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Host-Guest Chemistry

Complexes between organic compounds simulate the substrate selectivity of enzymes.

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The remarkable abilities of enzymes to catalyze organic reactions and regulate their occurrence challenges the chemist to devise simpler organic compounds that will perform similar functions. Only recently have the structures of the active sites of enzymes become well enough understood (*1*) to provide models of the synthesis of nonpeptide organic systems that might simulate enzymatic behavior. This article describes the genesis of our research on what we will call "host-guest chemistry."

The first step in enzymatic catalysis is the formation of highly selective molecular complexes that orient the reactants and catalysts. Complexes form at very high rates, and frequently are in equilibrium with their components. In later stages, covalent bonds are made and broken. Finally decomplexation occurs. Competitive complexation-decomplexation processes often account for enzyme inhibition and for enzymatic regulatory processes in cells.

Modified cyclodextrins have been studied as models for enzyme systems (*2, 3*). Cyclodextrins are natural products composed of six to eight glucopyranoside units bound head to tail in cycles at their 1- and 4-positions. The ether oxygens and hydrogens turn inward, and the hydroxyl groups turn outward in these sleeve-shaped compounds. The lipophilic hole of the six-unit cyclodextrin nicely accommodates a benzene ring. In the cyclodextrin enzyme model, this lipophilic hole is used to bind the lipophilic part of a substrate molecule. Catalytic sites are constructed by derivatizing the hydroxyl groups at the top or bottom of the sleeves. Some stereospecificity has been observed both in complexation and catalysis in such systems in water as medium (*3*).

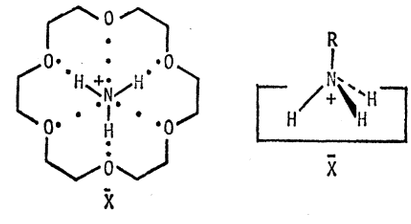
Since complexation and decomplexation are the first and last steps in an enzymatic reaction, we decided first to study complexation. In host-guest chemistry, the host molecule is the larger, and the guest molecule is the smaller of the two. The host molecule must "recognize" by complexing best those guest molecules that contain the array of binding sites and steric features that complement those of the host. The self-evident postulate that two objects cannot occupy the same space at the same time indicates that host and guest must be compatible with respect to shape if they are to complex. The simple attraction of positive and negative charges accounts for much of the binding between host and guest molecules.

The stereoelectronic relationships between the two-dimensional objects of Fig. 1 illustrate these ideas. If object A is the host and contains a cavity shaped as drawn with charges or dipoles placed as shown on the edge of the cavity, only object B can serve as a guest. Ion-pairing, ion-to-dipole, and dipole-to-dipole binding forces would hold B to A. Object C is the mirror image of B, and cannot be moved in the plane into the cavity for steric reasons. Object D will fit the cavity sterically, but the electrostatic binding sites of host and potential guest are mislocated. Object E will fit the cavity sterically, the electrostatic binding sites of host and potential guest are positioned properly, but are of a noncomplementary charge type. Object F possesses a shape similar to the cavity and possesses properly positioned binding sites of complementary charge type, but is larger than the cavity.

The first part of this article indicates how molecular complexes between organic molecules and ions are structured. In the second part, host molecules that distinguish between enantiomeric guest molecules are described. The third part deals with the molecular basis for designing an amino acid–resolving machine. The fourth part describes host molecules designed for metal cations.

Structure and Binding in Molecular Complexes

The "Pedersen Papers," the first of which appeared in 1967, demonstrated the feasibility of synthesizing large cyclic polyethers (a type of crown compound) composed of ethyleneoxy units (*4, 5*). The ability of these systems to complex and lipophilize the alkali metal cations was demonstrated (*4, 5*). The simple crown compounds were also found to complex ammonium and alkylammonium salts (*4, 5*). A close examination of space-filling, scale molecular models (CPK; Corey, Pauling, Koltun) of an alkylammonium ion complexed to a cyclic ether composed of six ethyleneoxy units suggests the complex has structure **1**. Each oxygen



1a (R group not included) **1b**

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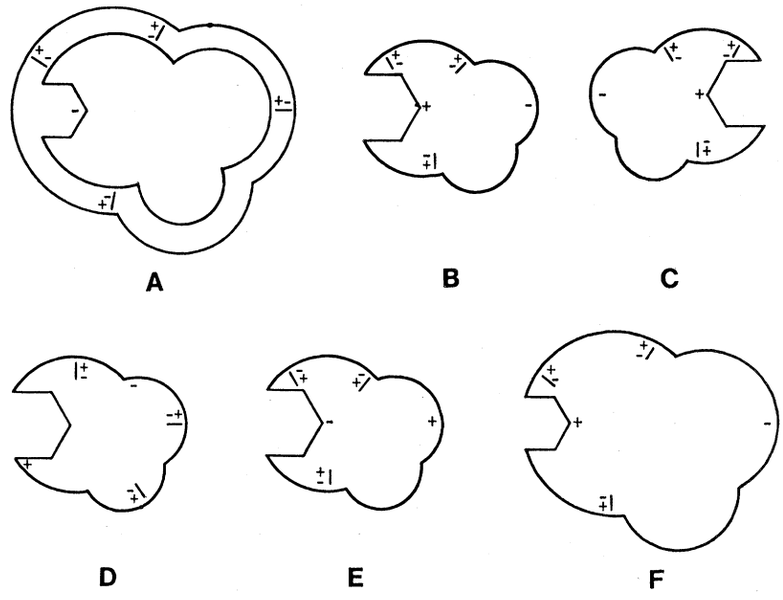


Fig. 1. Stereoelectronic relations between two-dimensional objects.

atom possesses two unshared electron pairs. All six oxygens of the cyclic ether are turned inward to provide dipole-to-ion binding forces between host and guest. Three hydrogen bonds and three oxygen-to-nitrogen interactions are visualized in structure **1a**. The ethylene units are turned outward and form a lipophilic disk around the hydrogens of the hydrophilic ammonium ion. The host molecule is roughly planar, and the nitrogen of the guest is situated slightly out of that plane at the apex of a shallow tripod. The alkyl (R) group attached to nitrogen extends along an axis perpendicular to the plane of the cyclic ether, as indicated in **1b**. The ammonium ion can complex at either of the two faces of the cyclic polyether. The counterion, x^-, in nonpolar media probably ion-pairs N^+ from the face opposite that occupied by the ammonium ion.

The cyclic ether part of complex **1** provides a good basic unit for complexing alkylammonium ions, but additional units are needed if host molecules are to have more shape and additional binding sites. The rigid binaphthyl unit incorporated into cyclic ether **2** provides useful structural features (*6*). The two naphthalene rings occupy different planes, each of which is perpendicular to the best plane of the cyclic ether. One of the naphthalene rings forms a wall that extends along the side of, and outward from, one face of the cyclic ether. The other naphthalene ring provides a wall along the side of, and outward from, the opposite face of the cyclic ether. Side chains attached at the 3-positions of these naphthalene rings extend along the side of, or over the faces of, the cyclic ethers (*7*). The cross section of the binaphthyl unit is shaped like a pair of pliers. Their attached oxygen atoms can be spaced as close together as in an ethylene glycol unit, or as far apart as in a propylene glycol unit. Partial rotation about the naphthalene-naphthalene bond provides this limited flexibility. However, in **2** the naphthalene rings do not rotate past each other except above 200°C (*8*).

Structure **2** as a basic unit provides a means of building counterions into host molecules to ion-pair with guest cations. In **3** a side chain has been attached at the 3-position of one of the naphthalene rings. The side chain terminates in a carboxyl group whose derived anion can rest comfortably centered just below the hole of the macrocycle (*7*).

Experimentally, a chloroform solution of **2** (0.05*M*) extracts *tert*-butylammonium hexafluorophosphate (0.1*M*) from an aqueous solution containing lithium hexafluorophosphate as a "salting out" agent (2*M*). The complex formed in the chloroform layer (**4**) is one-to-one, cyclic ether to salt. When washed with pure water, the chloroform solution retains the cyclic ether, but the salt passes into the water layer. A chloroform solution of **3** complexes *tert*-butylamine on a one-to-one molecular basis to form **5**, and the complex is undisturbed when the chloroform solution is washed with water (*7*). The "built-in" counterion in **5** stabilizes that complex relative to **4**, but not so well that the rates of complexation-decomplexation are slowed down enough to be observed at −40°C in proton magnetic resonance experiments (*9*). Two other types of host-guest complementary relationships between organic compounds are exemplified in **6** and **7**. Structure **6** is postulated for the observed one-to-one complex in chloroform between guanidinium tetraphenylborate and the cyclic ether composed of nine ethyleneoxy units (*10*). Molecular models (CPK) of **6** suggest a wreathlike structure in which the planar guanidinium ion is hydrogen-bonded to six oxygens of the cyclic ether. The remaining three oxygens provide direct dipole-to-ion interactions with the three nitrogens that share the positive charge.

Although aryldiazonium tetrafluoroborate salts are ordinarily insoluble in nonpolar media, cyclic ether **2** solubilizes these salts by complexation on a one-to-one molar basis in chloroform (*11*). Structure **7** for the complexes formed is suggested by an examination of molecular models (CPK). In **7**, the rod-shaped diazonium ion (the guest) carrying a positive charge is closely embraced by the six oxygens of the cyclic ether (the host). The six ion-dipole interactions in **7** are strong enough to bind host to guest. When the hole of the cyclic ether is decreased in size by one ethyleneoxy unit as in **8**, complexation is not observed. Molecular models indicate that the hole is too small to accommodate the $-N^+ \equiv N$ moiety; and complexation is not observed when open-chain ether **9** is substituted for its cyclic counterpart (**2**). Apparently the hole must be formed prior to complexation, and the diazonium ion is not able to organize the side chains of **9** when they are not joined to form a cyclic structure. Substitution by two methyl groups of the ortho positions of benzenediazonium tetrafluoroborate sterically prevented that salt from complexing **2**. However, the 3,4-dimethylbenzenediazonium salt gave a one-to-one complex. Complexes such as **7** exhibited pi-pi charge-transfer colors. These suggest that the electron-deficient benzene ring of the guest is somewhat pi-complexed to the electron-rich naphthalene rings of the host (*11*), although this interaction is not a prerequisite for complexation.

These results demonstrate feasibility for synthesizing host molecules that will bind polar guest molecules in a highly structured way. These host

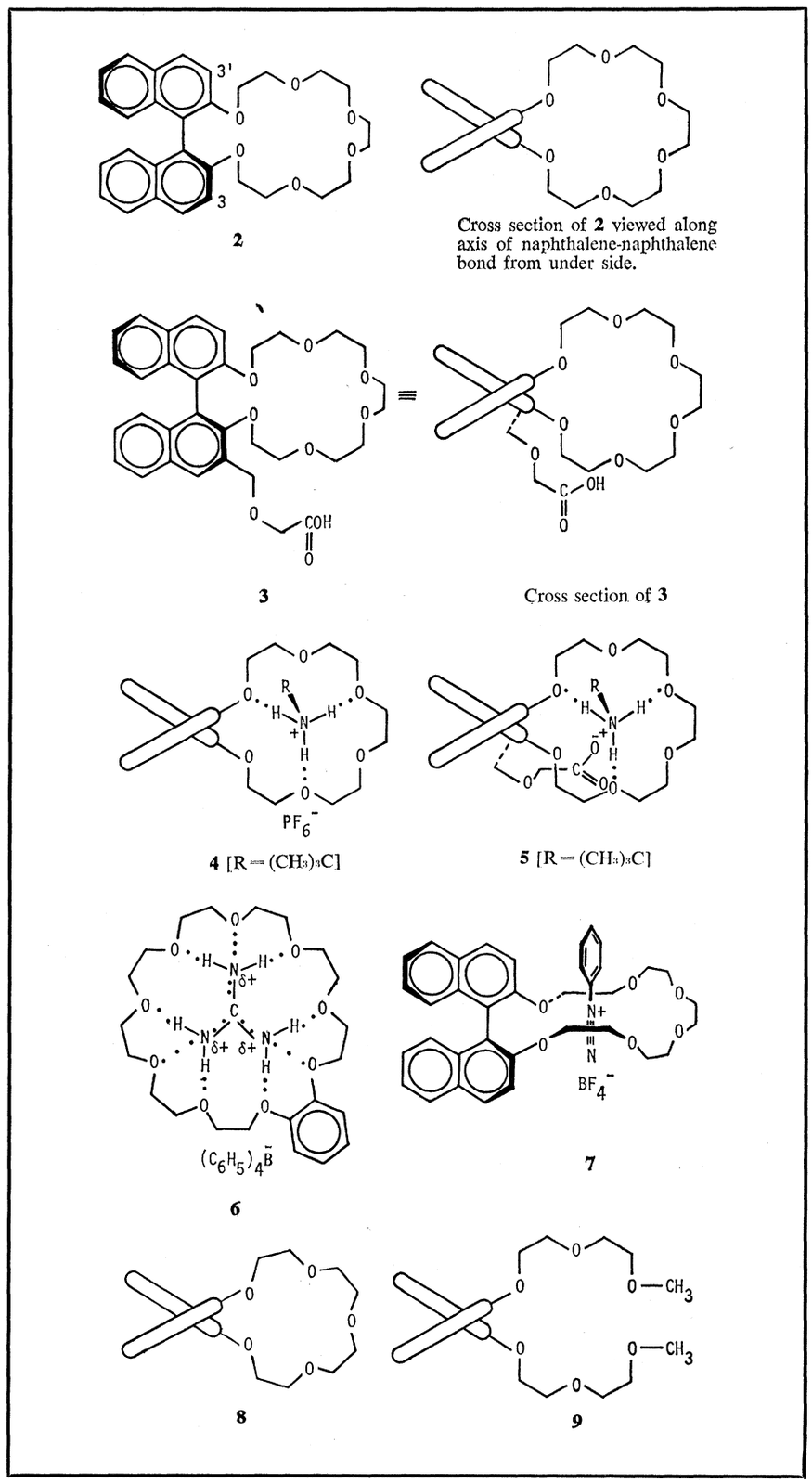
molecules differ from the cyclodextrins (*2*, *3*) in the following ways. The cyclodextrins are natural products with lipophilic insides and hydrophilic outsides, and their complexes are limited to water as medium. Our host molecules tend to be more hydrophilic in their insides and lipophilic on their outsides, and complexation can be observed in a variety of media. The cyclodextrins can be modified chemically to a limited extent to arrange for complementary binding features between host and guest. Our host molecules are synthetic, and therefore capable of complete design of complementary binding features between host and guest.

Host Molecules that Distinguish between Enantiomers in Complexation

A characteristic of many enzyme systems is their ability to distinguish between enantiomers in reaction catalysis. The active sites of the enzymes are asymmetric, and two enantiomers are complexed differentially and react at different rates. Enzyme-substrate complexes are diastereometric, possess different free energies, and have different potentialities for reaction. We describe in this section how a synthetic, optically active host molecule was designed, prepared, and found to distinguish in complexation between enantiomers of a racemic guest molecule (*8*). The optically active host molecule was then used to separate completely the enantiomers of the guest molecule by liquid-liquid extraction (*12*).

Examination of CPK molecular models of complexes formed between the optically active cyclic ether (*SS*)-**10** and the enantiomers of α-phenylethylamine salts [(*R*)-**11** and (*S*)-**11**] indicate that the steric relationships between (*SS*)-**10** and (*R*)-**11** are more compatible than those between (*SS*)-**10** and (*S*)-**11**. Host molecule (*SS*)-**10** is particularly attractive because of its symmetry properties and shape. The four planes of the four naphthalene rings are perpendicular to the best plane of the oxygen atoms, and form walls along the sides of the macrocycle. Thus the space above, below, and along the sides of the macrocycle is divided by the four walls into four cavities, two above and two below the macrocycle. The two top cavities of (*SS*)-**10** are illustrated in Fig. 2, in which the ethyleneoxy units are omitted for simplicity. These cavities are all chiral (handed or asymmetric) and are all equivalent. This feature eliminates much ambiguity with respect to the structures of the complexes formed between (*SS*)-**10** and (*R*)- or (*S*)-**11**. The same complex is formed when (*R*)-**11** complexes the top or bottom face of (*SS*)-**10**. The same complex results when the phenyl of (*R*)-**11** is placed in any of the four cavities of (*SS*)-**10**.

In practice host cyclic ether (*SS*)-**10** was prepared in an optically pure state, and then dissolved in chloroform. Racemic salt (*R*)(*S*)-**11** was prepared



and dissolved in a 2.5*M* aqueous solution of $NaPF_6$. The two solutions were shaken together at −14°C, and the layers were separated. The chloroform layer was found to contain more than twice as much complex (*SS*)-**10** · (*R*)-**11** as (*SS*)-**10** · (*S*)-**11**. The amine salt, when isolated from the complex, was a mixture of about 67 percent (*R*)-**11** and 33 percent (*S*)-**11** (*8, 13*). As was predicted from examination of molecular models, host molecule (*SS*)-**10** experimentally exhibited chiral recognition toward the enantiomers of **11**, and complexed preferentially the predicted enantiomer, (*R*)-**11**. The concept of chiral recognition underlies such familiar acts as selecting from a pair of gloves, the right-handed glove to put on the right hand.

A total optical resolution of racemic **11** was realized. A 2.5*M* $NaPF_6$ aqueous solution was absorbed into silica of high surface area, and the resulting wetted solid was packed into a chromatographic column to form a stationary "liquid" phase. Racemic **11** was placed at the top of the column. Chloroform-containing host molecule (*SS*)-**10** was passed through the column as a liquid, mobile phase while the column was held at −14°C. The chloroform solution emerging from the bottom of the column was monitored conductometrically. The host molecule eluted the (*R*) enantiomer of the salt (**11**) completely from the column before any of the (*S*) enantiomer appeared (*12*).

Many variants of the general ideas illustrated by these experiments are envisioned. Systems are being devised for thin-layer, solid-liquid, liquid-liquid, and gas-liquid chromatographic optical resolutions. Criteria for optical purity and for determining absolute configuration are being developed.

Molecular Basis for Designing an Amino Acid–Resolving Machine

Both in and out of living systems, amino acids can be converted to proteins. Of the 20 different amino acids that compose proteins derived from animals, 17 conform to the general structural formula (*S*)-**12**. Of these 20 different amino acids, 8 are essential to the diet for optimum growth of higher animals and humans. All of these 8 possess the generalized formula (*S*)-**12**. Balanced diets that include meat provide the essential amino acids, but specialized diets provide amounts

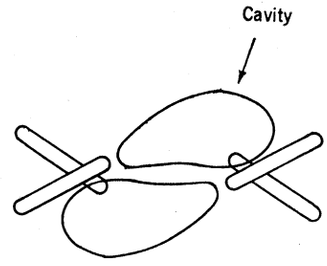


Fig. 2. Cavities above the macrocycle (*SS*)-**10**.

of some of the essential amino acids too small for proper growth. Such diets require supplementation by protein from sources such as soybeans. Synthetic amino acids, or peptides formed from them, also are a possible source. Unlike amino acids derived from natural protein, which possess only the structure (*S*)-**12**, synthetic amino acids are composed of equal mixtures of (*S*)-**12** and (*R*)-**12**. These two formulas and the compounds they represent relate to one another as your right hand relates to your left hand. Only the molecules of structure (*S*)-**12** are dietarily useful directly, and the conventional separation of the left- and right-handed molecules at the end of a synthesis usually depends on tedious fractional crystallizations. A generally useful amino acid–resolving machine would be a welcome device. The molecular basis for design of such a machine is described as it evolved as a concept. The concept has been demonstrated to be experimentally feasible (*14*).

The α-amino acids when neutral are zwitterions (inner salts). They are highly polar, high melting, and insoluble in all but polar solvents. In the crystal lattice, they, in a sense, "complex" one another, whereas in water they are heavily solvated. The ammonium and carboxylate groups provide ideal binding sites for complexation by an appropriately structured host molecule. Cyclic polyethers bind ammonium ions. Carboxylate ions ion-pair with ammonium ions. A secure complex between the ammonium group of an amino acid and a cyclic polyether might form if a carboxyl group attached to the arm of a host polyether is located directly below the hole, the top of which is covered by the ammonium ion. The carboxylate ion of the amino acid might be protonated in the complex, and bound to the host by two hydrogen bonds between the carboxyl of the guest molecule and an appropriately located carboxyl group attached to the host molecule. Even in the vapor phase, acetic acid is somewhat dimerized by such hydrogen bonding. The idealized structure **13** formulates the five hydrogen bonds and ion-pairing that is envisioned as holding the complex together. Structure **13** also contains a rigid, chiral steric barrier that complements the difference in size of the H atom and R groups attached to the asymmetric (starred) carbon of the host amino acid. The arms carrying the two carboxyl groups for convenience in synthesis are attached to the chiral barrier. Finally, this idealized structure is such that the same complex is formed regardless of whether the amino acid complexes the top or bottom face of the macro ring.

Examination of CPK molecular models of a large number of possible complexes led to structure **14** as the simplest molecule that might both complex and show chiral recognition toward α-amino acids. These and other molecular models have been used as compasses to provide directions in the vast ocean of conceivable molecules that might be synthesized for trial. Structure **15** portrays the sterically compatible complex between (*S*)-**14** and the amino acid (*S*)-**12**. In this complex, the hydrogen attached to the asymmetric carbon of the generalized amino acid is held close to the chiral barrier, and the much larger R group is oriented away from the barrier. Complex **16** involves (*S*)-**14** and (*R*)-**12**. The positions of the small hydrogen and large R group are inverted. Thus complex **15** should be more stable than **16** for steric reasons.

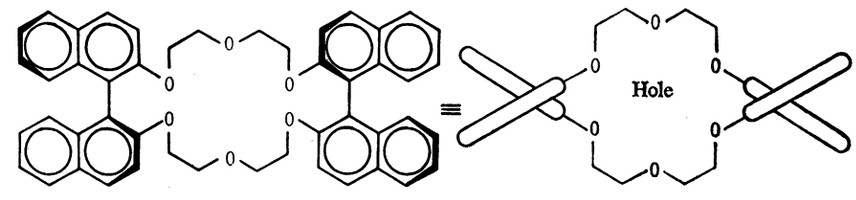
Experimentally, not only has (*S*)-**14** of established absolute configuration been prepared in an optically pure state, but many structural variants have been synthesized as well (*14*). The binaphthyl unit provides the necessary rigid chiral barrier since the two naphthalenes do not rotate with respect to one another below 200°C (*8*). Arms attached at the 3- and 3′-positions carry terminal carboxyl groups located over or along side the hole of the macrocyclic polyether. Finally, rotation of the molecule 180 degrees around the axis shown at the right of the structure reproduces the molecule. A consequence of this symmetry property is that the macro ring does not have "sidedness." In other words, the same complex is produced if the amino acid sits above or below the best plane of the polyether ring.

Many proportions of water, chloro-

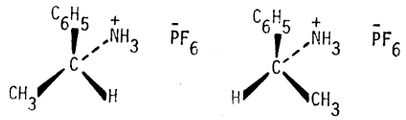
form, and acetic acid, when shaken together, form two layers. Cyclic ether **14**, when dissolved in such mixtures, resides mainly in the chloroform–acetic acid layer. Amino acid **12** in these mixtures is distributed mainly in the water–acetic acid layer. When dissolved together in the solvent mixture, **14** and **12** complex and alter the solubility of one another. Manipulation of the proportions of the three solvents and the amounts of **14** and **12** provides two experimental results. In the first, 50 percent of the dissolved cyclic ether is drawn into the aqueous layer by complexation with the amino acid, and the other 50 percent remains in the chloroform layer. In the second, 50 percent of the amino acid is drawn into the chloroform layer by complexation with cyclic ether, and the other 50 percent remains in the water layer. In the first experiment, the complex is distributed mainly in the aqueous layer. In the second, the complex is mainly in the chloroform layer.

Racemic cyclic ether (*R,S*)-**14** has been completely resolved into optically pure (*R*)-**14** and (*S*)-**14** by the optically pure amino acid, (*S*)-valine [**12**, R = $(CH_3)_2CH$-]. As predicted, (*S*)-valine complexed (*S*)-ether better than (*R*)-ether, and 1.7 times as much (*S*)- as (*R*)-ether was drawn into the aqueous phase. A continuous liquid-liquid extraction provided complete separation. A stationary water–acetic acid phase containing dissolved (*S*)-valine was absorbed into silica. A benzene solution saturated with water–acetic acid and containing racemic cyclic ether was washed as a mobile phase past the stationary aqueous phase. The (*S*)-ether was held in the stationary aqueous (*S*)-valine phase longer than was the (*R*)-ether, so the (*R*)-ether was eluted from the column first, followed by the (*S*)-ether. Complexation-decomplexation occurred many times as the two solutions contacted one another (*14*).

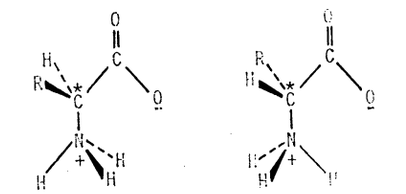
The foundation has been laid for completely resolving racemic amino acids with optically active cyclic ether (*S*)-**14** (*14*). As predicted, (*S*)-ether complexed (*S*)-valine better than (*R*)-valine. Thus 1.3 times as much (*S*)- as (*R*)-valine was drawn from a water–acetic acid layer into a chloroform–acetic acid layer by (*S*)-ether. What remains to be done is to pass racemic amino acid in an aqueous solution past an organic solution of optically active (*S*)-ether in a liquid-liquid countercurrent extraction. This could be ac-



(*SS*)-**10** (*SS*)-**10**

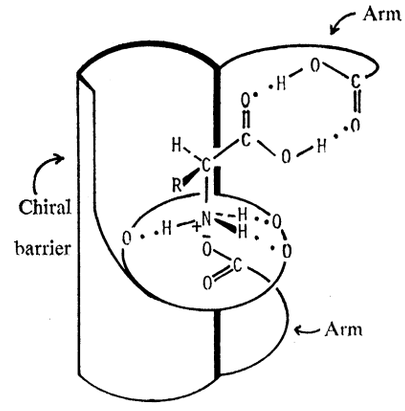


(*R*)-**11** (*S*)-**11**



(*S*)-Amino Acid (*R*)-Amino Acid

(*S*)-**12** (*R*)-**12**



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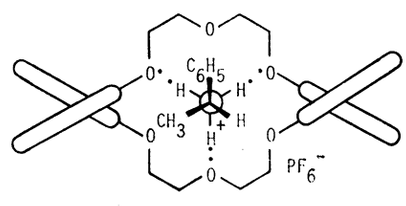
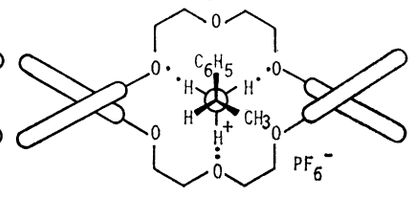


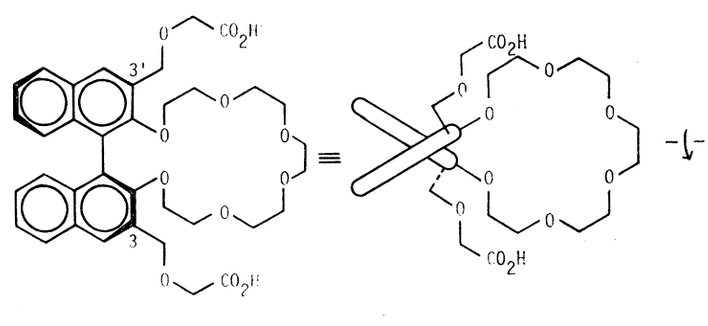
Complex of (*SS*)-**10** with (*R*)-**11**

Sterically favorable

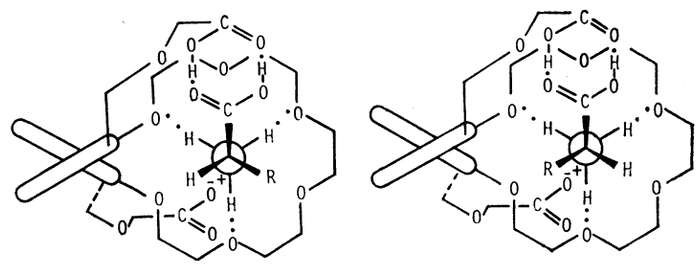


Complex of (*SS*)-**10** with (*R*)-**11**

Sterically unfavorable



(*S*)-**14** (*S*)-**14**



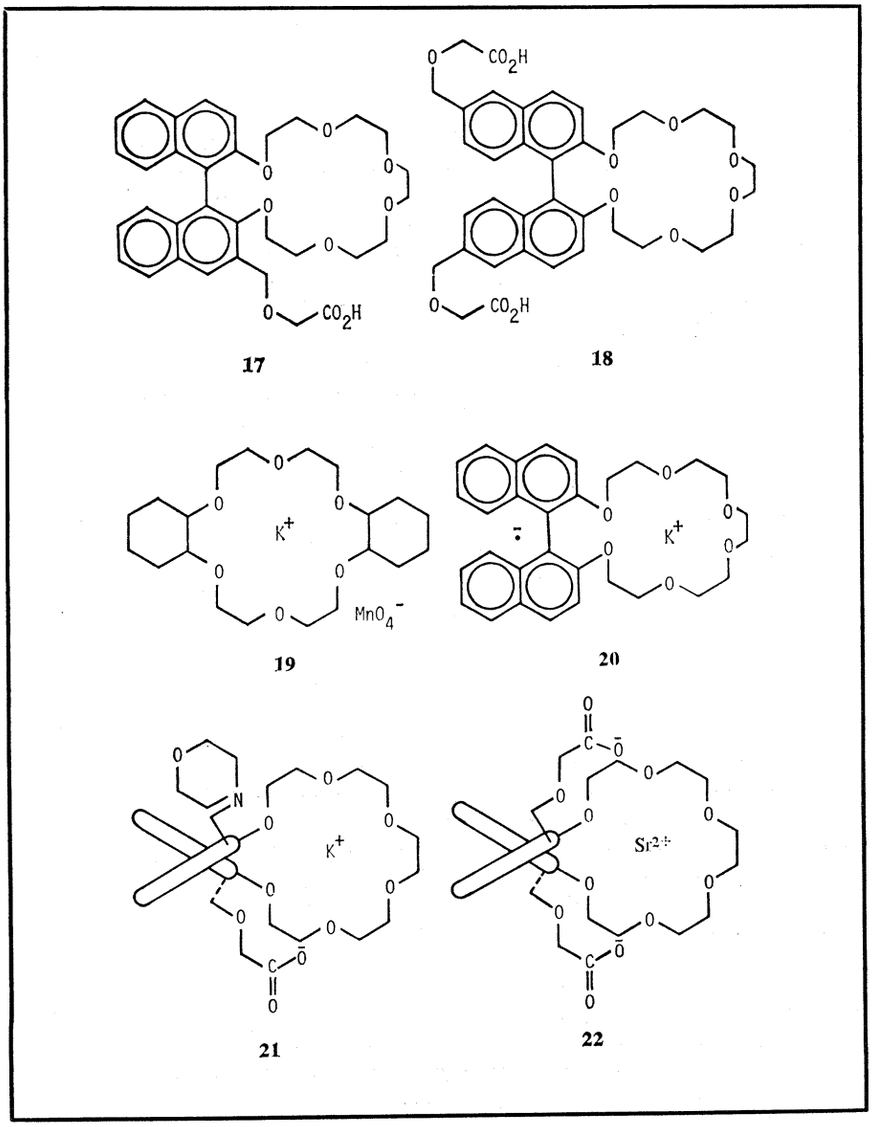
15 **16**

From (*S*)-**14** and (*S*)-**12** From (*S*)-**14** and (*R*)-**12**

complished with a liquid-liquid countercurrent machine. Alternatively, the organic phase containing the optically active host ether might be absorbed into a solid support and an aqueous phase containing the amino acid could be passed over it. A third possible method involves attaching the cyclic ether by covalent bonds to a solid support and passing the amino acid over that material. Any of these three methods might be automated and made continuous.

High efficiency of an amino acid–resolving machine based on these methods would require fulfillment of the following conditions: (i) The chiral recognition should be high. (ii) The host molecule should be stable so it could be used thousands of times. (iii) The weight of amino acid resolved per unit weight of other materials per unit time should be as high as possible. (iv) The host molecule and all solvents and supports should be reasonably inexpensive. Compound **14**, although stable and not difficult to prepare, does not have high enough chiral recognition.

Design of future molecules depends on the soundness of conclusions drawn from the facts about differential complexation of amino acids by cyclic ether **14**. That the results were qualitatively predicted provides only permissive evidence that the roles assigned each molecular part of the host were actually performed. Therefore several structural variants of **14** were examined. Compound **17** complexed amino acids well but gave very low chiral recognition (*14*). Compound **18** failed to complex amino acids well enough to have its chiral recognition tested (*15*). The arm of **17** easily allows the carboxyl group to center below the hole of the cyclic ether and to help bind the amino acid to the cycle. The absence of an arm above the cyclic ether allows rotation about the C–N bond of the amino acid, and a variety of geometric relationships between the chiral barrier and the asymmetric carbon are possible. Thus chiral recognition is lost. The carboxyl groups of **18** reach only to the edge of the hole of the cyclic ether. Although host-guest carboxyl-to-carboxyl hydrogen bonding is ideal in models (CPK) of complexes of **18**, carboxylate-to-ammonium ion-pairing is not possible. Apparently strong complexation requires carboxylate-to-ammonium ion-pairing, but chiral recognition depends both on carboxyl-to-carboxyl hydrogen bonding and ion-pairing.



Host Molecules Designed for Metal Cations

Investigators such as Pederson (*4*), Lehn (*16*), Simon (*17*), Eisenman (*18*), Christensen (*19*), Frensdorff (*5*), and their co-workers have demonstrated in many beautiful experiments the abilities of cyclic polyethers, cyclic antibiotics, and bicyclic amino polyethers to complex and lipophilize the alkali metal cations. A visible example is the deep purple color that develops when a benzene solution of the cyclic ether of complex **19** dissolves potassium permanganate in benzene (*20*). In the complex formed, the potassium ion is "solvated" by a cage of six oxygens tied together by hydrocarbon ethylene units. The resulting organometallic cation is ion-paired with the external permanganate ion.

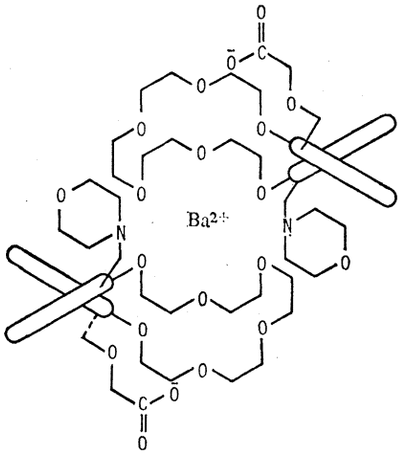
We have synthesized cyclic ether host molecules that incorporate counterions for the metal cations. Complex **20** is also a visible example. A solution of cyclic ether in a dry tetrahydrofuran solution at −80°C dissolves 1 gram-atom of potassium metal to form a deep green solution. The resulting one-to-one complex provides a lipophilic residence for both the potassium ion and the electron of the original metal. The potassium ion is visualized as entering the hole of the cyclic ether, and the electron is transferred to the aromatic system which delocalizes both the charge and spin of the electron (*10*). Interestingly, **19** is an oxidizing agent (*20*) and **20** is a reducing agent (*10*).

Very stable complexes are formed when host and guest are matched to one another with respect to charge type and in size. For example, in complexes **21** and **22**, the diameter of the cyclic

ether is between 2.4 and 3.1 angstroms (*7*). The single positive charge of the potassium ion in **21** matches the single negative charge of the carboxylate ion in **21**. The carboxylate and potassium ions form an "intramolecular" contact ion-pair. The two positive charges of the strontium ion in **22** match the two negative charges of the two carboxylate anions, whose oxygens can also serve as ligands of the strontium.

Complexes **21** and **22** have remarkable properties (*7*). Both exhibit parent ions in their mass spectra. Complex **21** is soluble in water and in organic solvents, and is stable to acids. We have not yet successfully separated host from guest. Complex **22** was formed by the cyclic ether scavenging strontium ion from a bulk sample of barium hydroxide. Barium ion [diameter of ~2.98 Å (*21*)] fits less comfortably than strontium into the hole of the host cycle, and forms a less stable complex (*7*).

Perhaps complex **23** is the most unusual (*7*). Two host molecules form a molecular sandwich with barium ion in the middle. The arrangement formulated provides the only way the carboxylate ions and the oxygens of the cyclic ether simultaneously can serve as ligands or counterions (or both) for the barium ion. One carboxylate ion contacts the barium ion through the hole of each cycle. The barium ion is completely buried in a lipophilic skin. The complex is soluble in organic solvents, is stable to chromatography, and does not precipitate barium sulfate when sulfuric acid is added to it dissolved in methanol-water. Apparently the sulfate ion is unable to rend the lipophilic skin of **23** at an appreciable rate.



23

Complex **23** provides an interesting example of how host and guest are structured by a variety of binding forces and steric repulsive interactions. Two contact ion-pairs and 12 ion-dipole interactions hold the three parts of the complex together. The steric repulsions between the two binaphthyl residues and the two cyclic ether moieties shape the complex. Molecular models (CPK) indicate that all of the space around the barium ion is occupied in **23**. This complex illustrates how two semiflexible, medium-sized organic molecules can be held together in a highly rigid relationship to one another by ligand-to-metal binding forces. Structural variants of **23** are imagined, which strategically place binding and catalytic sites at the disposal of possible reactants. Unlike the other examples in this article, a metal ion provides much of the organization for the complex.

Proper design of hole size, heteroatom type, and the number of "built-in" counterions should provide host molecules with a wide range of differential complexing abilities of many of the metal cations of the periodic table. Ion lipophilization is important to ion transport through membranes, to homogeneous catalysis, to the design of structured "shift reagents," and to the design of inorganic reagents that will perform reactions in nonpolar organic solvents.

Molecular evolution provides chlorophyll, hemoglobin, and vitamin B_{12} as instructive examples of complexes composed of metal ions and an array of ligands and counterions structured into cages by covalent bonds. Although the chemist lacks the time span of nature to produce equally interesting substances, he has certain advantages. He has nature's example. He is not limited to functional groups that are stable to water. He can perform experiments at a variety of temperatures. He might know in advance what specific task his compounds are designed to perform.

References and Notes

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