Host–Guest Complexation. 1. Concept and Illustration[1a]

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Abstract: This paper describes studies of structured molecular complexation between macrocyclic polyethers or open-chain analogues as hosts and *tert*-butylammonium, guanidinium, and arenediazonium salts as guests. The results provide conclusions important to investigations of structured molecular complexation. (1) Corey–Pauling–Koltun molecular models of potential complexes can be used as a rough means of evaluating potentially complementary host–guest relationships. (2) Convergence in host compounds that positions binding sites prior to complexation results in higher binding energies than when guests must impose convergence during complexation. (3) Matching of sizes, shapes, and electronic properties of binding portions of hosts and guests is a necessary requisite to strong binding.

The term *complexation* names a phenomenon easy to recognize but difficult to define because of its many manifestations. Complexation is found between organic compounds, or between metals and ligands. The phenomenon is observed in the gas, liquid, and solid phases, as well as at phase interfaces. The terms *activated complex* and *transition state* are synonymous, and here the term *complex* applies to a system at an energy maximum rather than the more usual energy minimum.

Complexes are composed of two or more molecules or ions held together in unique structural relationships by electrostatic forces other than those of full covalent bonds or of ionic crystals. These forces are of a pole–pole, pole–dipole, or dipole–dipole variety. More specifically, molecular complexes are usually held together by hydrogen bonding, by ion pairing, by π acid to π base interactions, by metal to ligand binding, by van der Waals attractive forces, by solvent reorganizing, and by partially made and broken covalent bonds (transition states). In ground-state complexes of organic compounds, the binding energies at any one site are usually small compared to those of covalent bonds, and high structural organization is usually produced only through multiple binding sites.

Complexation plays a central role in biological processes, such as enzyme catalysis and inhibition, replication, genetic information storage and retrieval, immunological response, and ion transport. Enough structural information is now known about the complexes involved to inspire organic chemists to design highly structured molecular complexes and to study the chemistry unique to complexation phenomena. Molecular evolution provides many examples of complexes whose features or functions might be modeled by synthetic, unnatural systems. The very existence of a vast natural structured complexation chemistry implies the possible creation of a body of organic structured complexation chemistry that does not have to pass the test of biological survival.

This series of papers describes studies of what we call host–guest complexation chemistry. A highly structured molecular complex is composed of at least one host and one guest component. A host–guest relationship involves a complementary stereoelectronic arrangement of binding sites in host and guest. The host component is defined as an organic molecule or ion whose *binding sites converge* in the complex. The guest component is defined as any molecule or ion whose *binding sites diverge* in the complex.[2] Guests can be organic compounds or ions, metals or metal ions, or metal–ligand assemblies. Since location of convergent binding sites usually involves more organization than location of divergent binding sites, the binding and supporting parts of hosts tend to be larger than the binding and supporting parts of guests, although large nonbinding parts can be attached to either hosts or guests to manipulate their properties. In general, simple guests are abundant, whereas hosts usually have to be designed and synthesized. In these studies, most host compounds are below 1500 in molecular weight.

Most naturally occurring host compounds are condensation copolymers of α-amino acids, of phosphoric acid and nucleoside, or of glucose (e.g., the cyclodextrins).[3] The earliest studied synthetic host compounds are the cyclic polyether crown compounds of Pedersen,[4] which are formally addition polymers of ethylene oxide, or copolymers of ethylene oxide and benzene oxide. These compounds provided ligand assemblies for binding metal and ammonium cations, alkylammonium cations, and thiourea. Simmons and Park's[5] *out–in* bicyclic amines acted as hosts to halide ions, whereas Lehn's[6] mixed ether–amino bicyclic cryptands were hosts to a variety of metal ions.

Prior to our work, hosts for metal ion guests had been much investigated, but little had been done to design and synthesize hosts for complexing organic guests. Our early papers dealt largely with organic-to-organic host–guest relationships.[7] In the design of hosts, Corey–Pauling–Koltun (CPK) molecular models are invaluable. They provide a compass in an uncharted sea of molecular possibilities of complementary relationships between hosts and guests. Since host–guest binding energies are small, little energy is available to deform bond angles or to compress groups during complexation. Space-filling scale models whose averaged atomic diameters, bond angles, and distances (based on x-ray crystal structure data) apply at room temperature provide a possible guide to prospecting for host structures to bind given organic guest compounds. Appropriately programmed computers might provide a less simple alternative.

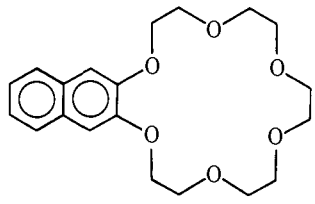
We report in this paper a survey of three different types of organic host–guest relationships. The first involves complexation between cyclic and noncyclic polyethers and *tert*-butylammonium salts. The second concerns complexation between guanidinium ion and cyclic polyethers.[8] The third treats complexation between arenediazonium salts and cyclic polyethers.[9] The results provide rough tests of the following: (1) whether molecular models can be used as a guide in the design of host compounds for specific complexation; (2) whether differing degrees of enforced convergence in hosts provide the expected differences in binding; (3) whether complementary vs. noncomplementary structural relationships between host and guest provide the expected correlation with binding affinities.

Complexation of *tert*-Butylammonium Salts

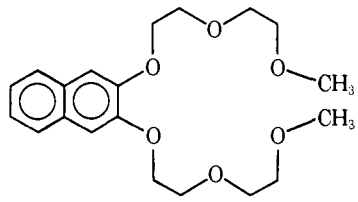
A fundamental question in host design is that of the effect of preorganization of binding sites on binding ability. The three hosts **1**,[4a] **2**, and **3** have been prepared by conventional methods. In **1**, the ring system enforces convergence of the oxygen binding sites. In **2**, the presence of the rigid naphthalene ring

in the middle of the chain directs the two attached arms in a semiconvergent arrangement. In **3**, no rigid units enforce any conformations. The basicity of the oxygens in all three structures should be intrinsically similar, and the differences lie in the extents to which guest must organize host to complex. Examination of CPK molecular models of possible complexes of *tert*-butylammonium ions with **1, 2,** and **3** suggests that the three acidic hydrogens attached to nitrogen can hydrogen bond alternate oxygens of **1, 2,** and **3** with 180° N-H···O bond angles, and that the three non-hydrogen-bonded oxygens can all contact the N^+ in between the hydrogen bonds without steric compression, provided the parts of the host have the appropriate conformations. Although imperfect, **3** is structurally the closest nonconvergent model available for **1** and **2**. For perfect complexation, the terminal naphthalene rings of **3** must occupy a specialized conformation. Thus the systems are designed to detect the effects of the guest having to organize the host in the complex vs. having the host largely preorganized.

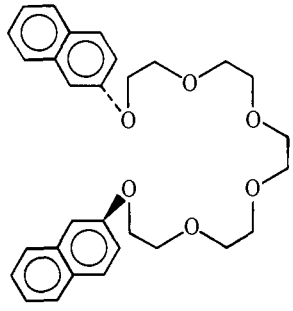
The *tert*-butylammonium and naphtho systems were chosen as probes in this and further studies[7a,c,f] both for practical and strategic reasons. The naphthalene-containing systems impart rigidity and lipophilicity to polyethers, can be used to manipulate the host shape around the binding site, and provide magnetic fields for NMR solution-structure investigation.[7f] The *tert*-butylammonium salt possesses the desired balance between hydrophilicity-lipophilicity, the nine C-H protons provide a strong singlet in the ^1H NMR, and the C_3 axis reduces the number of conformations possible about the N-C bond in the complex. Structure **4** is suggested by CPK molecular model organization for the complex between **1** and this ion.[10]



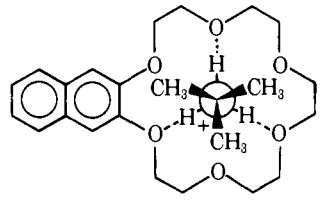
1 (26), ClO_4^- scale



2 (0.026), ClO_4^- scale
(4.5), PF_6^- scale



3 (0.0738), PF_6^- scale



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The extraction constants, K_e, were estimated by distribution experiments of guests between $CDCl_3$ and D_2O in the presence of hosts. Integration of appropriate ^1H NMR peaks of the $CDCl_3$ layer provided equilibrium concentrations of complexes and free host, and the ^1H NMR spectra of the D_2O layers indicated the presence of <0.5% of host in any form. In identical extraction experiments carried out in the absence of host, no *t*-Bu protons could be detected in the $CDCl_3$ layers from their ^1H NMR spectra.

$$[H]_{CDCl_3} + [t\text{-}BuNH_3^+]_{D_2O} + [X^-]_{D_2O} \underset{}{\overset{K_e}{\rightleftharpoons}} [t\text{-}BuNH_3^+ \cdot H \cdot X^-]_{CDCl_3}$$

Hosts **1, 2,** and **3** possessed such widely different binding powers that two different *tert*-butylammonium salts had to be employed. Thus **1** and **2** were compared with $t\text{-}BuNH_3ClO_4$ as guest. Hosts **2** and **3** were compared with $t\text{-}BuNH_3PF_6$ as guest. The latter scale involved an aqueous phase 4 M in $LiPF_6$, which to some extent salted the guest out of the aqueous phase and into the host of the organic phase. The ^1H NMR data coupled with the amounts of the materials employed provided estimates of the K_e values. The equations involved and the controls are described in the Experimental Section.

Values of K_e are listed beneath each formula. A comparison of the values indicates that **1**, whose oxygens converge, is ~3 powers of 10 better at complexation than **2**, whose oxygens only partially converge, which in turn is ~1.5 powers of 10 better than **3**, in which no rigid unit enforces convergence. Clearly enforced convergence of binding sites in these simple systems enhances complexation by substantial factors.

Complexation of Guanidinium Salts

Molecular models (CPK) of guanidinium ion complexed to 27-crown-9 produce a wreath-like structure containing a C_3 axis with six linear hydrogen bonds and three oxygen electron pair to N^+ contact interactions. Both from a geometric and electronic point of view, the host-guest relationship appears to be almost perfectly complementary. Accordingly, guanidine was compared with other bases for its ability to act as a template and catalyst in the formation of benzo-27-crown-9 polyethers, and to complex the cyclic polyethers once formed.

In initial experiments, potassium *tert*-butoxide, guanidine, and tetramethylguanidine were compared for their abilities to produce benzo-27-crown-9 (**5**) (vs. mainly polymer) from octaethyleneglycol ditosylate and catechol in tetrahydrofuran at reflux. Compound **5** was isolated and characterized. Then the yields based on catechol (completely consumed) were determined by GLC with an internal standard. Table I records the results, which indicate that K^+ > guanidinium ion > tetramethylguanidinium ion in bringing together the reacting ends of the intermediate that leads to **5**.

The templating properties of K^+ for preparing crown ethers are well established.[4a,f] The x-ray structure of the KI complex of dibenzo-30-crown-10 indicates the host wraps around the guest in a tennis-ball-seam arrangement with the electrons of the oxygen pointing generally inward.[11]

The yield of **5** with guanidine (23%) was a factor of 10 higher than the yield with tetramethylguanidine (2%). An attractive explanation for this difference is suggested by structure A, which depicts the organization and consequent stabilization of the final transition state for closure of the host of the guest to give complexed product.

In runs 4-7 (Table I), potassium *tert*-butoxide, guanidine, tetramethylguanidine, and tetrabutylammonium hydroxide in tetrahydrofuran were compared for their abilities to produce benzo-9-crown-3 (**6**),[4a] dibenzo-18-crown-6 (**7**),[4a] and tribenzo-27-crown-9 (**8**) from catechol and diethylene glycol ditosylate. The structure of tribenzo-27-crown-9 (**8**) was established by its synthesis from **9** and **10** under the conditions of run 4 (24% isolated yield) and run 5 (15% isolated yield).

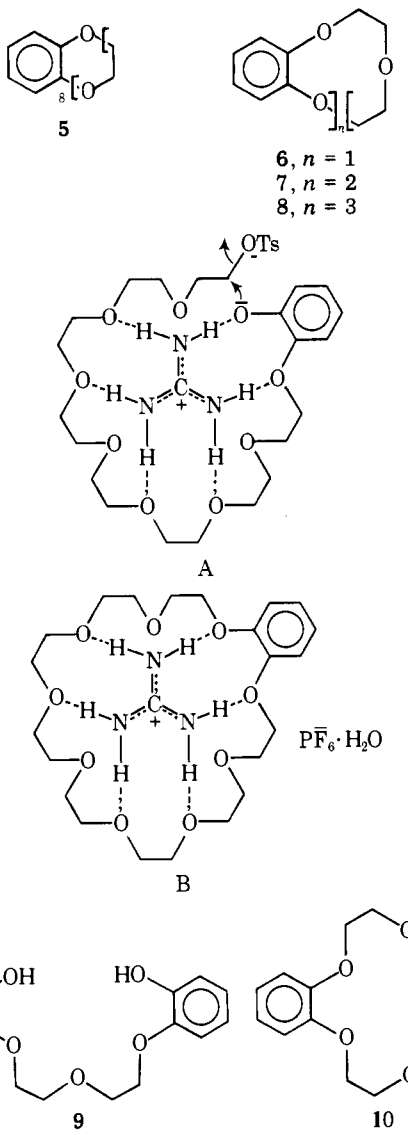
The yields of **6, 7,** and **8** in runs 4-7 were determined by GLC with an internal standard. The results indicate that the second unimolecular reaction that produced the smallest cycle

Table I. Effect of Yields of Cyclic Ethers on Base in Catechol Reactions in Tetrahydrofuran-*tert*-Butyl Alcohol at Reflux until Catechol Was Consumed

Run no.	Base	Glycol ditosylate	% yields of cycles based on catechol			
			5	**6**	**7**	**8**
1	*t*-BuOK	Octaethylene	59			
2	$HN{=}C(NH_2)_2$	Octaethylene	23			
3	$HN{=}C[N(CH_3)_2]_2$	Octaethylene	2			
4	*t*-BuOK	Diethylene		5	44	20
5	$HN{=}C(NH_2)_2$	Diethylene		4	25	11
6	$HN{=}C[N(CH_3)_2]_2$	Diethylene		11	6	0
7	$(n\text{-Bu})_4N^+OH^-$	Diethylene		15	23	5.5

(**6**) was more favored by the large nontemplating tetrabutylammonium and tetramethylguanidinium ions. More interestingly, K^+ > guanidinium ion > tetrabutylammonium ion > tetramethylguanidinium ion in assembling the four molecules that produce **7** and the six molecules that give **8**. As in the production of benzo-27-crown-9 (**5**), the ability of guanidinium ion to favor the larger rings suggests the ion acts as a template during the reaction, but again less effectively than K^+. These ions apparently complexed and stabilized the transition states for the final ring-closing reaction. An examination of CPK models of guanidinium ion and dibenzo-18-crown-6 (**7**) indicates that three of the six hydrogens of the ion can linearly hydrogen bond three of the oxygens of **7**, while the other three oxygens are within van der Waals contact distance of either the central carbon or the two hydrogen-bonding nitrogens. In the ion, positive charge is distributed on all ten atoms. The tetrabutylammonium ion with its point charge gives much higher yields of the larger cycles than tetramethylguanidinium ion with its dispersed charge (runs 6 and 7). The 27-membered ring cycles (**5** and **8**) are just large enough to encircle the nitrogen of the tetrabutylammonium ion (CPK models). Two butyl groups protrude from one side and two from the other side of the model complex. However, the fact that this ion provides higher yields of the smaller cycles than the largest indicates that ring closure is not dependent on encirclement of the guest by the host.

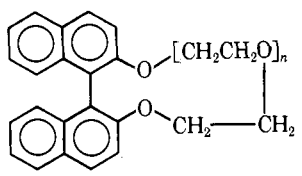
Cycles **5**, **7**, and **8** in $CDCl_3$ (unlike **6**) solubilized by complexation (^1H NMR spectral criterion) on a 1 mol to 1 mol basis otherwise insoluble crystalline guanidinium tetraphenylborate, but failed to solubilize the tosylate or thiocyanate salts. Extraction of a 0.5 M $LiPF_6$ aqueous solution (pH 5, LiOH adjusted) of guanidinium chloride with **5** dissolved in $CDCl_3$ resulted in 0.84 mol of salt extracted per mole of host. From the solution crystallized the one-to-one adduct as the $PF_6^-\cdot H_2O$ salt (probably structure **B**). Similar extractions of chloroform solutions of **7** and **8** (4 M $LiPF_6$) gave complexes containing two host and three guest components. Cycles **5**, **7**, and **8** in $CDCl_3$ were compared in their abilities to extract guanidinium thiocyanate solutions from water. Whereas monobenzo cycle **5** extracted almost a molar amount, the other two extracted less than a 0.05 M amount. Thus **5** is the best host for guanidinium ion, probably because of the number, location, and basicity of its oxygens.



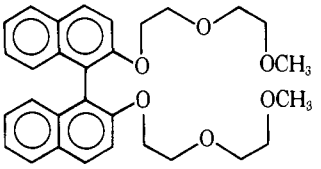
Complexation of Arenediazonium Salts

A further test of CPK molecular models as a means of designing host-guest complementary relationships involves the matching of the $^+N{\equiv}N$ and $C{\equiv}O^+$ groups of arenediazonium and arylacylonium to the appropriately sized holes of cyclic polyethers. The C≡C group of CPK models possesses a diameter equivalent to ~2.8 Å, whereas the $^+N{\equiv}N$ cylindrical diameter is estimated as ~2.4 Å from the x-ray contour map of benzenediazonium chloride.[12] The diameter of the hole of 18-crown-6[13] in models is the equivalent of ~2.6 Å with all oxygens turned inward. The equivalent diameters of the holes of models of the four 2,2′-substituted-1,1′-binaphthyl cyclic polyethers are listed in those gauche conformations with the oxygens turned inward and close to coplanar, and with an Ar-Ar dihedral angle of ~78°.[14] The C≡C group of $C_6H_5C{\equiv}C$ in models very closely fits into the hole of 18-crown-6, and more comfortably into the holes of **12** and **13**, but not of **11**. Six adjacent oxygens of **14** are difficult to organize around the C≡C group for steric reasons, and because of the multiplicity of conformations. Models suggest **12** should be the best host for ArN_2^+.

Compounds **11**, **12**, and **13** were prepared (45, 60, and 75%, respectively) by treating 2,2′-dihydroxy-1,1′-binaphthol with



11, n = 3, hole = ~2.2Å
12, n = 4, hole = ~2.7Å
13, n = 5, hole = ~3.7Å
14, n = 7, hole = ~5.6Å



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the appropriate polyethylene glycol ditosylates in tetrahydrofuran–potassium *tert*-butoxide without high dilution.[7a] Cycle **14** was produced (25%) in 50% tetrahydrofuran–*tert*-butyl alcohol with guanidine as base. Open-chain model compound **15** was prepared by conventional reactions.

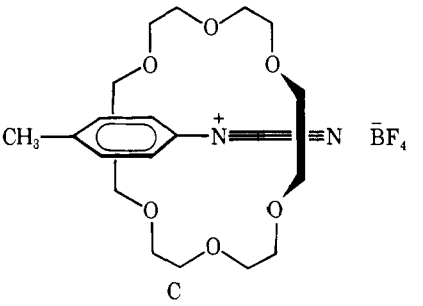
We have compared the abilities of 18-crown-6, **11, 12, 13, 14,** and open-chain model compound **15** to solubilize by complexation arenediazonium and arylacylonium salts in nonpolar media. A solution of 18-crown-6 in $CDCl_3$ solubilized solid *p*-toluenediazonium tetrafluoroborate[15])**16**) to give a guest to host molar ratio of 0.8. The complex showed a small but real shift in the methylene singlet of the host in the 100-MHz ^1H NMR spectrum from 3.62 to 3.58 ppm. Similarly a solution of cycle **12** gave a ^1H NMR spectrum whose four $ArOCH_2$ protons provide an 11-line multiplet centered at 4.06 ppm. This solution dissolved 0.9 mol of **16**/mol of cycle (NMR). The four $ArOCH_2$ protons of the new solution gave two multiplets, one of six lines at 3.89 and one of seven lines at 4.21 ppm. Likewise, **13** complexed 0.6 mol of **16, 14** a trace of **16,** but both cycle **11** and open-chain model **15** failed to draw a detectable (NMR) amount of **16** into solution.

The behavior of other salts with the 6-oxygen cycle, **12,** was similarly examined. A $CDCl_3$ solution of **12** solubilized 4-hydrogen-, 4-methoxy-, 4-chloro-, 4-nitro-, and 3,4-dimethylbenzenediazonium tetrafluoroborate salts in guest to host molar ratios of 0.3, 0.9, 0.8, 0.9, and 1.0, respectively. However, the sterically hindered 2,6-dimethylbenzenediazonium tetraphenylborate was not complexed by either **12** or 18-crown-6. Models indicate that the two methyl groups occupy the space in 2,6-dimethylbenzenediazonium ion occupied by the host wrapped around the $^+N{\equiv}N$ group of the benzenediazonium ion.

Interestingly, the complexes of the binaphthyl-20-crown-6 (**12**) exhibited yellow to red colors, which suggests that π–π complexation between the arenediazonium ion (π acid) and a naphthalene ring (π base) occurs. No such colors were observed for the complex between 18-crown-6 and *p*-methylbenzenediazonium ion. Molecular models of the complex between **12** and **16** indicate the aromatic nuclei of host and guest can comfortably occupy parallel planes, and are within van der Waals contact distance when the $^+N{\equiv}N$ group is inserted in the holes.

Both oxygen basicity (aryl vs. alkyl attachment) and the character of the aryl groups influenced the crown's complexing ability. Thus **16** was complexed by dibenzo-18-crown-6[4a] in $CDCl_3$ to give a guest to host molar ratio of 0.4. Similarly a solution of salt **16** in acetone solubilized essentially otherwise insoluble dibenzo-18-crown-6 to give a *host* to *guest* ratio of 0.23. However, (±)-bisbinaphtho-22-crown-6[7b] in $CDCl_3$ did not complex **16,** probably because the oxygens are not basic enough.[7b]

These data strongly support structures for the complexes in which the host fits like a collar around the $^+N{\equiv}N$ neck of the guest. Open-chain polyether **15** differs from cycle **12** by only two hydrogen atoms. The fact that **12** complexes **16** well and **15** fails to do so indicates the importance to complexation of preorganized convergence in the host. The failure of small cycle **11** to complex **16** and the poor complexation behavior of large cycle **14** indicates the hole size is important. The failure of **12** to complex the 2,6-dimethylbenzenediazonium ion indicates the $^+N{\equiv}N$ group must deeply penetrate the hole to complex well. Structure C is envisioned for the complex between **16** and 18-crown-6.



C

Attempts were made to form azoarene-crown rotaxanes[16] by treating the complex between **12** and **16** in dichloromethane with *N,N*-dimethylaniline,[17] *p*-tolylmagnesium bromide,[15b] *p*-tolyllithium,[15b] or di-*p*-tolylzinc[18] in ether at 25 or −78 °C. Only nonencircled, conventional products were obtained. Thus essentially quantitative yields of 4-chloro-4′-*N,N*-dimethylaminoazobenzene were obtained in CH_2Cl_2 at −78 °C with 2 equiv of 18-crown-6 present to solubilize *p*-chlorobenzenediazonium tetrafluoroborate. The solubilization rate of this salt in CH_2Cl_2 increased dramatically at the lower temperature, a fact that suggests a large negative entropy for dissolution–complexation. The 18-crown-6 was readily recovered at the end of the reaction.

Benzoyl hexafluorophosphate (**17**) was solubilized in $CDCl_3$ by both **12** (guest to host molar ratio, 0.5) and 18-crown-6 (ratio of 0.25). The expected ^1H NMR spectral changes were observed at 25 °C when **12** became complexed. Slow benzoylation of the naphthalene rings of **12** accompanied complexation. Attempts to stabilize diphenylmethyldiazonium trifluoroacetate in $CDCl_3$ with **12** gave equivocal results. No complexation between **12** and methyl isocyanide in $CDCl_3$ was observed.

These results may be of synthetic use in reactions that involve arenediazonium or arylacylonium salts as reactants, and where lipophilic solvents are required. Since the hosts appear to stabilize the functional groups by complexation, the hosts may act as protective groups under certain circumstances. In any case, the hosts lipophilize the salts, and act as dispersing agents at a molecular level.

These three studies provide conclusions important to further investigations of highly structured molecular complexation between organic entities. (1) Corey–Pauling–Kolton molecular models of potential complexes can be used in a limited way to evaluate potentially complementary host–guest relationships. (2) Convergence in host compounds that positions binding sites prior to complexation results in higher binding energies than when guests must bring about convergence during complexation. (3) Matching of sizes, shapes, and electronic properties of the binding portions of hosts and guests is a necessary requisite to strong binding.

Experimental Section

Instruments and Solvents. All ^1H NMR spectra were taken in $CDCl_3$ unless otherwise specified on a Varian HA-100 spectrometer, and chemical shifts recorded in δ (ppm) from internal tetramethylsilane. Mass spectra were taken on an AEI model MS-9 double focusing mass spectrometer at 70 eV. Melting points were taken on a Thomas–Hoover apparatus and are uncorrected. All solvents were distilled immediately prior to use, particularly THF, DMF, CH_2Cl_2, and $CHCl_3$.

Glycols and Their Ditosylates. Commercially available di-, tri-, and tetraethylene glycol were distilled through a 6-in. Vigreux column, and only the center fraction was used. The others were prepared as

described earlier.[13a,19] The octaethylene glycol ditosylate preparation illustrates the method used for the other ditosylates. A solution of 15 g of octaethylene glycol[19] in 45 mL of dry pyridine was cooled to −5 °C, and a solution of 16.9 g of tosyl chloride in 30 mL of dry pyridine was added with stirring at a rate so that the temperature of the reaction mixture never exceeded 2 °C. After 18 h at 4 °C, the reaction mixture was poured over crushed ice, and the resulting aqueous solution was extracted with CH_2Cl_2. The organic layer was washed (0 °C) with 6 N HCl solution, with brine, dried, and evaporated at 25 °C to give a viscous oil which was chromatographed on silica gel (2% C_2H_5OH in CH_2Cl_2) to give 16.5 g (60%) of the ditosylate as a heavy oil. No decomposition was observed on the column over a 36-h period. Ditosylates were stored at 0 °C. Anal. Calcd for $C_{30}H_{46}O_{13}S_2$: C, 53.08; H, 6.83. Found: C, 52.92; H, 6.83.

2,2′-Bis(1,4,7-trioxaoctyl)-1,1′-binaphthyl (15) and Related Ethers 11–13. The synthesis of **15** serves as a prototype for the preparation of ethers **1–3**. To a solution of 14.3 g (0.050 mol) of 2,2′-dihydroxy-1,1′-binaphthyl in 150 mL of tetrahydrofuran (THF) was added 7 g of KOH pellets (85%) (0.11 mol) in 5 mL of water, followed by 27.4 g (0.10 mol) of 3,6-dioxaheptyl tosylate dissolved in 50 mL of THF. The solution was stirred under nitrogen at 70 °C for 5 h and then at 45 °C for 16 h. The cooled reaction mixture was filtered from 21 g of potassium tosylate, the solvent was evaporated under vacuum, and the brown oil was chromatographed on 500 g of alumina. Elution of the product with ether–pentane (2:3) gave 19.8 g (81%) of a light yellow oil which solidified, mp 52.5–54.5 °C. The solid was recrystallized from pentane–CH_2Cl_2 to give white prisms, mp 55.5–56.5 °C. Anal. Calcd for $C_{30}H_{34}O_6$: C, 73.45; H, 6.99. Found: C, 73.61; H, 7.02. The mass spectrum gave M^+ at *m/e* 490, and the ^1H NMR was as expected.

By the same method from 2,3-dihydroxynaphthalene and pentaethylene glycol ditosylate was produced in 78% yield, 2,3-naphtho-18-crown-6 (**1**),[4a] mp 110–111.5 °C. Similarly, 2,3-bis(1,4,7-trioxaoctyl)naphthalene (**2**) was prepared in 37% yield from 2,3-dihydroxynaphthalene, mp 27–29 °C, the mass spectrum gave M^+ at *m/e* 364, and the ^1H NMR was as expected. Anal. Calcd for $C_{20}H_{28}O_6$: C, 65.92; H, 7.74. Found: C, 65.66; H, 7.64. Similarly, 1,16-bis(β-naphthyl)-1,4,7,10,13,16-hexaoxahexadecane (**3**) was prepared from pentaethylene glycol ditosylate and β-naphthol in 34% yield, mp 71–72.5 °C, the mass spectrum gave M^+ at *m/e* 490, and the ^1H NMR spectrum was as expected. Anal. Calcd for $C_{30}H_{34}O_6$: C, 73.45; H, 6.99. Found: C, 73.53; H, 7.08.

2-(2′-Chloroethoxy)ethyl 2″-Tetrahydropyranyl Ether (18). To 200 g of 2-(2′-chloroethoxy)ethanol was added 202 g of dihydropyran and 1 drop of concentrated hydrochloric acid (exotherm). After 1 h, enough tribenzylamine was added to raise the pH of the reaction mixture from 5 to 6.5. The resulting liquid was distilled under vacuum to give 322 g (96%) of the tetrahydropyranyl ether as a colorless liquid, bp 87–88 °C (0.5 mm). Anal. Calcd for $C_9H_{17}ClO_3$: C, 51.78; H, 8.21. Found: C, 51.70; H, 8.32.

1,2-Bis(5-hydroxy-3-oxa-1-pentyloxy)benzene (19). A solution of 68 g of the above chloro ether (**18**) in 150 mL of 1-butanol was added dropwise (stirring) to a mixture of 11.0 g of catechol and 8.2 g of NaOH in 300 mL of boiling 1-butanol. The resulting mixture was stirred under reflux for 15 h and an additional 2.9 g of NaOH was added. After an additional 15 h at reflux, the cooled reaction mixture was filtered from NaCl (14.9 g), concentrated (vacuum), and heated at 120 °C bath temperature under 50 μm to give 47 g of residue. This tetrahydropyranyl ether was cleaved by heating it with 1 g of pyridine hydrochloride under vacuum (50 μm) for 1 h at 155–160 °C. The residue was distilled at 50 μm to give 1.5 g of forerun followed by 19.5 g (68%) of diol **19** as a colorless oil, bp 185–187 °C (50 μm). The ^1H NMR spectrum was as expected. Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.75. Found: C, 59.03; H, 7.87.

The bistosylate of **19,** compound **10,** was prepared in 69% yield in the usual way, and was a viscous oil with the expected ^1H NMR spectrum. Anal. Calcd for $C_{28}H_{34}O_{10}S_2$: C, 56.55; H, 5.75. Found: C, 56.24; H, 5.90.

Bis[2-(*o*-hydroxyphenoxy)ethyl] Ether (9). Although reported previously,[4a] a more satisfactory preparation of **9** is reported here. To a stirred refluxing solution of 27.6 g of catechol and 3.45 g of NaOH in 200 mL of water under nitrogen was added dropwise (3 h) 6.04 g of bis(2-chloroethyl) ether. The reaction mixture was refluxed for an additional 48 h (neutral) and cooled, and the **9** that separated was recrystallized twice from benzene to give 6.0 g (48%), mp 84–86 °C after sublimation. The compound gave the expected ^1H NMR spectrum and molecular ion in the mass spectrum. Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.05; H, 6.55.

Solutions of Guanidine, Tetramethylguanidine, and Tetrabutylammonium Hydroxide in Various Solvents. The procedure is illustrated for guanidine in *tert*-butyl alcohol as solvent. To a solution of 17.8 g of potassium *tert*-butoxide under nitrogen was added 18 g of guanidinium sulfate, and the slurry was stirred for 16 h. The mixture was filtered rapidly under nitrogen through a fine, fritted disk filter funnel, and the residue was washed with 75 mL of *tert*-butyl alcohol. Aliquots (0.50 mL) of the combined filtrates were titrated in water (pH meter) against 0.105 N hydrochloric acid, and the *tert*-butyl alcohol solution found to be 0.70 M in guanidine. Solutions of guanidine in methanol, ethanol, and 1-butanol were similarly prepared. Concentrations were adjusted by evaporation or additions of solvent followed by titrations.

Solutions of tetramethylguanidine were prepared by adding the neat liquid to the desired solvent, and titrating aliquots to determine concentrations.

A solution of tetrabutylammonium hydroxide in *tert*-butyl alcohol was prepared as follows. A 1-in. diameter column of anion-exchange resin Dowex 1-X8 (100–200 mesh) of 100 mL wet (water) volume was prepared and washed with 5 L of 10% aqueous solution of NaOH (the first 200 mL were backwashed up the column). The column was washed with distilled water to a pH of 7, and then with *tert*-butyl alcohol ($n^{26}D$ 1.3849) until the column eluate was $n^{26}D$ 1.3835. A warmed solution of 25 g of tetrabutylammonium iodide in 200 mL of *tert*-butyl alcohol was passed through the column warmed by a heating tape. The column was eluted with 120 mL of the alcohol to give 320 mL of solution which was evaporated under vacuum to 110 mL. Titration of aliquots of the *tert*-butyl alcohol solution in water with hydrochloric acid in water indicated the alcohol solution to be 0.052 M. It was stored at −1 °C.

Tribenzo-27-crown-9 (8) from Ether Bisphenol 9 and Ditosylate 10 (Procedure 1). To a stirred mixture of 1.04 g (9.3 mmol) of potassium *tert*-butoxide in 50 mL of refluxing THF under nitrogen was added dropwise (1 h) a solution of 1.34 g of **9** (4.6 mmol) and 2.80 g (4.7 mmol) of **10.** The mixture was refluxed for 48 h, cooled, neutralized with aqueous hydrochloric acid, and filtered from salt. The filtrate was evaporated under vacuum and dissolved in CH_2Cl_2, and the solution was washed twice with 40% methanol in water (v), 0.5 M in KOH to wash out phenols. The solution was washed with brine, dried and evaporated, and the residue was chromatographed on 60 g of silica gel. The product was eluted with 0.5% ethanol in CH_2Cl_2 and sublimed at 160 °C at 50 μm to give 0.600 g (24%) of **8,** mp 91–92 °C. Recrystallization of this material from absolute ethanol gave material, mp 93.5–94.5 °C, M^+ at *m/e* 540, and ^1H NMR spectrum at δ 6.9 (s, 12, ArH), 4.0 (m, 24, CH_2CH_2). Anal. Calcd for $C_{30}H_{36}O_9$: C, 66.65; H, 6.71. Found: C, 66.52; H, 6.81.

Substitution of 15 mL of a 0.97 M solution of guanidine in *tert*-butyl alcohol for the potassium *tert*-butoxide in Procedure 1 gave a 14% yield of **8**, mp 91–92 °C.

Benzo-9-crown-3 (6), Dibenzo-18-crown-6 (7), and Tribenzo-27-crown-9 (8) from Catechol and Ethylene Glycol Ditosylate. A representative (not composite) of several procedures is illustrated. To a stirred, refluxing solution under nitrogen of 4.06 g of catechol and 15.5 g of diethylene glycol ditosylate in 320 mL of dry benzene was added dropwise (4 h) 100 mL of 1.07 M guanidine in 1-butanol. After 48 h at reflux the mixture was cooled, neutralized to pH 7 with 10% HCl in water, and evaporated under vacuum. The residue was shaken with water and dichloromethane, the organic layer was washed with water, 5% NaOH in water, and brine, and was dried and evaporated. The residue was crystallized from benzene and the solid was recrystallized from ethanol to give 2.0 g (25%) of **7**,[4a] mp 159–161 °C. The original filtrates were evaporated and the residue was chromatographed on 100 g of silica gel with 50% (v) ether–pentane as the mobile phase. Cycle **6**[4a] was obtained from the first 400 mL of column eluent, and was sublimed at 50 °C (0.05 mm), weight 0.40 g (5%), mp 69–70 °C. Cycle **8** was eluted with 20% pentane in diethyl ether. It was purified by fractional molecular distillation, and was collected at 160 °C (0.05 mm), weight 0.95 g (12%), mp 93.5–94.5 °C, undepressed by admixture with material prepared by procedure 1.

Benzo-27-crown-9 (5). Application of procedure 1 (see above) to catechol and octaethylene glycol ditosylate in equal molar proportions (two of *t*-BuOK) gave **5** in 21% isolated yield, mp 69–70 °C (from ethanol–ether); the mass spectrum M^+, *m/e* 444; ^1H NMR δ 6.85 (s, 4, ArH), 4.0 (m, 32, CH_2CH_2). This reaction was not monitored for

consumption of catechol as was run 1 in Table I, and the lower yield probably reflects incomplete reaction and losses associated with isolation, particularly the extractions and distillations. Anal. Calcd for $C_{22}H_{36}O_9$: C, 59.44; H, 8.16. Found: C, 59.38; H, 8.28.

2,2′-Binaphtho-29-crown-9 (14). To 10 mL of a solution of 9.7 mmol of guanidine in *tert*-butyl alcohol was added 50 mL of dry THF and the solution was heated to reflux under nitrogen. To this stirred solution was added dropwise (2 h) a 60-mL solution containing 0.85 g (2.9 mmol) of 2,2′-dihydroxy-1,1′-binaphthyl and 2.0 g of octaethylene glycol ditosylate in THF. After 20 h at reflux the mixture was cooled, acidified (10% aqueous HCl) to pH 2, and evaporated under vacuum. The residue was shaken with CH_2Cl_2 and water, the organic layer was washed with 10% aqueous NaOH, 5% KOH in 50% CH_3OH-H_2O (v), and dried, and the solvent was evaporated under vacuum. The residue was chromatographed on 100 g of Alumina (MCB, activated, 80–325 mesh) and the product eluted with ether (first five 200-mL fractions). The product was molecularly distilled at 215–220 °C (100 μm) to give 0.46 g (25%) of **14**, whose mass spectrum gave M^+ at *m/e* 620, and whose ^1H NMR spectrum gave δ 8.0 (m, 4, ArH), 7.3 (m, 8, ArH), 4.3 (m, 4, $ArOCH_2$), and 3.7 (m, 28, CH_2OCH_2). Anal. Calcd for $C_{36}H_{44}O_9$: C, 69.65; H, 7.14. Found: C, 69.35; H, 7.08.

2,2′-Binaphtho-17-crown-5 (11), 2,2′-Binaphtho-20-crown-6 (12), and 2,2′-Binaphtho-23-crown-7 (13). The procedure is illustrated with the preparation of **12**. A mixture of potassium *tert*-butoxide (2.36 g), 3.00 g of 2,2′-dihydroxy-1,1′-binaphthyl, and 5.72 g of pentaethylene glycol ditosylate in 140 mL of dry THF was stirred under nitrogen at reflux for 5 h, and evaporated under reduced pressure. The residue was shaken with water and CH_2Cl_2 and the organic layer was washed with brine, dried, and evaporated under reduced pressure to give 6.1 g of a brown oil, which was chromatographed on alumina. The product (**12**) was eluted with ether to give 2.90 g (60%), mp 130–130.5 °C: mass spectrum M^+ at *m/e* 488; ^1H NMR δ 7.83 (m, 4, ArH), 7.26 (m, 8, ArH), 4.04 (m, 4, $ArOCH_2$), and 3.5 (complex m, 16, CH_2OCH_2). Anal. Calcd for $C_{30}H_{32}O_6$: C, 73.75; H, 6.60. Found: C, 73.88; H, 7.76.

Compound **11** was prepared similarly from 2,2′-dihydroxy-1,1′-binaphthyl and tetraethylene glycol ditosylate in 45% yield, mp 107–108.5 °C. Anal. Calcd for $C_{28}H_{28}O_5$: C, 75.68; H, 6.31. Found: C, 75.82; H, 6.28.[20] Compound **13** was prepared similarly from 2,2′-dihydroxy-1,1′-binaphthyl and hexaethylene glycol ditosylate in 39% yield, mp 110–111 °C.[21] Anal. Calcd for $C_{32}H_{36}O_7$: C, 72.16; H, 6.81. Found: C, 72.04; H, 6.87. Substitution of tetrabutylammonium hydroxide for potassium *tert*-butoxide in the preparation of **11** reduced the yield to about 20%.

***tert*-Butylammonium Hexafluorophosphate and Perchlorate.** Hexafluorophosphoric acid diethyl etherate was added to ether–CH_2Cl_2 in a Teflon beaker and was vigorously stirred while the solution slowly was titrated (aliquots in water) to pH 6.5 with a dry ether solution of *tert*-butylamine (freshly distilled from KOH). The solution was evaporated and dried at 25 °C for 24 h at 0.1 mm to give the salt as a hygroscopic solid, mp 114–124 °C (open capillary).[22]

Anhydrous HCl was passed through a solution of 18.3 g of *tert*-butylamine (freshly distilled from KOH) in 350 mL of anhydrous diethyl ether at 10 °C. The solution was stirred (2 h) and evaporated under vacuum, and the solid residue was dried at 0.1 mm at 25 °C for 24 h. This solid was dissolved in 500 mL of 1:1 (v) $CHCl_3$–CH_3CN. To this solution was added 29.4 g of anhydrous NH_4ClO_4. The resulting slurry was stirred for 24 h at 25 °C and filtered, and the filtrate was evaporated. The solid residue was recrystallized from chloroform to give 21.6 g (50%) of *t*-$BuNH_3ClO_4$ as white needles, mp 129–130 °C. Anal. Calcd for $C_4H_{12}ClNO_4$: C, 27.67; H, 6.97. Found: C, 27.77; H, 6.97.

Determination of Relative Concentrations of Hosts and *tert*-Butylammonium Salts in $CDCl_3$ Phase in Distributions Between $CDCl_3$ and D_2O. Cycle **1** and open-chain model compound **2** were used in the following distribution experiments. In a 3-mL centrifuge tube at 24 °C was placed 0.3 mL of a 1.0 M solution of *t*-$BuNH_3ClO_4$ in D_2O, and 0.6 mL of a 0.125 M solution of host in $CDCl_3$. The stoppered tube was stirred vigorously with a magnetic bar and centrifuged to cleanly separate the layers, and the lower $CDCl_3$ layer was transferred by syringe to an NMR tube. The relative amounts of guest and host in $CDCl_3$ were determined by integrations of the *t*-Bu proton singlet and the total aromatic protons. The presence of hosts in the D_2O phase could not be detected in the ^1H NMR spectra of those phases.

These measurements allow values of the parameter R to be determined, which is the mole ratio of guest to host in the chloroform phase. If $A^+X^-_i$ is the initial amount of guest salt used, and the equilibrium amount of guest cation in D_2O is $A^+_{D_2O}$, of complexed salt in $CDCl_3$ is $A^+{\cdot}H{\cdot}X^-_{CDCl_3}$, of complexed cation in D_2O is $A^+{\cdot}H_{D_2O}$, and of uncomplexed salt in $CDCl_3$ is $A^+X^-_{CDCl_3}$, then on a mole basis, $A^+X^-_i = A^+_{D_2O} + A^+{\cdot}H{\cdot}X^-_{CDCl_3} + A^+{\cdot}H_{D_2O} + A^+X^-_{CDCl_3}$. But $A^+_{D_2O} + A^+{\cdot}H{\cdot}X^-_{CDCl_3} \gg A^+{\cdot}H_{D_2O} + A^+X^-_{CDCl_3}$. Thus $A^+_{D_2O} = A^+X^-_i - A^+{\cdot}H{\cdot}X^-_{CDCl_3}$. Similarly if H_i is the initial amount of host used, and the equilibrium amount of uncomplexed host in $CDCl_3$ is H_{CDCl_3}, of complexed host in $CDCl_3$ is $A^+{\cdot}H{\cdot}X^-_{CDCl_3}$, of host in water is H_{D_2O}, and of complexed host in water is $A^+{\cdot}H_{D_2O}$, then on a mole basis, $H_i = H_{CDCl_3} + A^+{\cdot}H{\cdot}X^-_{CDCl_3} + H_{D_2O} + A^+{\cdot}H_{D_2O}$. But $H_{CDCl_3} + A^+{\cdot}H{\cdot}X^-_{CDCl_3} \gg H_{D_2O} + A^+{\cdot}H_{D_2O}$. Thus $H_i = H_{CDCl_3} + A^+{\cdot}H{\cdot}X^-_{CDCl_3}$ and $[H_i]_{CDCl_3} = [H]_{CDCl_3} + [A^+{\cdot}H{\cdot}X^-]_{CDCl_3}$. Equation 1 expresses R in terms of a ratio of measured concentrations in the chloroform phase. Equation 2 expresses $[H]_{CDCl_3}$ in terms of the measured quantities $[H_i]_{CDCl_3}$ and R.

$$R = \frac{A^+ \cdot H \cdot X^-}{H_i} = \frac{[A^+ \cdot H \cdot X^-]_{CDCl_3}}{[H]_{CDCl_3} + [A^+ \cdot H \cdot X^-]_{CDCl_3}} = \frac{[A^+ \cdot H \cdot X^-]_{CDCl_3}}{[H_i]_{CDCl_3}} \quad (1)$$

$$[H]_{CDCl_3} = [H_i]_{CDCl_3}(1 - R) \quad (2)$$

The values of R were found to be 0.94 for **1** and 0.025 for **2** in the above distribution experiments that involve *t*-$BuNH_3ClO_4$.

The above relationships allow the concentration of the guest cation in the aqueous phase at equilibrium, $[A^+]_{D_2O}$, to be expressed in terms of measurable values. Since $A^+{\cdot}H{\cdot}X^-_{CDCl_3} = RH_i$, then $A^+_{D_2O} = A^+X^-_i - RH_i$. If V_{CDCl_3} and V_{D_2O} are the volumes of $CDCl_3$ and D_2O used in determining R values, then $A^+_{D_2O} = V_{D_2O}[A^+]_{D_2O}$, $A^+X^-_i = V_{D_2O}[A^+X^-_i]_{D_2O}$, and $H_i = V_{CDCl_3}[H_i]_{CDCl_3}$. Combining these expressions gives

$$[A^+]_{D_2O} = [A^+X^-_i]_{D_2O} - (V_{CDCl_3}/V_{D_2O})R[H_i]_{CDCl_3} = Q \quad (3)$$

Open-chain model compounds **2** and **3** were used in the following distribution experiments. In a 3-mL centrifuge tube were placed 0.50 mL of a solution of 2 M *t*-$BuNH_3PF_6$ and 4 M $LiPF_6$, and 0.60 mL of 0.125 M host in $CDCl_3$. The stoppered tube was cooled to 0 °C and magnetically stirred vigorously for 3 min at 0 °C. Integrations of the ^1H NMR spectra of the $CDCl_3$ layers (*t*-Bu proton singlet and the total aromatic protons) gave R values of 0.98 for **2** and 0.46 for **3**. The presence of hosts in the D_2O phases could not be detected in the ^1H NMR spectra of these phases.

Estimation of Extraction Constants Between Hosts and *tert*-Butylammonium Salts in $CDCl_3$. From the values of R determined in the last sections, values of K_e (the extraction constant) were estimated. Equations 4 and 5 define K_e in terms of equilibrium concentrations of defined species (see last sections).

$$[H]_{CDCl_3} + [A^+]_{D_2O} + [X^-]_{D_2O} \overset{K_e}{\rightleftharpoons} [A^+ \cdot H \cdot X^-]_{CDCl_3} \quad (4)$$

$$K_e = \frac{[A^+ \cdot H \cdot X^-]_{CDCl_3}}{[H]_{CDCl_3}[A^+]_{D_2O}[X^-]_{D_2O}} \quad (5)$$

Combination of eq 5 with eq 1 and 2 gives eq 6, which expresses K_e in terms of measurable quantities. When $[A^+]_{D_2O} = [X^-]_{D_2O}$ (e.g., when X^- was ClO_4^-), then eq 6 and 3 give eq 7. When $[A^+] \neq [X^-]$ because of added common ion salt to the aqueous phase for salting out purposes (e.g., when $LiPF_6$ was added and X^- was PF_6^-), then $[X^-]_{D_2O} = [A^+]_{D_2O} + [LiPF_6]_{D_2O}$ where $[LiPF_6]_{D_2O}$ is the concentration of $LiPF_6$ added to the D_2O phase. In this case, eq 6 and 3 give eq 8. Transfer of $LiPF_6$ into the $CDCl_3$ phase either in the absence or presence of these hosts was negligible.[23]

$$K_e = \frac{R[H_i]_{CDCl_3}}{[H]_{CDCl_3}[A^+]_{D_2O}[X^-]_{D_2O}} = \frac{R}{(1 - R)[A^+]_{D_2O}[X^-]_{D_2O}} \quad (6)$$

$$K_e = R/(1 - R)Q^2 \quad (7)$$

$$K_e = R/(1 - R)Q\{Q + [LiPF_6]\} \quad (8)$$

The following assumptions were made in the derivation of eq 1–8: (1) in water, the guest salt was dissociated; (2) in chloroform, the guest salt was associated but monomeric; (3) essentially no host was distributed into the water layer; (4) all the guest salt in the chloroform layer formed a 1:1 complex with the host.

Gas Liquid Partition Chromatographic Determination of Yields in

Runs 1–7. An F and M Model 720 GLC machine was fitted with either columns A or B composed of SE-30 stationary phase absorbed on non-acid-washed Chromosorb W, 80–100 mesh. Helium was the carrier gas at a flow rate of 60 mL/min. Column A was 2 ft by 0.25 in. i.d. and was 30% by weight stationary phase. Column B was 1 ft by ⅜ in. i.d., and was 10% by weight stationary phase. Compound **5**[4a] (retention time, 4 min) was measured against benzophenone (retention time, 11 min) as an internal standard on column A, injection temperature 300 °C, detector temperature at 310 °C, column temperature 140 °C. Column B was used for **4, 6,** and **7** at injection temperatures of 350 °C and detector temperatures of 370 °C. Cycle **4** (retention time 10 min) was measured against cycle **11** as a standard (retention time 36 min) with a 260 °C column temperature. Cycle **6** (retention time 38 min) was measured against cycle **12** as a standard (retention time 16 min) with a 300 °C column temperature. Cycle **7** (retention time 12 min) was measured against cycle **11** as a standard (retention time 24 min) with a 275 °C column temperature. Calibration curves of the weight ratios vs. GLC peak area ratios for known mixtures were prepared, and linearity was observed for the detector response over the entire range used for analysis. All peaks were separated by base lines, and their integrated areas determined with a polar planimeter. For the analysis of each reaction mixture, duplicate aliquots between 1 and 10 mL, depending on the expected yield, were mixed with 10–60 mg of the appropriate internal standard, and injections of 30–100 μL were made into the machine. Different amounts of internal standard were added to each aliquot; two injections of each aliquot were made. Each yield reported in Table I represents four analyses, and (average deviation)/(average yield) × 100% < 5% in each run.

In runs 1–7, the basic solutions were added via syringes and the ditosylate solutions were added dropwise to THF solutions stirred at reflux under nitrogen. All reactions were run until all catechol was consumed (TLC), and the yields of Table I are based on catechol. Run 1 involved 0.11 g (1 mmol) of catechol in 42.5 mL of THF, 2.5 mL of *t*-BuOH containing 2.2 mmol of *t*-BuOK, and 0.678 g (1 mmol) of octaethylene glycol ditosylate. After 24 h at reflux, a further 1 mL of *t*-BuOH containing 1.1 mmol of *t*-BuOK and 5 mL of THF were added, and the reaction mixture was refluxed for another 12 h. It was then cooled, acidified with HCl–H_2O to pH 2, and solvent was evaporated. The residue was distributed between CH_2Cl_2 and H_2O. The organic layer was dried and evaporated, and the residue was dissolved in exactly 10 mL of dimethylformamide. This solution was used for GLC analysis. Run 2 was initially identical with run 1 except guanidine was substituted for *t*-BuOK. Since the reaction was not over after 36 h, over the subsequent 48 h of reflux 4.4 mmol of additional base and 0.46 g (0.6 mmol) of additional octaethylene glycol ditosylate in 25 mL of 4:1 (v) THF–*t*-BuOH were added in two equal installments, and the product was isolated as before. Run 3 was identical with run 2 except tetramethylguanidine was substituted for *t*-BuOK. After the initial 36 h, during the subsequent 48 h of reflux, was added in three equal installments 5.1 mmol of additional base, 1 mmol of octaethylene glycol ditosylate, and 37.5 mL of 4:1 (v) THF–*t*-BuOH. Runs 4, 5, and 7 were made as follows. A mixture of catechol, 2.03 g or 18.7 mmol, in 50 mL of 1:1 (v) THF–*t*-BuOH, 13 mmol of base in 50 mL of *t*-BuOH, and 3.9 g (9.4 mmol) of diethylene glycol ditosylate in 50 mL of THF was refluxed for 5 h. Solutions of base and ditosylate equivalent to those initially used were added, and the mixture was refluxed for an additional 12 h. Again solutions of base and ditosylate equivalent to those initially used were added, and an additional 5 h of reflux completed the reaction. Run 6 was not complete after being subjected to this procedure (TLC), so at 12-h intervals at reflux were added 25 mL of 1:1 THF–*t*-BuOH containing 13 mmol of base and an equivalent basic solution plus 2 g (4 mmol) of additional diethylene glycol ditosylate in 25 mL of THF, respectively. The final mixture was refluxed for an additional 8 h. The products for runs 4–7 were analyzed identically. The cooled reaction mixture was acidified to pH 2 with 10% HCl in water, evaporated under vacuum, and the residue was shaken with CH_2Cl and water. The organic layer was water washed, dried, adsorbed on 40 g of silica gel, and chromatographed on this and an additional 35 g of silica gel. Ether containing 2–4% ethanol eluted the cyclic products, which as a whole were dissolved in 100 mL of dimethylformamide and GLC analyzed. Table I records the results.

Guanidinium Tetraphenylborate. Sodium tetraphenylborate (0.342 g or 1 mmol) was dissolved in a minimum amount of water and mixed with 0.095 g (1 mmol) of guanidinium chloride dissolved in a minimum amount of water. The salt that separated was collected, water washed, and dried at 25 °C for 24 h under high vacuum, mp 170–172 °C.

Complexation Experiments Between Cyclic Ethers and Guanidine Salts. The ability of host compounds to solubilize guanidine salts in $CDCl_3$ was measured by ^1H NMR. A solution of 20–40 mg of host in 0.70 mL of $CDCl_3$ (0.064–0.12 M) was shaken for 5 min with 2 equiv of the solid salt in a stoppered vial. The solution was filtered into an NMR tube, Me_4Si was added, and the NH protons at δ 6.7 (br s) in the spectrum were integrated against the ArH protons. Complexation was accompanied by loss of resolution in the methylene absorption of the cycles. With cycles **5, 7, 8,** and guanidinium tetraphenylborate, 1 mol of cycle solubilized 1 mol of salt within error (±0.1), whereas **6** failed to solubilize a detectable amount. Cycles **5–8** in $CDCl_3$ failed to solubilize any detectable amounts of guanidine tosylate or thiocyanate salts (0.05 mol of salt/mol of cycle).

Solutions (0.8 mL) of cycles **5–8** (0.08 M) were shaken in a vial for 2 min with 5.5 M solutions of guanidinium thiocyanate in water (0.35 mL). The layers were separated, and the ^1H NMR spectra of the $CDCl_3$ solution were recorded. Integration of the NH and ArH signals indicated that cycle **5** solubilized 1.0 mol of salt, and the other cycles solubilized <0.05 mol.

Crystalline complexes were obtained in the following experiments. An aqueous solution 4 M in $LiPF_6$ (adjusted to pH 5 with LiOH) and 1.2 M in guanidinium hydrochloride was prepared. A 0.10 M solution of cycle **7** in $CHCl_3$ was prepared, and 0.8 mL of this solution was shaken with 0.2 mL of the aqueous solution. A precipitate formed at the interface, which was washed with water and chloroform and dried at 78 °C (100 μm), mp 150–200 °C dec. Anal. Calcd for $C_{43}H_{72}F_{18}N_9O_{15}P_3$: C, 37.16; H, 5.22. Found: C, 37.20; H, 4.88. Analysis showed no chlorine. The composition of the complex appears to be about 2:3:3 cycle–guanidinium hexafluorophosphate–water.

A 0.05 M solution of cycle **8** in $CHCl_3$ (0.8 mL) was shaken with 0.4 mL of the 4 M $LiPF_6$ and 1.2 M guanidinium hydrochloride solution. The precipitate that formed at the interface was washed with water and chloroform, and was recrystallized from chloroform and dried at 25 °C in a desiccator, mp 110 °C dec. Anal. Calcd for $C_{63}H_{90}F_{18}N_9O_{18}P_3$: C, 44.61; H, 5.34. Found: C, 44.83; H, 5.35. Analysis showed no chlorine. The composition of the complex appears to be 2:3 of cycle–guanidinium hexafluorophosphate.

A 0.08 M solution of cycle **5** in $CDCl_3$ (0.8 mL) was shaken with 0.8 mL of a 0.5 M aqueous solution of $LiPF_6$ (pH adjusted to 5 with LiOH) that was 0.5 M in guanidinium chloride. The ^1H NMR spectrum of the $CDCl_3$ solution indicated 0.83 mol of guest/mol of host was extracted. The chloroform solution was allowed to evaporate, and the crystals that separated were washed with chloroform and dried at 25 °C in a desiccator, mp 130–140 °C dec. Anal. Calcd for $C_{23}H_{44}F_6N_3O_{10}P$: C, 41.32; H, 6.60. Found: C, 41.11; H, 6.73. This complex corresponds to the composition 1:1:1 of cycle–guanidinium hexafluorophosphate–H_2O.

Complexation Between Cycles and Arenediazonium or Benzoyl Salts. Many of the arenediazonium tetrafluoroborates were prepared as before.[15a] Our yields and melting points followed those of the literature.[18] The salt, 2,6-dimethylbenzenediazonium tetrafluoroborate was unstable, yield 57%, mp 80–80.5 °C dec. In $(CD_3)_2CO$ solution, nitrogen evolution was too high for ^1H NMR to be recorded. The 3,4-dimethyl salt (65%) gave mp 89.5–90 °C dec: ^1H NMR $(CD_3)_2CO$) δ 2.40 (s, 3, CH_3), 2.50 (s, 3, CH_3), 7.72 (d, 1), and 8.45 (d, 1, 5,6-ArH, J_{AB} = 9 Hz), 8.48 (s, 1, 2-ArH).

Complexation experiments were conducted as follows. A mixture of 0.5 mL of $CDCl_3$ and a large excess of the arenediazonium salt was shaken in a vial and the ^1H NMR recorded. Only trace amounts of the salts were detectable. About 50-mg samples of potential host compounds were dissolved in 0.5 mL of $CDCl_3$ and shaken in a vial with a large excess of the arenediazonium salt. The mixture was filtered into an NMR tube through glass wool, and its ^1H NMR spectrum recorded. Integrations of the OCH_2CH_2O protons of the host against the ArH or CH_3 groups of the arenediazonium salts provided estimates of the ratios of guest to host in solution.

The same procedure was used for benzoyl hexafluorophosphate, except all operations were carried out in a drybox except the taking of the spectra. When 2,2′-binaphtho-20-crown-**6** (**12**) was host, after complexation the mixture was quenched with 10% NaOH in water. The cycle was recovered by extraction and chromatography on alumina, and its ^1H NMR spectrum in the ArH region was only slightly altered, indicating that only a small amount of benzoylation had occurred. Benzoylation of a small amount of material did occur, however,

as shown by the fact that the compound gave a positive test with 2,4-dinitrophenylhydrazine reagent.

Attempts to Form Host Collared Diazo Compounds. Treatment of *p*-methylbenzenediazonium tetrafluoroborate (**16**) complexed 1:1 with cycle **12** in CH_2Cl_2 at −75 °C with the following reagents gave the following products: *p*-tolyllithium in ether gave six products (TLC), only *p*-$CH_3C_6H_4N_2C_6H_4CH_3$-*p* (4%) being identified; *N,N*-dimethylaniline in CH_2Cl_2 gave (85%) *p*-$CH_3C_6H_4N_2C_6H_4N(CH_3)_2$-*p*. Di-*p*-tolylzinc in ether–tetrahydrofuran added to a solution at −10 °C of 1:1 **16** and 18-crown-6 in CH_2Cl_2 gave 40% *p*-$CH_3C_6H_4N_2C_6H_4CH_3$-*p* and about five other products. Similar results were obtained with *p*-chloro- and *p*-methoxybenzenediazonium salts. No evidence of host-collared diazo compounds could be detected among any of these products using ^1H NMR and chromatographic behavior as criteria.

References and Notes

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Intramolecular Oxidative Coupling of Diphenolic, Monophenolic, and Nonphenolic Substrates

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Abstract: A series of diphenolic, monophenolic, and nonphenolic 1,3-diarylpropanes were used as model substrates in a search for efficient new methods for intramolecular oxidative coupling. Vanadium oxytrichloride was found to be an effective oxidant for all three types of substrate under appropriate conditions. Thallium(III) trifluoroacetate and silver(II) trifluoroacetate gave good yields of monophenolic coupling.

It has long been recognized that an intramolecular oxidative phenol coupling reaction (Scheme I) serves as the key step in the biosynthesis of many classes of natural products,[1] and that the nonenzymic analogue of this transformation can lead to elegantly simple laboratory syntheses of these compounds.[2] However, full realization of this synthetic potential has been limited by the low yields usually encountered when the coupling step is carried out in the laboratory.[3] The major problems associated with making this approach synthetically useful are (1) generating the electron-deficient intermediate (Scheme I) under conditions that minimize polymerization resulting from intermolecular coupling of either the substrate or the intramolecularly coupled product, and (2) controlling the sites

Scheme I