00 (m, ArH, 6 H), and 2.33 (s, CH_3, 6 H); mass spectrum (70 eV) *m/e* 246 (M^+), 231 ($M - CH_3$); IR (KBr) 980 (P – OH) cm^{-1}. Anal. Calcd for $C_{14}H_{15}O_2P$: C, 68.29; H, 5.73; P, 12.58. Found: C, 68.27; H, 5.68; P, 12.55.

Bis(*o*-tolyl)phosphinyl Chloride. To a stirred suspension of 5.0 g (20.3 mmol) of acid **2** in 20 mL of dry PCl_3 at 25 °C was added 4.2 g (20.3 mmol) of PCl_5. Evolution of HCl was observed and the reaction mixture became homogeneous after a few minutes. The reaction mixture was stirred at 25 °C for 0.5 h and then refluxed for 2.5 h. The solvent was removed in vacuo (ca. 25 mm) and the residue was distilled under high vacuum through a short path head to give 4.35 g (77%) of product as a water-white viscous oil which solidified upon standing: bp 142–145 °C (0.03 mm); ^{1}H NMR ($CDCl_3$) δ 8.12–7.7 (m, ArH, 2 H), 7.65–7.05 (m, ArH, 6 H), and 2.30 (s, CH_3, 6 H). This material was used in the next step without further purification.

2-(4,4-Dimethyl-2-oxazolino)phenylbis(2-methylphenyl)phosphine Oxide (4). This compound was prepared by two methods. To a stirred suspension of 0.46 g (18.9 mmol) of sublimed and activated magnesium and a crystal of iodine in 50 mL of dry THF at 25 °C was added dropwise a solution of 4.06 g (16.0 mmol) of 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline in 50 mL of dry THF. After the addition was complete, the reaction mixture was refluxed for 2 h and cooled to 25 °C. A solution of 4.9 g (14.2 mmol) of the above phosphinyl chloride in 75 mL of dry THF was added dropwise, over a period of ca. 1 h, to the Grignard solution. The resultant mixture was refluxed for 18 h. The reaction mixture was cooled and poured into ice cold 10% aqueous NH_4Cl. The resultant aqueous emulsion was extracted with four portions of CH_2Cl_2, the organic phases were combined, washed with brine, and dried ($MgSO_4$), and solvent was removed in vacuo to give 4.9 g of a yellow glass. The crude product was chromatographed on 120 g of silica gel and eluted with increasing volumes of acetone in CH_2Cl_2, 15:85 to 4:6 (v:v), to give 3.3 g (52%) of **4** as a white powder, mp 95–97 °C.

The second method was superior. To a solution, which was being stirred, of 2.6 g (14.1 mmol) of the same aryl bromide in 125 mL of dry THF cooled to −78 °C in a dry ice–acetone slush was added via syringe 6.2 mL (14.2 mmol) of a 2.3 M solution of BuLi in hexane. After the mixture had been stirred at −78 °C for 1 h, a solution of 4.9 g (14.2 mmol) of the above phosphinyl chloride in 25 mL of THF was added via syringe. The reaction mixture was allowed to slowly warm to 25 °C and was then stirred for 14 h. A few drops of H_2O were added. The solvent was removed in vacuo, and the residue was distributed between CH_2Cl_2 and H_2O. The phases were separated, the aqueous phase was washed with CH_2Cl_2, the organic phases were combined, washed with brine, and dried ($MgSO_4$), and the solvent was removed in vacuo leaving 5.2 g of a yellow foam. The crude product was purified (as in the first method) to give 3.8 g (67%) of **4** as a white solid which was recrystallized from Et_2O–petroleum ether: mp 96–98 °C; ^{1}H NMR ($CDCl_3$) δ 7.0–8.0 (m, ArH, 12 H), 3.67 (s, OCH_2, 2 H); 2.83 (d, J_{P-CH} = 1 Hz, $ArCH_3$, 6 H), and 1.17 (s, $C(CH_3)_2$, 6 H); mass spectrum (70 eV) *m/e* (M^+), 398 ($M^+ - CH_3$), and 305 (base, $M^+ - C_5H_8NO$); IR (KBr) 1740 cm^{-1} (C=O). Anal. Calcd for $C_{25}H_{26}NO_2P$: C, 74.42; H, 6.49. Found: C, 74.20; H, 6.35.

Bis(2-methylphenyl)(2-carbomethoxyphenyl)phosphine Oxide (5). Oxazoline **4** was converted directly to the carbomethoxy compound by the method of Meyers et al.[15b] A solution of 1.25 g (3.1 mmol) of **4** in 25 mL of CH_3OH containing 1.0 mL of concentrated H_2SO_4 and 1.25 mL of H_2O was refluxed for 36 h. The reaction mixture was distributed between CH_2Cl_2 and H_2O, and the phases were separated. The aqueous phase was extracted with two portions of CH_2Cl_2, the organic phases were combined, washed with 5% aqueous $NaHCO_3$ and H_2O, and dried ($MgSO_4$), and the solvent was removed in vacuo to give 1.1 g (100%) of **5** as a white solid which was used in the next reaction without further purification. An analytical sample was prepared by recrystallization from CCl_4–Et_2O: mp 114–116 °C; ^{1}H NMR ($CDCl_3$) δ 7.0–7.9 (complex m, ArH, 12 H), 3.33 (s, OCH_3, 3 H) and 2.37 (d, J_{P-CH} = 1 Hz, $ArCH_3$, 6 H); mass spectrum (70 eV) *m/e* 364 (M^+), 349 ($M^+ - CH_3$), and 305 ($M^+ - CO_2CH_3$); IR ($CHCl_3$) 1735 cm^{-1} (C=O). Anal. Calcd for $C_{22}H_{21}O_3P$: C, 72.52; H, 5.81; P, 8.50. Found: C, 72.54; H, 5.62; P, 8.51.

Bis(2-bromomethylphenyl)(2-carbomethoxyphenyl)phosphine Oxide (8). To a stirred solution of 1.1 g (3.02 mmol) of **5** in 75 mL of dry CCl_4 was added 1.07 g (6.04 mmol) of NBS, and the suspension was brought to reflux. A catalytic amount of dibenzoyl peroxide (ca. 0.1 g) was added, and the reaction mixture was refluxed for 3 h. The reaction mixture was cooled and filtered. The filtrate was

washed twice with 10% aqueous $NaHSO_3$ and once with brine and dried ($MgSO_4$), and the solvent was removed in vacuo, leaving 1.5 g of a yellow foam. The crude product was chromatographed on 125 g of silica gel and eluted with acetone–CH_2Cl_2, 2.5:97.5 (v:v), to give 0.71 g (40%) of **8** as a white powder which was recrystallized from Et_2O–petroleum ether: mp 161–163 °C; ^1H NMR ($CDCl_3$) δ 8.1–6.9 (complex m, ArH, 12 H), 5.03 (s, CH_2Br, 4 H), and 3.58 (s, OCH_3, 3 H); mass spectrum (70 eV) *m/e* 441 ($M^+ - {}^{79}Br$); IR ($CHCl_3$) 1735 cm^{-1} (C = 0). Anal. Calcd for $C_{22}H_{19}Br_2O_3P$: C, 50.60; H, 3.67; P, 5.93. Found: C, 50.65; H, 3.68; P, 6.00.

1-(2-Carboxyphenyl)-2,3:19,20-dibenzo-5,8,11,14,17-pentaoxa-1-phosphacycloeicosa-2,19-diene 1-Oxide (11). To a refluxing, rapidly stirred suspension of 0.23 g (4.8 mmol) of NaH (50% oil dispersion) in 200 mL of dry THF was added dropwise over a period of 20 h a solution containing 1.15 g (2.2 mmol) of **8** and 0.43 g (2.2 mmol) of tetraethylene glycol[4d] in 300 mL of dry THF. After the addition was complete, the reaction mixture was refluxed for 3 h and allowed to cool. The solvent was removed in vacuo and the residue was distributed between CH_2Cl_2 and H_2O. The resultant emulsion was clarified by the addition of concentrated hydrochloric acid (to pH 1). The phases were separated, the aqueous phase was extracted with four portions of CH_2Cl_2, the organic phases were combined, washed with H_2O, and dried ($MgSO_4$), and the solvent was removed in vacuo, leaving 1.0 g of a viscous orange oil. This oil was triturated with pentane to remove the mineral oil, and the residue was purified by gel permeation chromatography. Two injections on column B (retention volume 201 mL) gave 0.32 g of a light yellow oil which was crystallized from Et_2O–CH_2Cl_2 to give 0.21 g (18%) of pure **11** as white microcrystals: mp 192–195 °C; ^1H NMR ($CDCl_3$) δ 11.45 (broad s, OH, 1 H), 8.4–8.1 (complex m, ArH, 1 H), 7.9–6.8 (complex m, ArH, 12 H), 4.8 (AB_q, J_{AB} = 13 Hz, $ArCH_2$, 4 H), and 3.5 (broad s, OCH_2CH_2, 16 H); mass spectrum (70 eV) *m/e* 540 (M^+) and 495 ($M^+ - CO_2H$); IR ($CHCl_3$) 3100–2800 (OH) and 1715 cm^{-1} (C = 0). Anal. Calcd for $C_{29}H_{33}O_8P$: C, 64.43; H, 6.15; P, 5.73. Found: C, 64.56; H, 6.08; P, 5.68.

1-(2-Carbomethoxyphenyl)-2,3:19,20-dibenzo-5,8,11,14,17-pentaoxa-1-phosphacycloeicosa-2,19-diene 1-Oxide (12). Using a procedure identical with that described for the preparation of **11**, 1.15 g (2.2 mmol) of **8** and 0.43 g (2.2 mmol) of tetraethylene glycol[4d] were treated with a refluxing suspension of 0.23 g (4.8 mmol) of NaH (50% oil dispersion) in dry THF. The residue remaining after the solvent was removed from the reaction mixture was dissolved in 15 mL of $CHCl_3$, and an excess of diazomethane[20] was added. The mixture was stirred for 5 min and acetic acid was added to destroy the excess diazomethane. The reaction mixture was diluted with 100 mL of $CHCl_3$, washed twice with 5% aqueous $NaHCO_3$ and once with brine and dried ($MgSO_4$), and the solvent was removed in vacuo, leaving 1.5 g of a viscous orange oil. The crude product was chromatographed on 50 g of alumina (activity 3, Merck) and eluted with 2-propanol–CH_2Cl_2, 3:97 (v:v), to give 0.9 g of a light yellow oil. The material thus obtained was purified by gel permeation chromatography (column B, retention volume 202 mL) to give 0.38 g (31%) of **12** which was crystallized from Et_2O to give transparent plates: mp 128.5–131 °C; ^1H NMR ($CDCl_3$) δ 8.0–6.8 (complex m, ArH, 12 H), 4.7 (AB_q, J_{AB} = 13 Hz, $ArCH_2$, 4 H), and 3.53 (broad s, OCH_2CH_2 and OCH_3, 19 H); mass spectrum (70 eV) *m/e* 554 (M^+), 539 ($M^+ - CH_3$), and 495 ($M^+ - CO_2CH_3$); IR ($CHCl_3$) 1735 cm^{-1} (C=O). Anal. Calcd for $C_{30}H_{35}O_8P$: C, 64.97; H, 6.63; P, 5.58. Found: C, 65.06; H, 6.47; P, 5.65.

Methyl Bis[(2-bromomethyl)phenyl]phosphinate (7). To a solution of 2.0 g (5.1 mmol) of bis(2-toly lphosphinyl chloride) in 75 mL of $CHCl_3$ at 25 °C was added an excess of an ethereal diazomethane solution.[20] After the reaction mixture had been stirred for 5 min, the excess diazomethane was destroyed with acetic acid. The reaction mixture was washed twice with 10% aqueous $NaHCO_3$ and once with brine and dried ($MgSO_4$), and the solvent was removed in vacuo to give 2.1 g (100%) of ester **3** as a light yellow viscous oil which was used in the next reaction without further purification: ^1H NMR ($CDCl_3$) δ 8.1–7.6 (m, ArH, 2 H), 7.5–7.0 (complex m, ArH, 6 H), 3.75 (d, J_{P-CH} = 11 Hz, OCH_3, 3 H), and 2.4 (broad s, $ArCH_3$, 6 H); IR ($CHCl_3$) 1035 cm^{-1} (P–O). To a stirred refluxing suspension of 1.85 g (7.1 mmol) of **3** and 2.60 g (14.2 mmol) of NBS in 75 mL of dry CCl_4 was added ca. 0.2 g of dibenzoyl peroxide. After being refluxed for 2 h, the reaction mixture was allowed to cool and was then filtered. The filtrate was washed with 10% aqueous $NaHSO_3$ and brine and dried ($MgSO_4$), and the solvent was removed in vacuo, leaving 3.1 g of a viscous yellow oil. The crude product was chromatographed on 200 g of silica gel eluting with acetone–CH_2Cl_2, 1:24 (v:v), to give 1.4 g (47%) of **7** as a water white oil: ^1H NMR ($CDCl_3$) δ 8.0–7.1 (complex m, ArH, 8 H), 4.90 (s, CH_2Br, 4 H), and 3.83 (d, J_{P-OCH_3} = 11 Hz, OCH_3, 3 H); mass spectrum (70 eV) *m/e* 416 ($M^+ - {}^{79}Br$), 337 (base, $M - {}^{79}Br$), and 258 ($M - 2\,{}^{79}Br$); IR ($CHCl_3$) 1035 cm^{-1} (P–O). Anal. Calcd for $C_{15}H_{15}Br_2O_2P$: C, 43.09; H, 3.62; P, 7.41. Found: C, 43.17; H, 3.61; P, 7.46.

1-Methoxy-2,3:19,20-dibenzo-5,8,11,14,17-pentaoxa-1-phosphacycloeicosa-2,19-diene 1-Oxide (13). To a rapidly stirred refluxing suspension of 0.25 g (5.26 mmol) of NaH (50% oil dispersion) in 200 mL of dry THF was added dropwise, over a period of 12 h, a solution containing 1.0 g (2.39 mmol) of **7** and 0.46 g (2.39 mmol) of tetraethylene glycol[4d] in 200 mL of dry THF. After the addition was complete, the reaction mixture was refluxed for 2 h and allowed to cool. A few drops of H_2O were added to quench the excess NaH, and the solvent was removed in vacuo. The residue was distributed between CH_2Cl_2 and H_2O, the aqueous phase was acidified (pH 1) with concentrated HCl, and the phases were separated. The aqueous phase was extracted with three portions of CH_2Cl_2, the organic phases were combined, washed with H_2O and brine, and dried ($MgSO_4$), and the solvent was removed in vacuo, leaving 0.8 g of a dark yellow oil. The TLC behavior of this crude material suggested that the phosphinate ester had been saponified. The crude product was dissolved in 10 mL of $CHCl_3$ and treated at room temperature with an excess of diazomethane.[20] The reaction mixture was stirred for 15 min, and the excess diazomethane was destroyed with acetic acid. The reaction mixture was diluted with 50 mL of $CHCl_3$, washed twice with 10% aqueous $NaHCO_3$ and once with brine, and dried ($MgSO_4$), and the solvent was removed in vacuo, leaving 0.8 g of a yellow oil. The crude esterified product was chromatographed on 125 g of alumina (activity 1, Merck) and was eluted with increasing ratios of 2-propanol–CH_2Cl_2, 1.5:98.5 to 5:95 (v:v), to give 0.36 g of a light yellow oil. Final purification was affected by gel permeation chromatography (column B, retention volume 205 mL) to give 0.21 g (23%) of pure **13** as a water white oil: ^1H NMR ($CDCl_3$) δ 8.2–7.2 (complex m, ArH, 8 H), 4.8 (AB_q, J_{AB} = 13 Hz, $ArCH_2$, 4 H), 3.77 (d, J_{P-CH} = 10 Hz, OCH_3, 3 H), and 3.7–3.4 (m, OCH_2CH_2, 16 H); mass spectrum *m/e* 450 (M^+); IR ($CHCl_3$) 1037 cm^{-1} (P–O). Anal. Calcd for $C_{23}H_{31}O_7P$: C, 61.32; H, 6.94; P, 6.95. Found: C, 61.12; H, 6.92; P, 6.95.

23-Oxo-4,7,10,13,16-pentaoxa-1,19-diazabicyclo[17.3.1]tricosane (16) and Its Dimer (17). To 1.00 g (10.0 mmol) of 2(1*H*)-tetrahydropyrimidone (Eastman Organic Chemicals) in 200 mL of dry THF was added 1.10 g (22.9 mmol) of NaH in 50% mineral oil dispersion followed quickly by hexaethylene glycol ditosylate[4d] dissolved in 100 mL of dry THF. The reaction mixture was refluxed under N_2 for 12 h, and the solvent was removed under reduced pressure. The residue was distributed between CH_2Cl_2 (100 mL) and water (60 mL). The aqueous phase was extracted with two 100-mL portions of CH_2Cl_2, the combined organic layers were dried (Na_2SO_4), and the solvent was removed to yield 4.08 g of oil. This material was chromatographed on 600 g of alumina (MCB, basic), and product was eluted with ethanol–CH_2Cl_2 mixtures. The macrocycles eluted with 6:94 (v:v) ethanol–CH_2Cl_2. This material was chromatographed on gel permeation column A in THF to give monomeric cycle **16**, 1.86 g (54%), and dimeric cycle **17**, 0.33 g (10%), as discrete bands with base line separation from each other and from higher oligomers. Cycle **16 (heavy oil) gave M^+ at 70 eV:** *m/e* 346; IR (neat) 1634 cm^{-1} (urea C = 0 stretch); ^1H NMR ($CDCl_3$) δ 1.92 (m, 2 H), 3.33–3.83 (m, 28 H); ^{13}C NMR ($CDCl_3$) (20 MHz) δ (intensity) 22.41 (13), 47.79 (25), 48.23 (24), 70.46 (100), 70.68 (57), 155.47 (18). Anal. Calcd for $C_{16}H_{30}N_2O_6$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.28; H, 8.70; N, 8.07. Dimeric cycle **17** (heavy oil) gave M^+ at 70 eV: *m/e* 692; IR (neat) 1634 cm^{-1} (urea, C = 0 stretch); ^1H NMR ($CDCl_3$) δ 1.90 (m, 4 H), 3.27–3.83 (m, 56 H). Anal. Calcd for $C_{32}H_{60}N_4O_{12}$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.34; H, 8.79; N, 7.94.

3,6,9,12,15-Pentaoxa-21-azabicyclo[15.3.1]heneicosa-17,19,1(21)-triene 21-Oxide (18). To a solution of 2,6-pyrido-18-crown-6[4c] (1.4 g, 4.7 mmol) in 50 mL of glacial acetic acid at 25 °C was added 2 mL of 30% H_2O_2, and the solution was heated to reflux for 3 h. An additional 1 mL of 30% H_2O_2 was then added, and the mixture was heated at 70–80 °C for 10 h. To the mixture was added 30 mL of water and the solution was evaporated under reduced pressure. The residue was dissolved in 50 mL of water saturated with Li_2CO_3, and the mixture was extracted with four 100-mL portions of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered, and evaporated to give a black oil. This material was chromatographed in THF on gel permeation column A to give the pyridine oxide cycle **18** as a colorless oil: 0.52 g (35%); M^+ at 70 eV, *m/e* 313; ^1H NMR ($CDCl_3$) δ 3.29 (m, OCH_2O, 16 H), 4.92 (s, $ArCH_2$, 4 H), 7.38 (m, ArH, 3 H). Anal. Calcd for $C_{15}H_{23}NO_6$: C, 57.46; H, 7.40; N, 4.47. Found: C, 57.59; H, 7.41; N, 4.43.

Determination of Association Constants (K_a) in Chloroform between Hosts and Picrate Salts. The K_a values were determined at 24–26 °C by the extraction into $CDCl_3$ from aqueous solutions of

picrate salts in the presence and absence of host by the method described earlier[5a] and later made more precise.[5d,e] Table I records the results based on the UV absorbance of the picrate ion in the $CDCl_3$ layer, except for those of 2,3-naphtho-18-crown-6 and 2,6-pyrido-18-crown-6. The R, K_a, and $-\Delta G°$ values for those hosts binding Li^+ were based on UV absorbances in the $CDCl_3$ layers, but for the other ions it was based on absorbances measured on the water layer.[5d,e] The values for 1,3-benzo-18-crown-6 measured previously are included in Table I for comparison purposes. Cyclic 2,6-pyrido-18-crown-6 was prepared earlier,[4c] but its K_a values for the picrates are reported here for the first time.

Registry No.—**1**, 18803-11-7; **2**, 18593-19-6; **3**, 69928-10-5; **4**, 69928-11-6; **5**, 69928-12-7; **6**, 68669-11-4; **7**, 69928-13-8; **8**, 69928-14-9; **9**, 69928-15-0; **9**·K·picrate, 69942-22-9; **9**·Rb·picrate, 69942-24-1; **9**·Cs·picrate, 69942-26-3; **9**·NH_4·picrate, 70131-36-1; **9**·Li·picrate, 69961-17-7; **9**·Na·picrate, 69961-15-5; **10**, 69928-16-1; **10**·Li·picrate, 69942-28-5; **10**·Na·picrate, 69942-30-9; **10**·K·picrate, 69942-32-1; **10**·Rb·picrate, 69942-34-3; **10**·Cs·picrate, 69942-36-5; **10**·NH_4·picrate, 70131-37-2; **11**, 69928-17-2; **11**·Li·picrate, 69942-38-7; **11**·Na·picrate, 69942-40-1; **11**·K·picrate, 69942-42-3; **11**·Rb·picrate, 69942-44-5; **11**·Cs·picrate, 69961-13-3; **11**·NH_4·picrate, 70145-48-1; **12**, 69928-18-3; **12**·Na·picrate, 69942-46-7; **12**·Li·picrate, 69942-48-9; **12**·K·picrate, 69942-50-3; **12**·Rb·picrate, 69942-52-5; **12**·Cs·picrate, 69942-54-7; **12**·NH_4·picrate, 70131-38-3; **13**, 69928-19-4; **13**·K·picrate, 69942-56-9; **13**·Rb·picrate, 69942-58-1; **13**·Cs·picrate, 69942-60-5; **13**·NH_4·picrate, 70131-39-4; **13**·Li·picrate, 69942-62-7; **13**·Na·picrate, 69942-64-9; **14**, 69928-20-7; **14**·Li·picrate, 69942-66-1; **14**·Na·picrate, 69942-68-3; **14**·K·picrate, 69942-70-7; **14**·Rb·picrate, 69942-72-9; **14**·Cs·picrate, 69942-74-1; **14**·NH_4·picrate, 70145-46-9; **16**, 69928-21-8; **16**·Li·picrate, 69942-76-3; **16**·Na·picrate, 69942-78-5; **16**·K·picrate, 69942-80-9; **16**·Rb·picrate, 69942-82-1; **16**·Cs·picrate, 69942-84-3; **16**·NH_4·picrate, 70145-50-5; **17**, 69928-22-9; **18**, 69928-23-0; **18**·Li·picrate, 69942-86-5; **18**·Na·picrate, 69942-88-7; **18**·K·picrate, 69942-89-8; **18**·Rb·picrate, 69942-91-2; **18**·Cs·picrate, 69942-93-4; **18**·NH_4·picrate, 70131-40-7; **19**, 53914-89-9; **19**·Li·picrate, 69942-95-6; **19**·Na·picrate, 69942-97-8; **19**·K·picrate, 69942-98-9; **19**·Rb·picrate, 69943-00-6; **19**·Cs·picrate, 69943-02-8; **19**·NH_4·picrate, 70131-41-8; **20**·Li·picrate, 64799-51-5; **20**·Na·picrate, 64799-49-1; **20**·K·picrate, 64851-30-5; **20**·Rb·picrate, 64822-96-4; **20**·Cs·picrate, 64799-34-4; **20**·NH_4·picrate, 64916-33-2; **21**·Li·picrate, 69943-04-0; **21**·Na·picrate, 69943-06-2; **21**·K·picrate, 69943-07-3; **21**·Rb·picrate, 69943-08-4; **21**·Cs·picrate, 69928-25-2; **21**·NH_4·picrate, 70131-35-0; 2-bromotoluene, 95-46-5; phenylphosphonic dichloride, 824-72-6; tetraethylene glycol, 112-60-7; ethylene glycol, 107-21-1; bis[2-(((2-hydroxyethoxy)methyl)phenyl)phenyl]-phosphine oxide, 69928-26-3; phosphorus oxychloride, 10025-87-3; 2-(2′-bromophenyl)-4,4-dimethyloxazoline, 69928-27-4; bis(*o*-tolyl)phosphinyl chloride, 59472-84-3; 2-(1*H*)-tetrahydropyrimidone, 1852-17-1; hexaethylene glycol ditosylate, 42749-27-9.

References and Notes

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Reduction of Cyclopropyl Halides. Stereochemistry of the Lithium Aluminum Deuteride Reduction of *r*-1-Chloro-*c*- and -*t*-2-methyl-2-phenylcyclopropane[1]

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The lithium aluminum deuteride reduction of *r*-1-chloro-*c*- and -*t*-2-methyl-2-phenylcyclopropane (**3a** and **2a**) in dimethoxyethane (DME) at 100 °C was shown to give a single deuterated isomer of 1-methylphenylcyclopropane (**4**). The isomer of **4** formed was found to be **4b** by ^1H NMR spectral comparison with an authentic sample of **4b** prepared by a stereospecific route. A mechanism for the $LiAlD_4$ reduction is given to account for the stereochemical results.

The reduction of *gem*-dihalocyclopropanes with lithium aluminum hydride ($LiAlH_4$) proceeds in a stepwise fashion to give monohalocyclopropanes and cyclopropanes.[2] Debromination of *gem*-bromofluorocyclopropanes with $LiAlH_4$ in refluxing tetrahydrofuran (THF) proceeds with complete retention of configuration.[3] The dechlorination of *gem*-chlorofluorocyclopropanes with $LiAlH_4$ in diglyme at 100 °C proceeds stereoselectively with predominant retention of

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