CHIRAL RECOGNITION IN COMPLEXATION OF GUESTS BY DESIGNED HOST MOLECULES*

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ABSTRACT

Host molecules have been designed and synthesized to selectively complex and lipophilize guest molecules. Examples of the use of the following binding interactions are given: hydrogen bonding, ion pairing, cation to n-electrons, carbonyl to n-electrons and *pi–pi* bonding. Multiheteromacrocycles have been prepared whose association constants with *tert*-butylammonium salts in chloroform range from < 50 to 10^6 M^{-1}. Host molecules with built-in counterions have been prepared that selectively complex and lipophilize metal and alkylammonium cations. Locations of complementary binding sites and noncomplementary steric barriers provide for selective binding by host molecules of candidate guest molecules. Locations of appropriate chiral barriers and multiple complexing sites in guest compounds have led to the complete optical resolution of host compounds by optically active amino acids, and of amino acid esters by optically active host compounds. Ratios of association constants for diastereomeric complexes in excess of ten have been obtained. A molecular basis for designing an amino acid resolving machine has been developed.

Central to nature's enzyme, transport and regulatory systems are highly structured molecular complexes. Large host molecules bind smaller guest molecules, and the chemical and physical properties of each are vastly altered. Nature's complexes are characterized by a high degree of structure, very high rates of formation and decomposition, and mutual structural recognition of host and guest. In enzymic catalysis, the rate-limiting transition state energies are lowered by complexation and orientation. In transport mechanisms, selection and lipophilization of polar entities are frequently accomplished by complexation. In regulatory systems, competitive complexation between inhibitor and substrate for sites of host molecules control

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equilibria through highly structured molecular complexes. Clearly, nature's evolutionary chemistry presents well-defined challenges to the synthetic organic chemist. With the sophistication of current synthetic, separation and analytic techniques, we believe that host compounds of lower than 2000 molecular weight can be designed and prepared that will exhibit some of the properties of nature's catalysts, carriers and regulators.

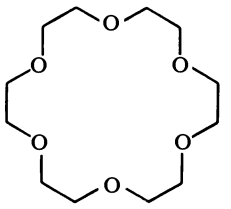
BINDING OF HOSTS TO GUESTS

Molecular complexes are held together by many different forces. Hydrogen bonding provides the most universal means of binding organic hosts to guests. Three varieties are available: pole–pole (e.g. $NH_4^+ \ldots \bar{O}H$); pole–dipole (e.g. $NH_4^+ \ldots :OH_2$); and dipole–dipole (e.g. $HOH \ldots :OH_2$). Pole–pole and pole–dipole interactions that bind metal cations to their counterions and their ligands have been the most used in preparing complexes. Less studied is the use of metal cations to organize host molecules for complexing organic guest molecules. Dipole–dipole interactions such as those between a carbonyl carbon and an electron pair of an amine or ether provide structuring possibilities that have been little examined. The multiple dipole–dipole van der Waals–London interactions frequently combine with exclusion from the water structure (hydrophobic bonding) to promote highly ordered molecular complexation[1]. The bilayer synthetic membranes[2], certain micelles[1] and the cyclodextrin complexes[3] provide examples. Charge transfer binding of pi-acids to pi-bases provides another type of intermolecular binding that usually involves large and rigid pi-systems[4]. All of these binding forces are potentially available to the synthetic organic chemist interested in designing host molecules for study of highly structured molecular complexation.

Many of these binding forces are those found in solvation and crystal lattices. In a sense, a host molecule provides an assembly of solvation sites tied together by covalent bonds. Both natural and synthetic hosts combine rigid with conformationally flexible units. For some purposes, an ideal host molecule brings to a complex the maximum molecular organization prior to complexation that is compatible with providing minimum energy barriers for specific guest molecules entering and leaving the complex. For other purposes, host molecules might be designed for complexes that represent such deep energy wells that their formation is essentially irreversible.

BINDING ABILITIES OF MULTIHETEROMACROCYCLES

Pedersen[5] in 1967 found that cyclic polyethers could be synthesized easily that acted as hosts for metal and ammonium cations. The beautiful symmetry properties of these compounds led him to name them 'crowns'. For example, compounds that contain the ring structure of **1** (**1** was named 18 crown-6) were found to complex and lipophilize potassium (**2**) and ammonium salts (**3**)[5]. This work stimulated our belief that host molecules could be synthesized that would bind biologically important organic compounds to produce highly structured molecular complexes. Our ultimate hope is to learn enough about complexation of ground states to extend our studies to transition states and catalysis.



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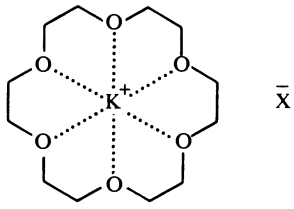

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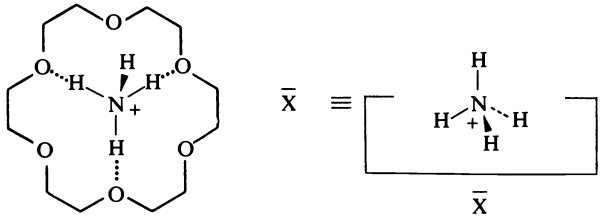

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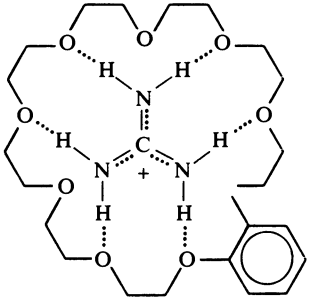
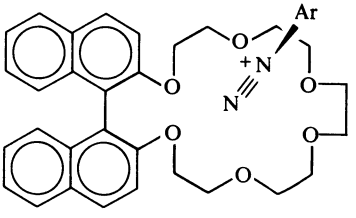
Examination of space-filling, scale molecular models (CPK or Corey, Pauling, Koltun) of the ammonium salt complex of **1** suggests that the complex possesses the structure visualized in **3**. Examples of the use of models to anticipate host–guest relationships are found in the preparability of complexes **4** and **5**. In **4** which has been crystallized, a quanidinium ion is embraced by benzo-27-crown-9[6]. The host molecule in **5** solubilizes aryldiazonium salts in dichloromethane[7]. The ring system with its electron pairs turned inwards binds the $\overset{+}{N} \equiv N$ group inserted into the hole. The aryl



$(C_6H_5)_4\bar{B}$

4



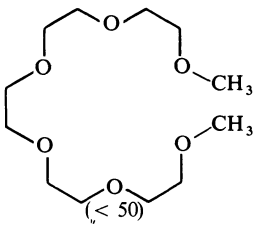
$B\bar{F}_4$

5

group is perpendicular to the best plane of the oxygens in the complex. Substitution of two methyl groups in the *ortho*-positions of the aryldiazonium ion sterically blocks complexation[7]. Molecular models of such a complex can not be assembled.

Multiheteromacrocycles **1** and **8**–**20**[8,9], and open-chain model com-

pounds **6** and **7**[10] were prepared* to determine which structural features contributed to the binding of these host molecules to primary alkylammon-



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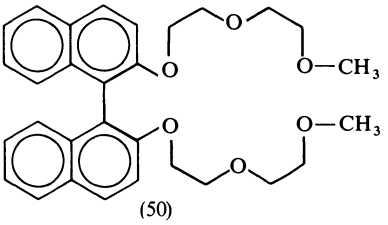

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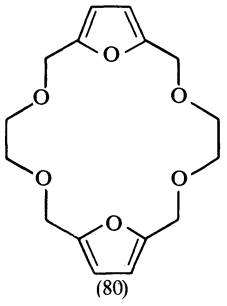

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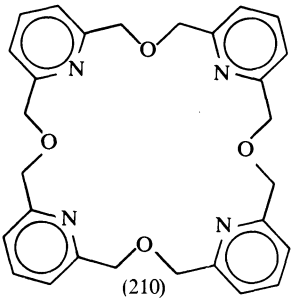


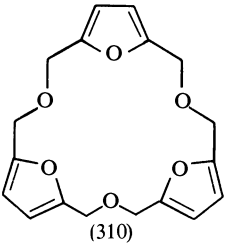
9

ium salts. Molecular models (CPK) of possible complexes guided the direction of our synthetic efforts. In effect, these models serve as a compass on an otherwise uncharted ocean of molecular possibilities.

The values of the association constants in chloroform of **1** and **6–20** with *tert*-butylammonium thiocyanate were estimated as follows[10]. By p.m.r. measurements, the equilibrium constants for reactions (1) and (2) were determined. The association constants (K_a) for reaction (3) were calculated from these constants. The values of K_a are placed in parentheses above the compound numbers assigned each structure. The compounds are listed in increasing order of their binding abilities (see page 332).

Interesting conclusions are suggested by these orders: (1) The most conformationally flexible polyether, **6**, has the lowest binding constant, followed by **7**, which contains the rigid 1,1′-binaphthyl unit. Open-chain polyether **6** is a poorer binder by over four powers of 10 than **1**, its cyclic counterpart. Similarly, the open-chain polyether **7** is poorer by a factor of > 8 than its cyclic counterpart, **11**. (2) Delocalization of the electron pairs on the furan oxygens appears to decrease their binding ability by factors of 12 to 16 per furan ring in the sequence of compounds **1**, **16**, **14** and **10**. Placement of two furan units directly across from one another as in **8** decreases the binding ability of the host by a factor of about 50 as compared with their placement in **14**. The hydrogen bonds in a complex of **14** *can*

* Pedersen first prepared **1**, **15** and **17** (see ref. 5).



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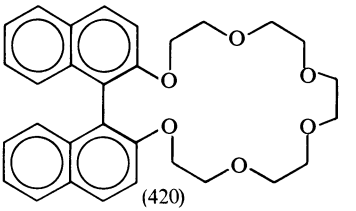

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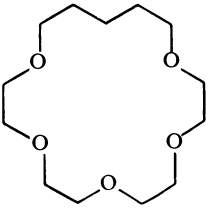

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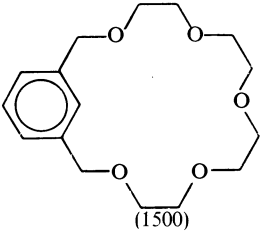

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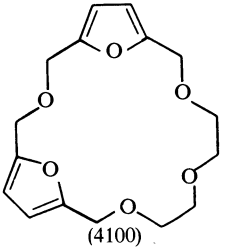

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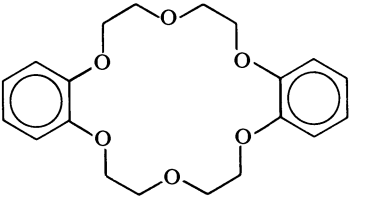

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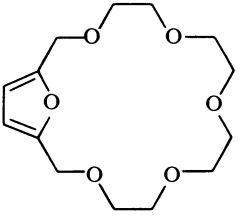

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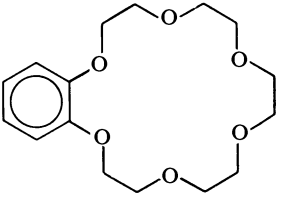

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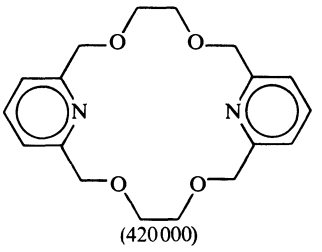

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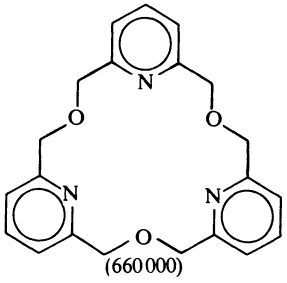

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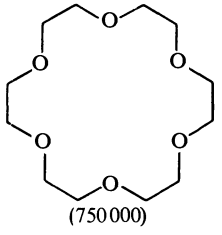

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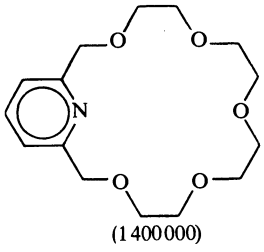

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20

$$[\textit{tert}\text{-}Bu\overset{+}{N}H_3]_{H_2O} + [S\bar{C}N]_{H_2O} \rightleftharpoons [\textit{tert}\text{-}Bu\overset{+}{N}H_3 \cdot S\bar{C}N]_{CHCl_3} \quad (1)$$

$$[\textit{tert}\text{-}Bu\overset{+}{N}H_3]_{H_2O} + [S\bar{C}N]_{H_2O} + [\text{host}]_{CHCl_3} \rightleftharpoons [\textit{tert}\text{-}Bu\overset{+}{N}H_3 \cdot \text{host} \cdot S\bar{C}N]_{CHCl_3} \quad (2)$$

$$[\textit{tert}\text{-}Bu\overset{+}{N}H_3 \cdot S\bar{C}N]_{CHCl_3} + [\text{host}]_{CHCl_3} \rightleftharpoons [\textit{tert}\text{-}Bu\overset{+}{N}H_3 \cdot \text{host} \cdot S\bar{C}N]_{CHCl_3} \quad (3)$$

involve only non-furanyl oxygens, but one hydrogen bond must involve a furanyl oxygen in a complex of **8** (a complex such as **3**). (3) Substitution of one methylene for one oxygen of **1** as in **12** decreases the binding ability by a factor of about 1500. This factor decreases to about 500 with cycle **13**, in which an aromatic CH is substituted for an oxygen. These results suggest that considerable binding is associated with $\ddot{O}:\ldots\overset{+}{N}$ interactions. (4) Substitution of one pyridine nitrogen for one oxygen of **1** in host molecule **20** increases the binding ability by a factor of about 2. Replacement of the three alternate oxygens of **1** with pyridyl nitrogens as in **19** provides little change in binding power. Two pyridine rings placed opposite to one another as in **18** reduces the complexing ability compared with the system containing only one pyridine ring (**20**) by a factor of about 3. Possibly pyridyl nitrogens form stronger hydrogen bonds than ether oxygens, but the $N:\ldots N^+$ interaction provides weaker binding than the $\ddot{O}:\ldots N^+$ interaction. The enlarged ring system of **9** provides poor binding, even though it contains pyridyl nitrogens. The binding sites are poorly organized to receive a $R\overset{+}{N}H_3$ ion (CPK models). (5) Inclusion of catechol units in the ring system of **1** reduces the association constant by a factor of about 5 for the first unit (**17**), and by

an additional factor of 10 for the second (**15**) when the two units are opposite one another. This effect probably reflects mainly electron delocalization of the ether oxygens into the benzene rings. (6) Substitution of the binaphthyl unit of **11** for an ethylene unit of **1** reduces its association constant by a factor of about 1900. In **11**, not only are the electrons of two of the oxygens delocalized into the naphthalene rings, but also the two oxygens to complex fully must be brought together by a decrease in the dihedral angle of the binaphthyl unit from its sterically most comfortable angle of 90° to about 75°. Inclusion of two binaphthyl units decreases the constant to where it is below that of **6**, and off the bottom of this particular scale [10].

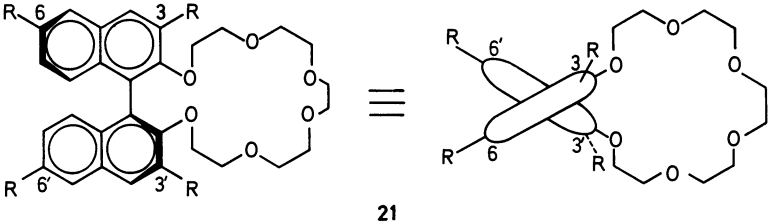
SHAPING OF HOST MOLECULES

The design of host compounds of manageable molecular weights for specific guest organic compounds involves special problems of molecular architecture. Appropriately sized cavities must be constructed, steric barriers put in place and binding sites located so that only specific guest compounds enjoy a structured relationship with the host. The problem of convergence of molecular parts in the host offers the most challenge. Since guest molecules are convex, host molecules must be concave. Many more atoms are needed to construct a hole than to fill one.

One aspect of convergence is the placing of *arms* and *steric barriers* in the host molecule. Both arms and rigid steric barriers divide the space around the central *hole* into *cavities*, which provide the host with *shape*. When *chiral recognition* between host and guest is desired, rigid *chiral barriers* must be included. The arms that *converge* on the hole might carry additional binding sites for the guest, or provide counterions for ionic guests. Arms also may occupy *divergent* positions on rigid units attached to the host. Divergent arms might carry substituents that allow manipulation of the hydrophilic–lipophilic balance of the host without affecting materially the shape of the cavities around the hole. Divergent arms might also be used to attach the host to a solid support, and provide a *spacer* between the support and the working part of the host.

The economics of synthesis and molecular size require that rigid units that can play multiple roles be incorporated into the ring systems. The binaphthyl unit of **21** and the [2.2]paracyclophanyl unit of **22** illustrate these points. The binaphthyl unit is rigid except for $\sim 30°$ amplitude of rotation about the Ar–Ar bond, and is chiral and optically stable to $\sim 200°$ (in **21**). Arms in the 3- and 3′-positions extend along the side of, over or under the hole of **21**. Substituents in the 6- and 6′-positions extend away from the multiheteromacrocycle. When symmetrically substituted, the compound possesses a C_2 axis, and therefore the macrocycle is not *sided*. The [2.2]paracyclophanyl unit of **22** is rigid and chiral, possesses a C_2 axis and offers a variety of positions to place arms[11]. Arms might be located in the 1-,2-,4-,9- and 10-positions that converge on the hole. Arms might be placed in the 1-,2-,7-,8-,9-,10-,15- and 16- positions that diverge from the hole. The configurations at carbons 1,2,9 and 10 when arms are attached determine whether the arms converge or diverge.

Metal complexes that involve the binaphthyl unit are exemplified in



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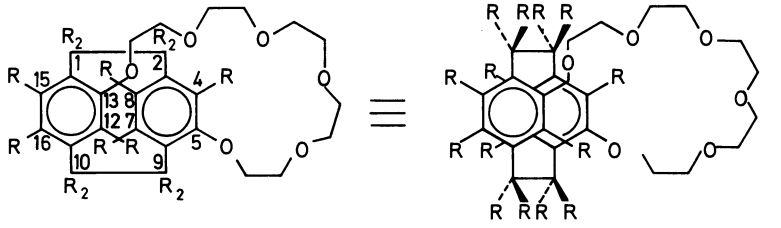
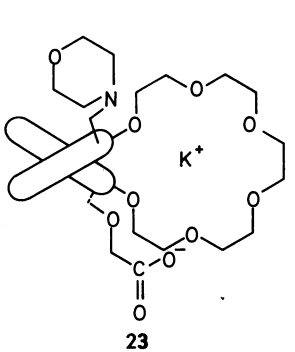


22

23–**27**[12]. In complexes **23**–**26**, the hole sizes have been adapted to the diameters of the metal ions, and the numbers of counterions that terminate the arms match the valence states of the metal cations. The arms with their attached counterions are centred over or under the hole. In **27**, the hole of



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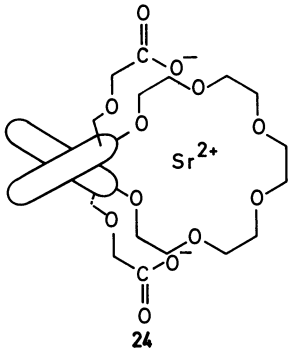

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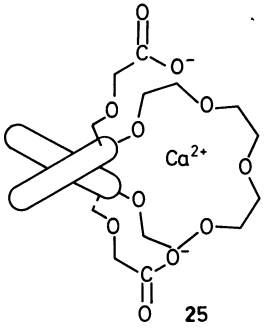

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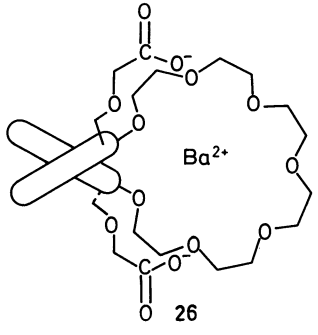

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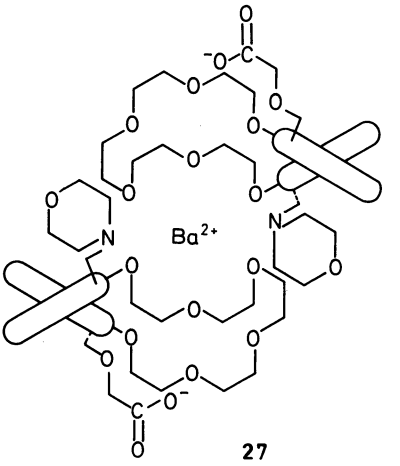
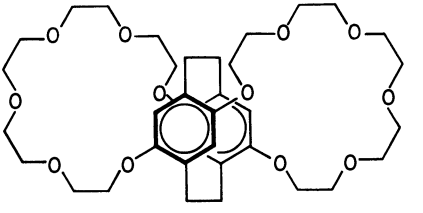


27

the host is too small to accommodate the Ba^{2+} ion. Consequently, the multiheteromacrocycles form halos above and below the ion and completely envelope it. The carboxylate counterions extend into the hole. The complex is extraordinarily stable and lipophilic, and is highly structured since the two large rings are pressed against one another.

Host compounds **28–30** have been prepared, and were found to complex and lipophilize two moles of primary alkylammonium salts[11]. Molecule **28** possesses three intersecting C_2 axes, and therefore possesses D_2 symmetry. It has not been obtained in an optically active state. Compound **31** was also prepared, and found to complex two moles of *tert*-butylammonium thiocyanate[11].



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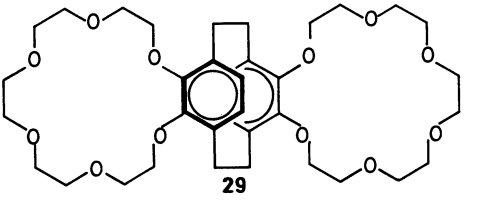

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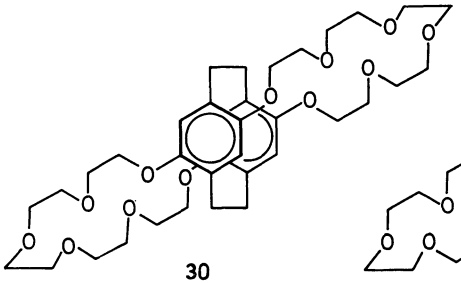

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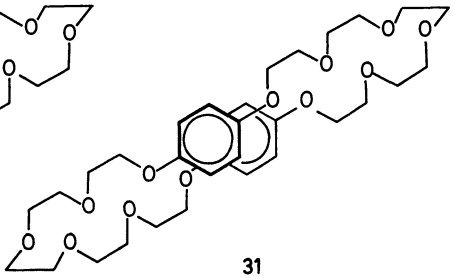


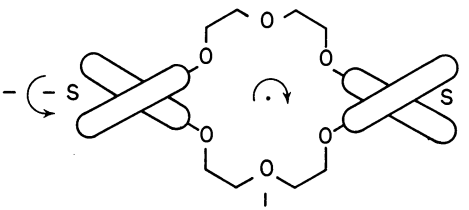
31

CHIRAL RECOGNITION IN COMPLEXATION OF AMINO ESTERS

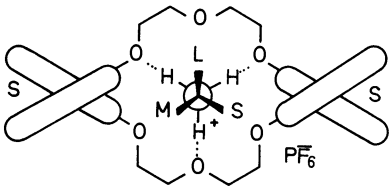
An important property of enzymes is their ability to discriminate between enantiomers in complexation and catalysis. One of our initial goals was to synthesize host compounds that would exhibit the property of *chiral recognition* of potential guest molecules. The biological and dietary importance of amino acids and the location of two polar groups on their asymmetric carbons made them and their derivatives ideal guest molecules. We hoped to provide a molecular basis for designing an 'amino acid resolving machine'.

Ideal host compounds for this purpose must possess the following properties: (1) They must be easily synthesized, as small as possible, stable and structurally manipulable to allow their solubility and spectral properties to be adjusted. (2) They must bind amino acids or their esters, and the rates of complexation–decomplexation must be very high. (3) They must contain chiral barriers so that one enantiomer of a guest racemate forms a diastereomeric complex of lower energy than does the other enantiomer. (4) They must be optically stable, and their maximum rotations and absolute configurations must be established. (5) For a host compound of known configuration, the configurations of the guest compounds leading to the more stable complex should be predictable in advance of experiment and rationalizable in terms of the structures of the diastereomeric complexes. (6) The host compound and its complexes must remain in one phase, in equilibrium with a second phase containing the uncomplexed guest compounds. Thus, by phase separation, complexed guest can be separated from uncomplexed guest.

Host compound **32** possesses many of the above properties. The substance and its enantiomer have been prepared by simple routes in optically pure forms, and their absolute configurations and maximum rotations established[13]. Cycle **32** contains two chiral barriers in the form of naphthalene rings whose planes are perpendicular to the best plane of the oxygens. Two of the naphthalene rings extend above and two below the plane of the oxygens. The space above and below the oxygen's plane is divided by the naphthalene walls into four chiral cavities, all of which are the equivalent of one another. The molecule contains three mutually perpendicular C_2 axes and therefore possesses D_2 symmetry. When **32** complexes an optically active alkylammonium salt whose asymmetric centre is adjacent to the primary ammonium group, the same complex is formed whether the alkyl-



32 D_2 symmetry



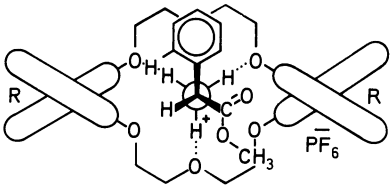
33 More stable complex

ammonium group complexes from the top or from the bottom of the host. In the complex, the large (L), medium (M) and small (S) groups attached to the chiral centre must distribute themselves into the two equivalent cavities. In **33**, L is distributed in one cavity and M and S in the second. The chiral cavities possess a pocket on one side (the left in **33**) and a barrier on the other (the right in **33**). Molecular models predict on steric grounds that M will reside in the pocket and S against the barrier in the more sterically stable diastereomeric complex. This model for the more stable complex is referred to as the *three-point binding model.*

The pure one-to-one diastereomeric complexes of (SS)-**32** and (RR)-**32** with the (R)-isomer of phenylglycine methyl ester hexafluorophate were prepared in $CDCl_3$, and their p.m.r. spectra examined. The results confirmed the structural expectations based on an examination of molecular models (CPK) of the two diastereomers, which are formulated as **34** and **35**[14] in *Figure 1.* Complex **35** was obtained in a crystalline state[14], and its x-ray structure is being determined[15].

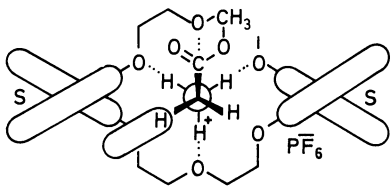
The p.m.r. spectra indicate the following: (1) The methyl protons in **35** are shielded and moved upfield compared with those of **34**. In models of **35**, the methyl is closer to an ether oxygen than in **34**. (2) The benzyl proton in **34** is shielded and moved upfield, but not in **35**. Models of **34** indicate that this proton is closer to the shielding cone of the naphthalene ring current than in **35**. (3) The *ortho*-protons of the phenyl group of **34** are shielded and moved upfield, but not in **35**. Models of **34** indicate that one of the *ortho*-protons lies in the shielding region of the naphthalene ring current, but this structural feature is absent in **35**. (4) The $ArOCH_2\underline{C}H_2O$ protons of the host are shielded and moved upfield in **34** compared with **35**. In models of **34**, two of the total of eight such protons sit directly under the phenyl group, and in its shielding region. In models of **35**, the plane of the phenyl group lies parallel to the plane of one of the naphthalenes, and the methylenes are not shielded. Appropriate p.m.r. experiments demonstrated that, in the presence of excess host, guest molecules were passed from host to host at rates faster than were observable on the p.m.r. scale at temperatures as low as $-40°$. Thus, the two *ortho*-protons of the phenyl in **34** were averaging, as were the eight central OCH_2 protons of **34**[14].

A molecular model (CPK) of **35** indicates that the carbonyl-carbon of the ester group is perfectly located to be bound by the electron pair of a central ether oxygen by a weak dipole–dipole interaction. This interaction is not possible in **34**, since the plane of the O—C=O atoms for steric reasons is perpendicular to the best plane of the macro ring. On purely steric grounds,



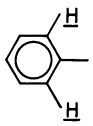
34

Three-point binding model



35

Four-point binding model

Protons	p.m.r. δ
$-CO_2C\underline{H}_3$	3.60
$C_6H_5-C\underline{H}$	4.59
	6.56
$ArOCH_2C\underline{H}_2O$	2.9 (broad)

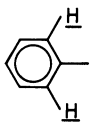
Protons	p.m.r. δ
$-CO_2C\underline{H}_3$	3.52
$C_6H_5-C\underline{H}$	4.97
	6.9 – 7.4
$ArOCH_2C\underline{H}_2O$	3.22

Figure 1. Models for structures of diastereomeric complexes

34 appears to be the more stable, and is an example of the general three-point binding model, **33**. However, if the ester-to-oxygen binding is substantial, then structure **35** offers the best compromise between steric and polar interactions. Structure **35** is referred to as the *four-point binding model.*

Cycle **32** is the prototype of a number of optically pure host compounds examined for their complexing power, and for the stereochemical direction and extent of chiral recognition[13]. Their chloroform solutions were shaken with aqueous solutions of the methyl esters of racemic amino acid salts of hexafluorophosphoric acid containing lithium hexafluorophosphate at temperatures that ranged from $-15°$ to 25°. The inorganic salt 'salted out' the organic salt, and by depressing the freezing point of water made temperatures as low as $-20°$ accessible. Low temperatures, high inorganic salt concentrations and low pK_as of the alkylammonium salt favoured extraction due to complexation. From 0.7 to 1.0 mole of organic salt per mole of host was extracted into the chloroform layer. Without the host compound present, no detectable amount of guest was extracted. Neither complexed nor uncomplexed host molecule could be detected in the aqueous layer. After equilibrating, the layers were separated, and the amino ester salt was isolated from the aqueous layer and its rotation taken. The amino ester salt complexed in the chloroform layer was washed out of the chloroform layer with water and was isolated, and its rotation was taken. From the values obtained, enantiomer distribution constants (EDC) were calculated, which

are defined by equation (4). In equation (4), D_A is the distribution coefficient (between the chloroform and water phases) of that enantiomer which forms the *more stable* complex with the host. Similarly, D_B is the distribution coefficient of that guest enantiomer which forms the *less stable* complex with the host. Thus, EDC values are always greater than or equal to unity, and provide a quantitative measure of chiral recognition.

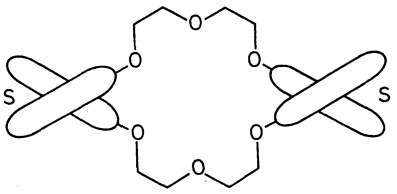
$$\text{EDC} = \frac{D_A}{D_B} \tag{4}$$

The EDC values and the more stable diastereomeric complexes of host molecule **32** with representative guest compounds are listed. With 1-phenylethylammonium hexafluorophosphate as a guest compound, the absence of an ester group makes the dominance of the three-point binding model predictable. With phenylglycine methyl ester salt and *p*-hydroxyphenylglycine ester salt, the more stable diastereomer also possessed the structure of the three-point binding model. However, with valine, phenylalanine and methionine ester salts, the more stable diastereomer possessed the structure of the four-point binding model. Thus, in the more crowded complexes, the three-point binding model dominates. In the less crowded complexes, the four-point binding model dominates[14], as is indicated in *Figure 2*.

The higher EDC value of 4.2 for the *p*-hydroxyphenylglycine ester salt as compared with the value of 3 for the phenylglycine ester salt is interesting. The remote point of attachment of the hydroxyl group in the former suggests that the EDC value difference is associated with an electronic effect. A plausible explanation involves the *pi–pi* interactions between the naphthalene ring that lies parallel to the phenyl ring in the four-point binding structure, **35**. The naphthalene ring is attached to an ether oxygen, and is a weak *pi*-base. The phenyl is attached to a methinylammonium ion, which makes it a weak *pi*-acid. Possibly weak charge-transfer attractive forces stabilize **35** slightly. Substitution of a hydroxyl group into the 4-position of the phenyl should decrease the *pi*-acidity of the phenyl, and destabilize the four-point relative to the three-point binding complex.

Molecular models (CPK) of **36** indicate that its methyl groups extend the chiral barriers of two of the naphthalene rings, and might increase its chiral recognition. The structure retains one of the C_2 axes, and therefore is not *sided* with respect to its complexing potentialities. The compound was prepared in an optically pure state and tested against phenylglycine methyl ester and methionine methyl ester hexafluorophosphates. The results shown in *Figure 3* indicate that this system possesses much higher chiral recognition than **32**, the parent compound without the methyl groups[14]. An interesting feature of the results is that with **32** as host and methionine ester salt as guest, the four-point binding model applies. With the more crowded **36** as host, the three-point binding complex dominates.

Other host compounds gave less chiral recognition. For example, **38** is the probable structure for the more stable complex (EDC = 1.2) between host compound **37** (stereoisomer of **36**) and phenylglycine methyl ester hexaflurophosphate [16]. Without the two methyl groups, **37** would contain a mirror plane. Complex **40** is the more stable diastereomer (EDC = 2.2)



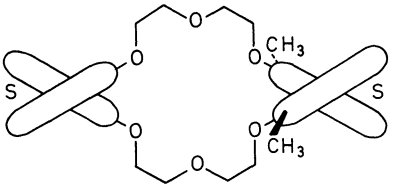
32
EDC

HPF_6 Salt of	(D_A/D_B)	Stabler model	T,°C
$C_6H_5-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-NH_2$	1.8	3-point	0
$C_6H_5-\underset{\displaystyle CO_2CH_3}{\underset{\vert}{CH}}-NH_2$	3	3-point	-15
$p\text{-}HOC_6H_4-\underset{\displaystyle CO_2CH_3}{\underset{\vert}{CH}}-NH_2$	4.2	3-point	-15
$C_6H_5-CH_2-\underset{\displaystyle CO_2CH_3}{\underset{\vert}{CH}}-NH_2$	1.8	4-point	-15
$(CH_3)_2CH-\underset{\displaystyle CO_2CH_3}{\underset{\vert}{CH}}-NH_2$	1.5	4-point	-15
$CH_3S(CH_2)_2-\underset{\displaystyle CO_2CH_3}{\underset{\vert}{CH}}-NH_2$	1.7	4-point	-5

Figure 2. Direction and extent of chiral recognition

between host compound **39** and phenylglycine methyl ester hexafluorophosphate[17]

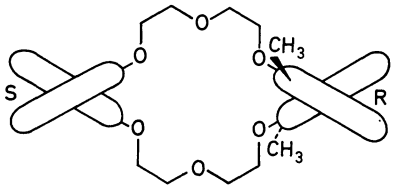
Our greatest expectations were dashed by our greatest failure. Potential host molecules **41** and **43** were prepared in an optically pure state. Compound **41** possesses one C_2 axis and therefore is not *sided*. The space above and below the best plane of the oxygens is divided into three cavities by the naphthalene walls, a large cavity (L'), a medium cavity (M') and a small cavity (S'). This compound was designed to provide a 'hand-in-glove' complex of type **42** with high chiral recognition. Unfortunately, the compound failed to complex any salts. Compound **43** possesses one C_3 axis and three mutually perpendicular C_2 axes, and therefore possesses D_3 symmetry. Such symmetry is rarely encountered in organic compounds. The space above and below the best plane of the oxygens is divided by the six naphthalene walls



36

HPF_6 Salt of	EDC (D_A / D_B)	Stabler model	T, °C
$C_6H_5-CH(CO_2CH_3)-NH_2$	12	3-point	24
$CH_3S(CH_2)_2-CH(CO_2CH_3)-NH_2$	2.2	3-point	-5

Figure 3. Effect on chiral recognition of extending the chiral barrier



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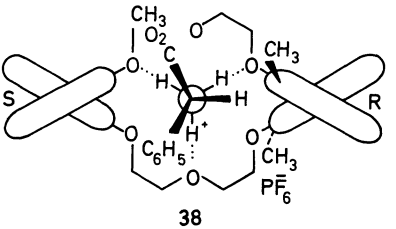

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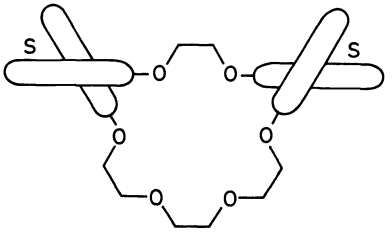

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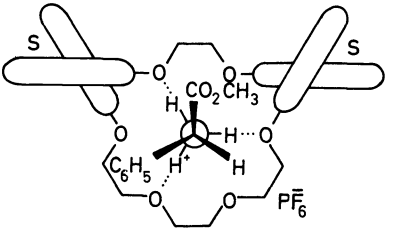
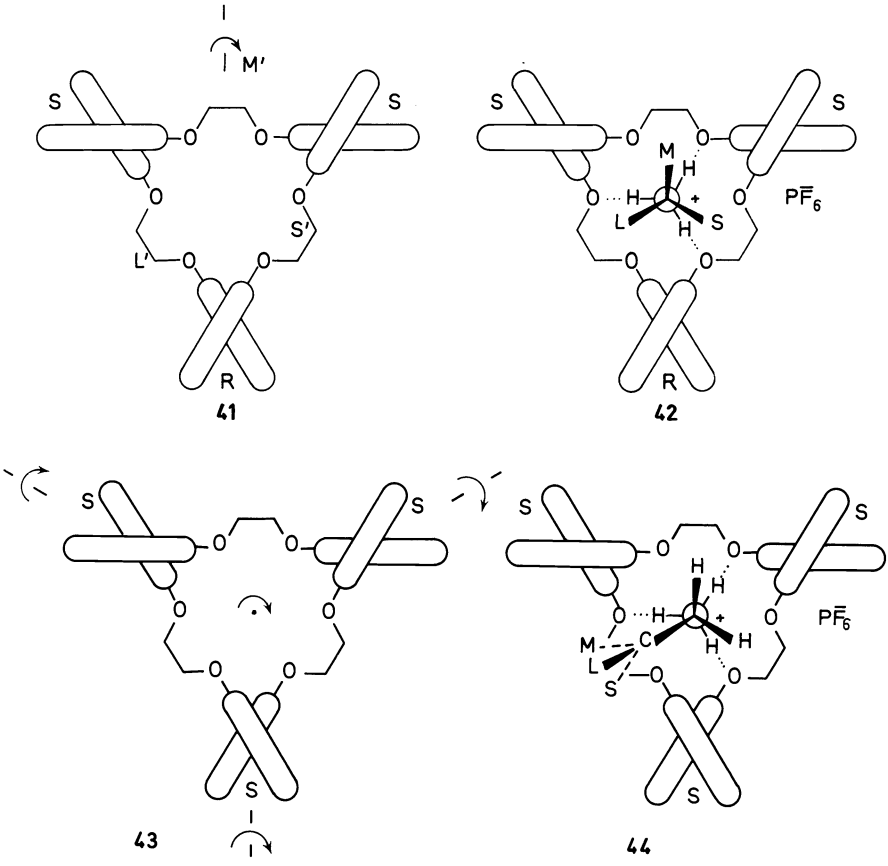


40

into six equivalent cavities, each of which is chiral in the same sense, and resembles the M′ cavity of **41**. This compound was designed to provide a complex of the type formulated in **44** with high chiral recognition. Both **41** and **43** contain six oxygens bound to naphthalene rings which reduce the basicity of the oxygens both by an inductive effect and by electron delocalization[18].



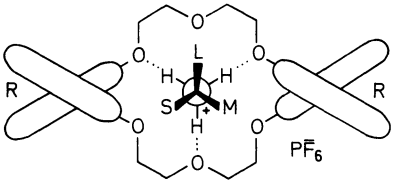
OPTICAL RESOLUTION OF AMINO ESTERS BY COMPLEXATION

Total separations of enantiomers of racemic amino ester salts were obtained by liquid–liquid chromatography. The hexafluorophosphate of an amine was dissolved in a chloroform solution that was 0.04–0.70 M in host compound, (RR)-**32**. This solution was added to the top of a jacketed silica-gel column maintained at the desired temperature (– 15° to 25°) on which was absorbed a 1–4 M solution of sodium or lithium hexafluorophosphate in water. The column was developed with more chloroform solution of the resolving agent. The enantiomers of the racemic salts were distributed between the phases in a continuous multiplate process. The enantiomer preferentially complexed and lipophilized by the host molecule was eluted first, followed by the other enantiomer. The column eluate was monitored for appearance of amine salt by the conductance of the chloroform solution, which was shown to be linear in the amine salt concentration. The complexed salt in the eluate was washed into water, isolated and characterized in representative cases[19].

The measure of the degree of separation of the two enantiomers is given by the separation factor, α, which is a function of the retention volumes of the components and the column's characteristics. If the column exhibits true liquid–liquid countercurrent extraction behaviour, then α = EDC. With the three salts listed in *Figure 4*, the three-point binding model applies.

Figure 5 is a plot of relative conductance of the column eluate against the ml of eluate for the chromatogram in which phenylglycine methyl ester hexafluorophosphate salt was completely resolved. The first peak eluted was the (RR)–(R) and the second the (RR)–(S) complex. Base-line separation of the two peaks (one for each enantiomer) was observed. Integration of the area underneath the first peak was 1.08 of the integrated area beneath the second peak. In theory, the area ratios should have been 1.00. The ratio of moles of host needed to elute all of the guest was 9.1. At the top of the peak for the enantiomer first eluted, the ratio was 2.1. At the top of the peak for the slower moving enantiomer, the ratio was 3.3. The column had 18 theoretical plates, and the resolution, R_s, was > 1.25[19].

These results demonstrate the feasibility of completely resolving primary amines and amino esters by multiplate extraction processes through chiral recognition in molecular complexation. The host molecule is stable and easy to recover, and has been used repeatedly. This technique should be applicable to the determination of absolute configurations, determination of



STABLER COMPLEX

Salt of	T,°C	EDC (D_A/D_B)	Separation factor (α)
$C_6H_5-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-NH_2$	25	1.5	1.5
$C_6H_5-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-NH_2$	-21	1.8	1.9
$C_6H_5-\underset{\displaystyle CO_2CH_3}{\underset{\vert}{CH}}-NH_2$	-13	2.5	2.5
$p\text{-}HOC_6H_4-\underset{\displaystyle CO_2CH_3}{\underset{\vert}{CH}}-NH_2$	-15	4.2	3.6

Figure 4. Correlation between enantiomer distribution constants (EDC) and separation factors (α)

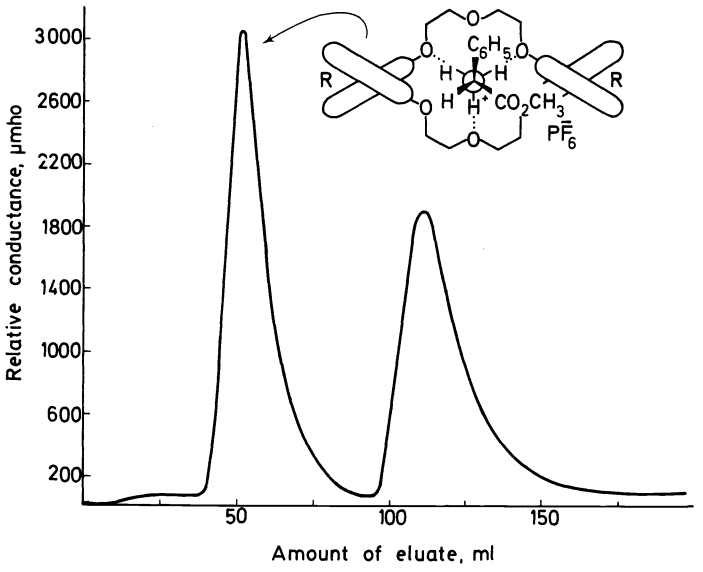


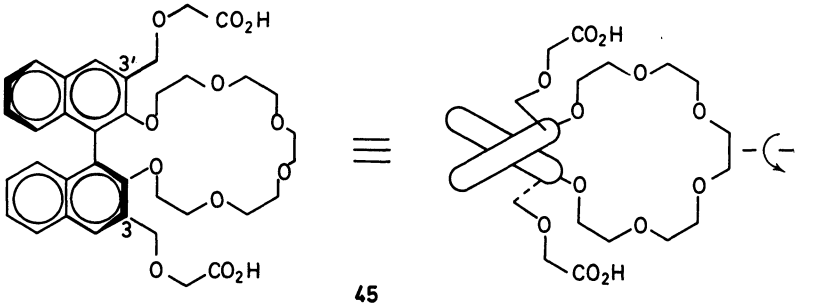
Figure 5. Optical resolution by chiral recognition in liquid–liquid chromatography

optical purity and separations of primary amine mixtures that differ in gross structure as well as configuration. Appropriate manipulation of the physical properties of the host molecule should allow development of liquid–liquid, solid–liquid and thin layer chromatographic systems applicable to a variety of problems.

CHIRAL RECOGNITION OF HOST STRUCTURES BY AMINO ACIDS

An examination of molecular models (CPK) suggested that compound **45** might possess structural features that would cause it to bind and lipophilize amino acids with chiral selectivity. The substance possesses a central macro-ring capable of binding the ammonium group. Two arms terminated by carboxyl groups are oriented over the top and bottom of the best plane of the ring's oxygens. The designed function of one carboxyl group was to hydrogen bond the carboxyl group of the amino acid. The second carboxyl provided an anion that could centre beneath the ammonium ion of a bound amino acid, and form an ion pair. The structure contains a binaphthyl unit to provide a chiral barrier against which might nestle the hydrogen attached to the asymmetric centre of a complexed amino acid of the proper configuration. The R-group attached to the asymmetric centre of that complexed amino acid extends away from the chiral barrier into space over the macro-ring. The host molecule before complexation contains a C_2 axis, so complexation at either face of the macro-ring produces the same complex. Formula **46** indicates the structure of the more stable diastereomeric complex suggested by the molecular models [20].

Compound **45** and its enantiomer were prepared in an optically pure



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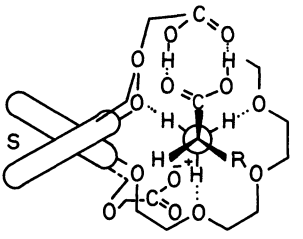


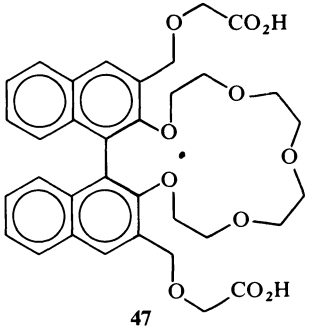
46

state, and their absolute configurations and maximum rotations were determined. The compounds proved optically and structurally stable to working conditions. Amino acids were found by p.m.r. spectral changes of host and guest to complex one another in acetic acid. By manipulation of the relative amounts of added chloroform and water to acetic acid solutions of the complex, two phases were generated. With one set of proportions, the water-rich phase contained only complexed host and excess amino acid, and the chloroform-rich phase contained only uncomplexed host compound. With a different set of preparations, the water-rich phase contained only uncomplexed amino acid, and the chloroform-rich phase contained only host and complexed amino acid. P.m.r. spectra of each phase allowed identification of its contents. These distribution experiments provided a means of determining the extent and direction of chiral recognition of optically active guest for racemic host in the water-rich phase, or of optically active host for racemic guest in the chloroform-rich phase, depending on which set of proportions of solvents were employed[20].

With molar equivalents of optically pure (R)-valine and racemic **45**, the proportions of solvent were adjusted to distribute half of **45** in each phase at equilibrium. The phases were separated, and the host compound isolated from the water-rich layer proved to be enriched in (R)-**45** to provide an EDC value of about 2.9.

The second type of experiment was conducted with optically pure (S)-**45** (1 equivalent) and racemic valine (2.4 equivalents), and a one-to-one complex formed in the chloroform-rich layer (p.m.r. spectra). The valine isolated from that layer was enriched enough in (S)-valine to provide an EDC value of about 1.5. In both experiments, the more stable diastereomer was that predicted to be the more stable, based on **46** as a model[20].

Structural variants of host compound **45** were prepared to test the role assigned each part of **46** in amino acid complexation and chiral recognition. Compound **47** contains one fewer ethylenoxy unit than **46** in its major ring, and failed to complex valine. Molecular models suggest that the ring is too small to accommodate an ammonium group. Compound **48** contains one more ethylenoxy unit than **45**, and although it complexed valine well, it gave essentially no chiral recognition. Molecular models of a valine complex of **48** suggest that the three most basic, alternate oxygens remote from the chiral barrier bind the ammonium ion. Thus, the two chiral elements of the complex are distant from each other, and no chiral recognition is expected. Compound **49** is an isomer of **45** in which the two arms are placed in the remote 6-positions of the binaphthyl unit. The compound possessed the same solubility characteristics as **45**, but was a poor complexer of valine, and exhibited no chiral recognition in complexation[21]. Compound **50** resembles **45** except that one arm is missing. The substance complexes valine well, but exhibits little chiral recognition[20].



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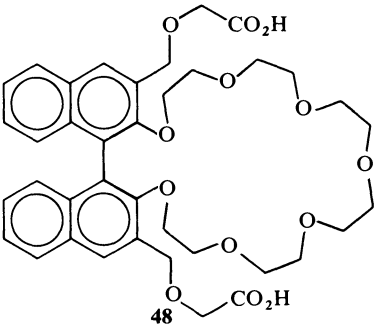

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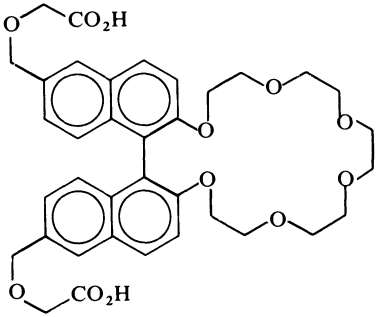

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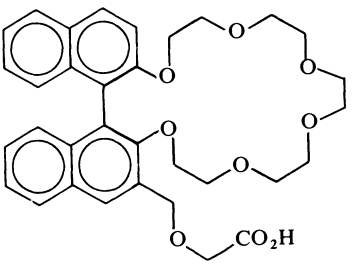
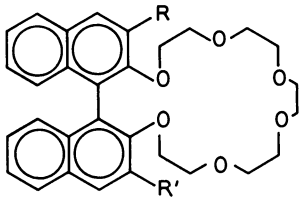


50

Other racemic compounds were prepared and examined for the ability of optically active valine to complex them with chiral recognition under the same conditions employed for the parent substance, **45**[21]. *Figure 6* lists the results. For compounds **51**–**55**, the EDC values were less accurate because the valine could not be confined as well to the water-rich layer as with **45**. In all cases in which chiral recognition was detected, the (R)(R) or (S)(S) diastereomers were the more stable, as with **45**[21].



Comp. No.	R	R'	Chiral recognition (EDC)	Separation factor (α)
45	$CH_2OCH_2CO_2H$	$CH_2OCH_2CO_2H$	2.9	3.1 - 3.2
51	$CH_2SCH_2CO_2H$	$CH_2SCH_2CO_2H$	~1.7	1.9-2.1
52	$CH_2CH_2CO_2H$	$CH_2CH_2CO_2H$	~1.1	1.0
53	$CH_2SCH_2CH_2CO_2H$	$CH_2SCH_2CH_2CO_2H$	~1.1	–
54	CH_3	$CH_2OCH_2CO_2H$	1.0	–
55	CH_2OH	$CH_2OCH_2CO_2H$	~1.3	–

Figure 6. Enantiomer distribution constants (EDC) and separation factors (α) for (R)-valine and arm-carrying host compounds

Substitution of a sulphur for the ether oxygens of the arms of **45** gave **51**. Somewhat lower chiral recognition resulted. However, **51** lipophilized its complexed valine much more than did **45**. Compounds **52–55** showed very little chiral recognition. Molecular models of complexes of **52** and **53** suggest that high-energy methylene-to-methylene conformational interactions would be involved in the hoped for host–guest carboxyl-to-carboxyl interaction. In the model of the complex of **52**, the upper arm is not long enough to provide good hydrogen bonding. In that of **53**, the larger number of atoms in the arm leads to congestion. Although the methyl group of **54** extends the chiral barrier, as do all of the arms, the compound exhibited *no chiral recognition.* Clearly, extension of the chiral barrier of the host on the side to which the guest is complexed does not provide chiral recognition. The hydroxymethylene arm of **55** appears to hydrogen bond the carboxyl group of the valine somewhat (EDC ~ 1.3), but the resulting complex is less structured than when carboxyl-to-carboxyl binding is possible, as in the complexes of **45** and **51**[21].

Racemic **45** was resolved to optical purity of both enantiomers by liquid–liquid chromatography. A solution of (S)-valine in 80 per cent acetic acid–20 per cent water absorbed on Celite served as the stationary phase, and

benzene carrying the host molecule was used as the mobile phase. As expected, the less fully complexed (R)-**45** emerged from the column first, followed by (S)-**45**, each of which was characterized[20].

Small analytical columns of the same kind were employed to determine the separation factors (α) of (S)-valine for four of the potential host compounds. The amount of the host compound in the column eluate was monitored by passing the solution through an ultra-violet detector cell. The mobile phase consisted of 9:1 benzene-pentane. Base-line separation was observed for **45**, and near-base-line separation for **51**. The enantiomer distribution constants (EDC) obtained in the partitioning experiments are not far from the separation factors of the column, even though the non-polar solvents were different. In the partitioning experiments, chloroform was the non-polar solvent; and in the columns, 9:1 benzene-pentane was employed. However, the chiral recognition occurred in the water-rich phase in both systems, and so the correlation is not surprising[22].

CONCLUSIONS

These results have demonstrated that host compounds can be designed and synthesized which possess complementary relationships to specified guest compounds. Binding constants can be systematically manipulated by structural changes in the host compounds. Polar guest compounds ordinarily only soluble in water can be lipophilized by covering their hydrophilic sites with the non-polar 'skin' of appropriately structured host compounds. Incorporation of chiral barriers in the host compounds leads to chiral recognition in complexation whose magnitude can be manipulated by structural changes. Total optical resolutions of host by guest, and of guest by host have been realized. A rational approach to highly structured molecular complexation has been developed based on the use of scale molecular models, synthetic techniques and applications of physical organic concepts of binding forces and steric effects.

REFERENCES

[1] W. P. Jencks, *Catalysts in Chemistry and Enzymology*, Part 2, p 323. McGraw-Hill: New York (1969).
[2] A. L. Lehninger, *Biochemistry*. p 208. Worth: New York (1970).
[3] D. W. Griffiths and M. L. Bender, *Advanc. Catal.* **23**, 209 (1973).
[4] L. J. Andrews and R. M. Keefer, *Molecular Complexes in Organic Chemistry*, p 44. Holden-Day: San Francisco (1964).
[5] C. J. Pedersen, *J. Amer. Chem. Soc.* **89**, 2495, 7017 (1967).
K. Madan and D. J. Cram, *J.C.S. Chem. Commun.* 427 (1975).
[7] G. W. Gokel and D. J. Cram, *Chem. Commun.* 481 (1973).
[8] J. M. Timko and D. J. Cram, *J. Amer. Chem. Soc.* **96**, 7159 (1974).
[9] M. Newcomb, G. W. Gokel and D. J. Cram, *J. Amer. Chem. Soc.* **96**, 6810 (1974).
[10] J. M. Timko, R. C. Helgeson, M. Newcomb, G. W. Gokel and D. J. Cram, *J. Amer. Chem. Soc.* **96**. 7097 (1974).
[11] R. C. Helgeson, J. M. Timko and D. J. Cram, *J. Amer. Chem. Soc.* **96**, 7380 (1974).
[12] R. C. Helgeson, J. M. Timko and D. J. Cram, *J. Amer. Chem. Soc.* **95**, 3023 (1973).
[13] E. P. Kyba, K. Koga, L. R. Sousa, M. G. Siegel and D. J. Cram, *J. Amer. Chem. Soc.* **95**, 2692 (1973).

[14] R. C. Helgeson, J. M. Timko, P. Moreau, S. C. Peacock, J. M. Mayer and D. J. Cram, *J. Amer. Chem. Soc.* **96**, 6762 (1974).
[15] K. N. Trueblood and I. Goldberg, private communication.
[16] P. Moreau and D. J. Cram, unpublished results.
[17] G. W. Gokel, J. M. Timko and D. J. Cram. *J.C.S. Chem. Commun.* 394 (1975).
[18] F. deJong, M. G. Siegel and D. J. Cram, *J.C.S. Chem. Commun.* 551 (1975).
[19] L. R. Sousa, D. H. Hoffman, L. Kaplan and D. J. Cram, *J. Amer. Chem. Soc.* **96**, 7100 (1974).
[20] R. C. Helgeson, K. Koga, J. M. Timko and D. J. Cram, *J. Amer. Chem. Soc.* **95**, 3021 (1973).
[21] R. C. Helgeson and D. J. Cram, unpublished results.
[22] L. A. Domeier and D. J. Cram, unpublished results.