Enantioselective and Diastereoselective Molecular Recognition of Neutral Molecules

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1 Introduction

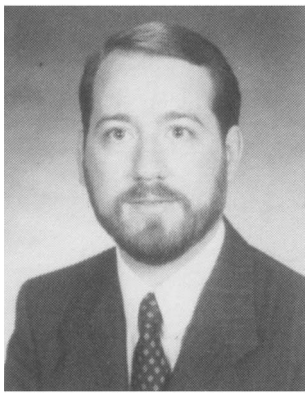
Selective molecular interactions that control or initiate specific physical functions are the essence of biological chemistry. The field of molecular recognition is concerned with studies of such phenomena. Biology without molecular recognition is unimaginable. Vital biochemical processes such as molecular transport, genetic information processing, and protein assembly involve molecular recognition and complexation as an essential action. An elucidation of the rules and restrictions which govern these intermolecular interactions is important for the understanding and manipulation of these processes. Therefore, the design and synthesis of synthetic receptors has become an important and rapidly growing field of chemistry.[1-3]

The exquisite control and efficiency seen in biochemical systems is a consequence of the great selectivity of molecular interactions that have evolved in biological organisms. A great deal remains to be learned about the ways in which selectivity can be achieved with synthetic receptors. Over the past 20 years, studies in molecular recognition have given chemists the tools that are needed to design, build, and evaluate enantioselective and diastereoselective host molecules, and considerable attention is now being focused on this area. Enantioselective host molecules carry great potential for synthetic, separative, and analytical purposes. This review will discuss the enantioselective and diastereoselective complexation of neutral organic molecules by synthetic hosts in solution and assess progress in the field. Binding studies involving charged molecules and binding studies where no attempt was made to test for diastereoselectivity or enantioselectivity will not be discussed.

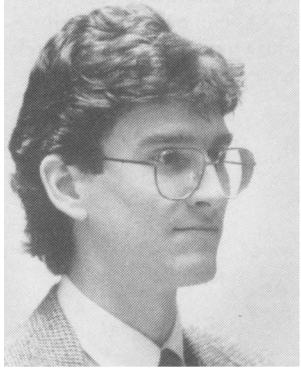
The forces involved in neutral molecular recognition and complexation are non-covalent intermolecular interactions – principally dipole–dipole interactions, dipole–induced dipole interactions, hydrogen bonding, London dispersion forces, π-stacking interactions, charge transfer interactions, and hydrophobic or solvophobic effects. It has been pointed out that in order for a receptor to exhibit enantioselectivity, it must have at least three points of interaction with one of the guest enantiomers, at least one of which must be steriochemically dependent. These interactions may be either attractive or repulsive.[4,5] Of course two adjacent molecules interact at all points simultaneously. In analysing selectivity one is often faced with the question of whether or not there indeed exist three (and only three) clearly identifiable regions of the system that are essential for enantioselective binding.

The two molecules involved in an association event are often called 'host and guest' or 'receptor and substrate'. 'Host' and 'guest' (and receptor and substrate) are rather ambiguous descriptors and one person's host can be another person's guest. Kitaigorodski recognized that when crystals form, the convex portions of one molecule fit into the concave portions of the next molecule.[6] When the two molecules that constitute the host–guest system interact according to Kitaigorodskii's model, it is usual to identify the molecule presenting the convex surface as the 'guest' and the 'host' is the molecule presenting the more concave aspect. Unfortunately, the nomenclature is complicated by the fact that both interacting molecules may be convex: there may be no definable concave surface. The final definition of host and guest in such systems is arbitrary. Fortunately, molecules behave the same no matter what label the chemist may assign!

To help organize this review, host compounds have been divided into two general classes. These classes are distinguished primarily by their size and by the shape of their binding sites. The first class consists of relatively small molecules with convex binding sites. Since by definition guests also bear convex binding sites, these hosts usually interact with a limited portion (less than half) of the guest surface. They are typically used as chiral solvating agents or as chiral stationary phases for HPLC. The second class consists of relatively large molecules with concave binding sites. These hosts typically bind a guest by encapsulating it within a cleft or pocket. Since the binding site of the host is concave, and the binding site of the guest is convex, they usually interact with each other at many different points over the surface of the guest. These hosts normally exhibit substantially stronger binding than the first class, and they have usually been more thoroughly studied and characterized.



Thomas H. Webb was born in 1962 in Aberdeen, Maryland. He received his B.S. from the University of Virginia in 1984 and is currently finishing his Ph.D. at the University of Pittsburgh with Craig Wilcox. His dissertation work is on the subject of hydrophobic molecular recognition of neutral molecules.



Craig Wilcox was raised in a small town in Illinois. His interests in chemistry date from early childhood. During his undergraduate studies at Illinois Institute of Technology, he worked with Kenneth Kopple, Sidney Miller, and David Gutman before moving to Caltech to study synthetic organic chemistry with Robert E. Ireland. After completing his dissertation on the total synthesis of polyether antibiotics, he studied physical organic chemistry for two years with Ronald Breslow at Columbia University. He is currently Professor of Chemistry at University of Pittsburgh where he is studying shape-selective aspects of molecular recognition, intermolecular forces, and biomimetic catalysis.

2 Chiral Solvating Agents

In 1965, Mislow and Raban first proposed that a non-racemic chiral solvent could cause a signal separation in the NMR spectra of enantiomeric solutes [7] This phenomenon was first demonstrated by Pirkle in 1966 when he reported different ^{19}F-NMR signals for the two enantiomers of (trifluoromethyl)phenylcarbinol when dissolved in optically active 1-phenylethylamine [8] This was soon extended to ^{1}H-NMR when he reported similar results with racemic phenylisopropylcarbinol dissolved in optically active 1-(1-naphthyl)ethylamine [9] Many other examples of such chiral solvating agents have since followed

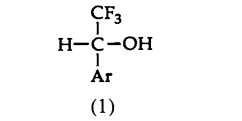
The primary applications for chiral solvating agents are for the determination of enantiomeric purity and absolute configuration Chiral solvating agents (CSAs) have a number of advantages over other techniques for these purposes More recent techniques, such as chiral HPLC, which involve the physical separation of the enantiomers, can be difficult and time consuming Spectroscopic methods, such as NMR, are much faster and less expensive Measurements of specific rotation, while very easy, are unreliable and are prone to error caused by contaminants Also, they can not be used to determine the enantiomeric purity of compounds not previously characterized To give separate NMR signals, the target enantiomers must be converted into diastereomers Adding a chiral solvating agent or lanthanide chiral shift reagent to bind to the target enantiomers is easier than chemically derivatizing them with covalently attached chiral auxiliaries Chiral solvating agents that do not contain metals are often preferable because they do not cause the spectroscopic line broadening often experienced with lanthanide chiral shift reagents

$$H(+) + G\text{-}(+) \overset{K}{\rightleftharpoons} HG(+\ +) \quad (1)$$

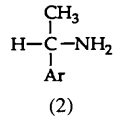
$$H(+) + G(-) \overset{K}{\rightleftharpoons} HG\text{-}(+,-) \quad (2)$$

In NMR studies, the signal separation of enantiomers in the presence of a CSA is caused by the formation of temporary diastereomeric complexes between the solute and the CSA, as shown in equations 1 and 2, where H-(+) is the optically active host CSA, and G-(+) and G-(−) are the enantiomeric solutes The NMR signal observed for each enantiomer is the time-averaged signal of both the complexed and the uncomplexed material This can give rise to signal non-equivalence in two ways First, a difference in association constants, K^+ and K^-, between the two enantiomers and the CSA, can cause one enantiomer to be preferentially bound This gives rise to different time-averaged NMR signals Second, the two enantiomers may have the same association constants with the CSAs, and therefore be bound in equal proportions, but the two diastereomeric complexes thus formed may have intrinsically different spectra Most cases will involve a combination of these two mechanisms Usually, large association constants are desirable in order to maximize the amount of shift separation and to allow low concentration of solute and of CSA to be used

Among the most widely employed CSAs, due both to their broad efficacy and their commercial availability, are the aryltrifluoromethylcarbinols (1) and 1-arylethylamines (2) developed by Pirkle and co-workers [8 9] These CSAs can bind to the solutes *via* two-point hydrogen bonding as shown in (3) and (4), and rely on the proximity of the aryl group to induce magnetic anisotropy CSAs of type 1 require solutes containing hydrogen bond accepting groups (A), and CSAs of type 2 require solutes containing hydrogen bond donating groups (D) Both types of CSAs also require a solute to contain a second functional group that is capable of binding to either the acidic carbinyl hydrogen or the aryl group of the CSA CSAs of type 1 have been found to be effective for solutes such as carboxylic esters, lactones, ethers, aryl amines, amine oxides, oxaziridines, phosphine oxides, sulfinates, sultines, sulfinate esters, sulfoxides, sulfites, and sulfinamides CSAs of type 2 have been found to be effective for solutes such as alcohols, carboxylic acids, and amides



(1)



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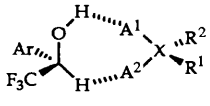
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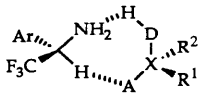
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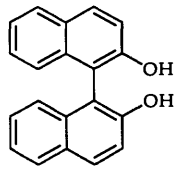

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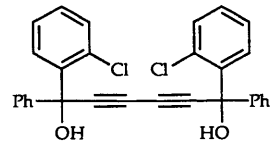

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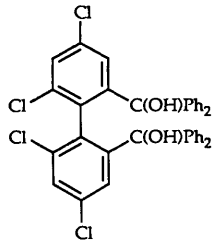
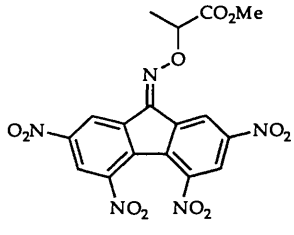


(7)

A number of different CSAs have also been developed by Toda and co-workers These CSAs can induce signal separation in hydrogen bond-accepting solutes 2,2′-Dihydroxy-1,1-binaphthyl (5) has been found to cause signal separation for amines, alcohols, sulfoxides, and selenoxides [10] 1,6-Di(*o*-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol (6) has been found to cause signal separation for amines, phosphine oxides, and arsine oxides [10] 4,4′,6,6′-Tetrachloro-2,2′-bis(hydroxydiphenylmethyl)-biphenyl (7) has been found to cause signal separation for amines, lactams, amine *N*-oxides, alcohols, sulfoxides, sulfoximines, selenoxides, phosphinates, phosphine oxides, and arsine oxides [11] These compounds have also been used to perform optical resolution on enantiomeric solutes by clathrate formation

It is not necessary for a CSA to be capable of forming hydrogen bonds in order to bind to the solute CSAs have also been designed which rely entirely on charge-transfer forces



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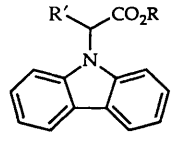
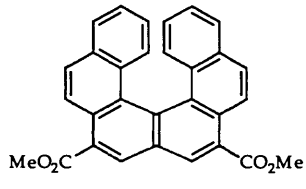


(9)

	R	R′
a	Me	H
b	Me	Me
c	Me	Et
d	Et	Et



(10)

Mannschreck *et al* have used the fluorene derivative (8) to induce signal splitting in the racemic carbazole derivatives (9) [12] Conversely, Balan and Gottlieb have used the optically active helicene (10) to induce signal splitting in racemic (8) [13]

A large number of other CSAs have also been developed Two good (though slightly outdated) reviews of the area are available [14 15] Most of the concave host molecules discussed in Section 4 can also function as CSAs

3 Chiral Stationary Phases

One of the principal techniques for the optical resolution of enantiomers is chiral chromatography The earliest chiral stationary phases (CSPs) used for this purpose were natural materials such as wool, paper, or cellulose Modern CSPs are usually synthetically designed for the resolution of certain classes of enantiomers New CSPs can be designed solely for the separation of a specific enantiomer, or they can be discovered by an educated process of trial and error Many CSPs have been discovered using the concept of reciprocity, by which a molecule that is found to be resolvable on an existing CSP is itself attached to a solid support and tested as a CSP Several generations of reciprocal CSPs have been developed in this manner [16]

In designing CSPs, it must be remembered that, unlike CSAs, CSPs require that the two enantiomers have different association constants in order to achieve separation To avoid long retention times and peak broadening, it is best if the CSP exhibits weak binding (low K_a) to the substrate, but at the same time, in order to achieve separation, it must exhibit a large difference in binding strengths (ΔK_a) between the two enantiomers

There are several different broad and overlapping classes of CSPs used today These include chiral polymer-based, protein-based, host–guest complex, ligand exchange, and donor–acceptor CSPs Most neutral organic compounds are separated on donor–acceptor (DA) CSPs These involve interactions between neutral functionality using hydrogen bonding, π donor–acceptor, dipole stacking, and steric interactions for binding and enantioselection

The first DA CSP was demonstrated in 1976 by Mikes *et al*, when several helicenes were resolved using (11), which probably relies entirely on π donor–acceptor interactions [17 18] The most common type of DA CSP available commercially is the Pirkle type, developed by W H Pirkle at the University of Illinois There are two types of Pirkle DA CSPs, the π-electron acceptors and the π-electron donors [19 20] The Pirkle π-electron acceptor DA CSPs are based on 3,5-dinitrobenzoyl derivatives of phenylglycine (12) and of leucine (13) They are used to separate enantiomers which are π-electron donors and contain aromatic functionality The Pirkle π-electron donor DA CSPs are based on *N*-(2-naphthyl)alanine (14) These are used to separate enantiomers such as amines, amino acids, alcohols, and thiols which have been derivatized with a π-electron acceptor Typical derivatives are those formed with 3,5-dinitrobenzoyl chloride (15) or 3,5-dinitrophenyl isocyanate (16) Both types of Pirkle DA CSPs rely on π donor–acceptor, hydrogen bonding, dipole stacking, and steric interactions to achieve selectivity and binding

Almost all DA CSPs rely on π–π interactions as a major source of their activity, though there are a few which do not One notable example of the latter type is a derivative of *N N'*-2,6-pyridinediylbis[(*S*)-2-phenyl butanamide] (17) developed by Feibush *et al* [21] It has been used to separate enantiomers of barbiturates, glutarimides, and hydantoins This DA CSP uses three hydrogen-bond interactions for binding, which mimic those responsible for DNA base pairing Since these three hydrogen-bond interactions are co-planar however, they are not capable of chiral discrimination This is achieved by the steric interactions of the chiral substituent groups

A wide variety of other CSPs have also been developed, several of which are available commercially Two excellent reviews of this area are available [22 23]

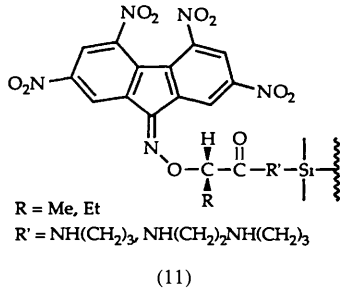
4 Concave Hosts

Concave hosts are differentiated from most CSAs and CSPs primarily by the nature of their binding sites Most CSAs and CSPs have convex binding sites and only interact with a minor portion of the guest surface Concave hosts interact with the guest in a much more intimate fashion They have large concave binding sites, and they enclose the guest in a cleft or pocket and interact with it from several converging directions This not only increases the strength of binding, but the selectivity as well Concave hosts can often function as special CSAs or CSPs

4.1 Hydrogen Bonding Hosts

Host molecules which utilize hydrogen bonding forces often exhibit strong binding as well as a high degree of enantioselection This is due to both the strength and the high degree of directionality of hydrogen bonds Minor changes in the geometry of the hydrogen bonds will greatly weaken them This directionality enables host molecules to be designed which bind guests strongly only in a particular conformation Minor deviations in the structure of the guests can greatly weaken binding by changing the conformation of the complex and distorting the geometry of the hydrogen bonds

A large number of enantioselective hydrogen bonding hosts have been designed by Rebek and co-workers [24–28] These hosts



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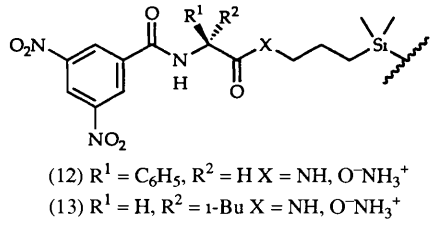
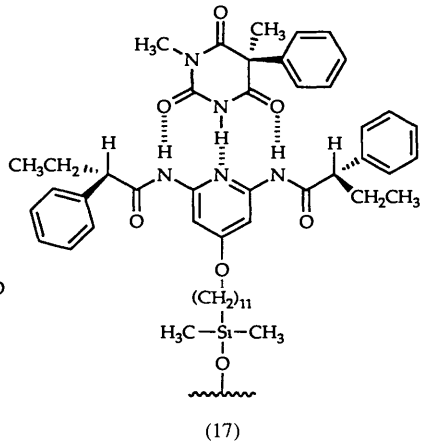


(12) $R^1 = C_6H_5$, $R^2 = H$ X = NH, $O^-NH_3^+$
(13) $R^1 = H$, $R^2 = i$-Bu X = NH, $O^-NH_3^+$



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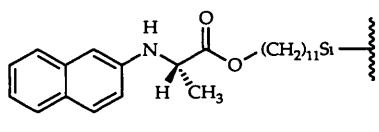

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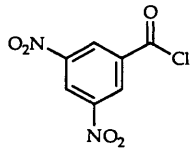

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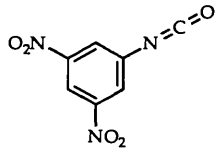

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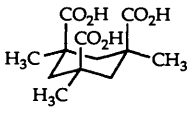

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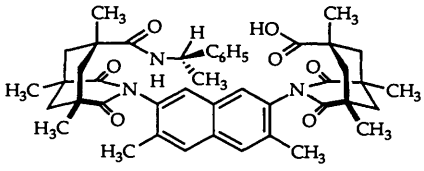

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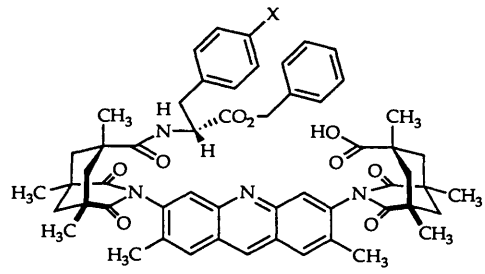
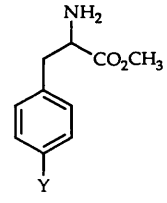
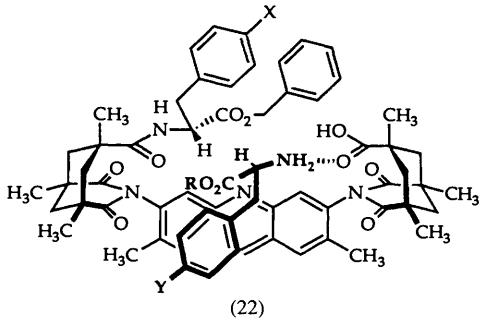


(20a) X = H
(20b) X = NO_2



(21a) Y = NO_2
(21b) Y = OH

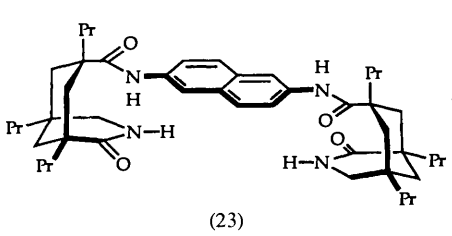


(22)

take advantage of the U-shaped relationship between the carboxyl functionalities in Kemp's triacid (18) and its derivatives By using two of these units, separated by a spacer, the Rebek team has been able to construct clefts containing convergently directed hydrogen bonding groups

The first enantioselective hosts of this type consisted of clefts containing chiral secondary amides Host (19) acts as a chiral solvating agent for racemic alcohols such as α-phenylethanol and menthol [24] Hosts (20a and b) act as chiral solvating agents for racemic phenylalanine derivatives (21a and b) [25] The phenylalanine derivatives are bound not only by a hydrogen bond between the guest amine and the host acid, but also by π stacking interactions between the phenyl ring of the guest and the acridine unit of the host Enantioselection is provided by steric repulsion between the ester of the guest and the bulky amide of the host Structure (22) has been proposed as the conformation of this complex

More recently, the Rebek group has synthesized chiral clefts containing convergent lactams and cylic imides [(23), (24), and (25)] The convergent lactams [(23) and (24)] have been found by ^{1}H-NMR to bind the diketopiperazines (26) and (27),[26 27] L-hydantoins [(28)—(31)], and L-hydroorotic acid methyl ester (32)[23] with a high degree of enantioselectivity (Table 1) Host (+)-(23) was found to bind *cyclo*-(L-leucyl-L-leucine) (27) with



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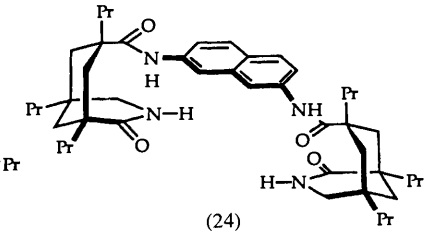

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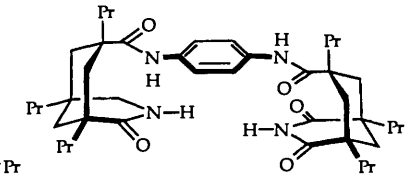

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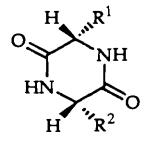
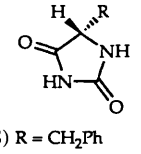
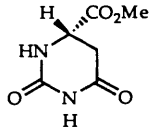


(26) R^1 = H, R^2 = i-Bu
(27) R^1 = R^2 = i-Bu



(28) R = CH_2Ph
(29) R = $CH_2CH(CH_3)_2$
(30) R = $CH(CH_3)_2$
(31) R = $CH(CH_3)CH_2CH_3$



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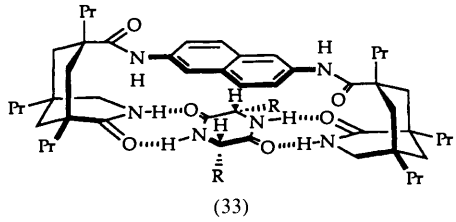


(33)

N-CBz-A1-A2-NHBn

(34) A1 = glycine; A2 = L-leucine
(35) A1 = L-leucine; A2 = glycine
(36) A1 = L-isoleucine; A2 = glycine
(37) A1 = A2 = L-isoleucine
(38) A1 = A2 = L-alanine

(N-CBz = *N*-carbobenzoxy
Bn = benzyl)

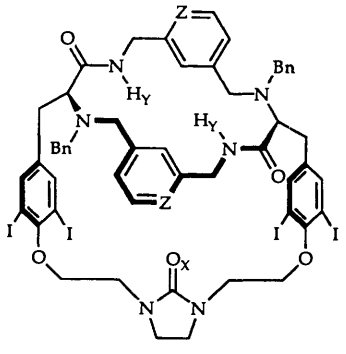
Table 1 Association constants[a] and $\Delta\Delta G$ values[b] of host (23) with guests (26) and (27), host (24) with guests (28)—(32), and host (25) with guests (34)—(38)

	Association constants, K_a (M^{-1}), for host						
Guest	(−)-(23)	(+)-(23)	(−)-(24)	(+)-(24)	(−)-(25)	(+)-(25)	$\Delta\Delta G^b$ (kcal mol^{-1})
(26)	73000	2900					−1 9
(27)	82000	840					−2 7
(28)			4800	1720			−0 6
(29)			1050[c]	390[c]			−0 6
(30)			7080	705			−1 4
(31)			7070	650			−1 4
(32)			380	2100			1 0
(34)					1672	1003	−0 3
(35)					4736	2340	−0 4
(36)					4250	2320	−0 4
(37)					62	134	0 5
(38)					320	405	0 2

Association constants were determined by NMR titrations in $CDCl_3$ carried out at 25°C [b] $\Delta\Delta G = \Delta G$ (−) enantiomer − ΔG (+) enantiomer The lower K_as for this guest are probably due to the fact that the $CDCl_3$ solution contained 10% d_8 THF

an association constant of approximately 82000 M^{-1}, while host (−)-(23) bound it with an association constant of approximately 840 M^{-1} This corresponds to a $\Delta\Delta G$ of 2 7 kcal mol^{-1}, which is among the largest observed for neutral substances The proposed conformation of the complex is shown in structure (33) For optimal binding, the guest is held in a rigid conformation by the four hydrogen bonds with the lactams Steric repulsions between the R groups of the guest and the naphthyl spacer of the host distort the disfavoured complex, severely reducing both the strength and number of the hydrogen bonds, thus reducing the strength of binding

Host (25) was found to exhibit enantioselectivity with dipeptides (34)—(38) (Table 1) [28] It is believed that the lower enantioselectivity found with the dipeptides is due to their greater flexibility and their ability to adopt multiple binding conformations



(39a) Z = CH
(39b) Z = N

Still and co-workers have also designed hosts (39a and b) which bind amide and amino-acid derivatives (Table 2) [29 30] In host (39a) the amides are bound by the hydrogen bonds $H_Y \cdots O_Y$ and $O_1 \cdots H_1$ Enantioselectivity is due to the steric interactions of the other substituents In host (39b), an additional hydrogen bond is allowed, $H_- \cdots Z$, which can lead to enhanced enantioselectivity Two additional reports by this group are included in the addendum to this review

Mendoza and co-workers were able to design a host (40) to bind enantioselectively to zwitterionic amino-acids containing aromatic side-chains [31] When an aqueous solution of racemic Trp or Phe was extracted with a CH_2Cl_2 solution of (40), only the L-enantiomers were extracted An HPLC analysis of the diastereomeric dipeptides prepared from the extracts and suitable L-Leu derivatives indicated the amount of D-enantiomer to be less than 0 5% for Trp and less than 2% for Phe It has been

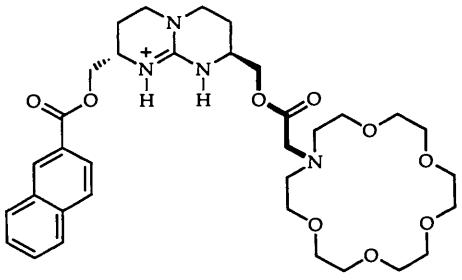
Table 2 Free energies of association[a] for hosts (39a and b) and various amides

		ΔG(kcal mol^{-1}) of binding for		
Guest	Solvent	(39a)	(39b)	$\Delta\Delta G^b$ (kcal mol^{-1})
(*S*)-PhCHMeNHCOMe	C_6D_6	−3 04		
(*R*)-PhCHMeNHCOMe	C_6D_6	−2 62		0 42
(*S*)-PhCHMeNHCOH	C_6D_6	−3 18		
(*R*)-PhCHMeNHCOH	C_6D_6	−2 85		0 33
(*S*)-PhCHMeNHCOEt	C_6D_6	−1 80		
(*R*)-PhCHMeNHCOEt	C_6D_6	−1 55		0 25
(*S*)-1-NpCHMeNHCOMe	C_6D_6	−2 56		
(*R*)-1-NpCHMeNHCOMe	C_6D_6	−2 31		0 25
(*S*)-BnOAlaNHCOMe	C_6D_6	−2 29		
(*R*)-BnOAlaNHCOMe	C_6D_6	−1 81		0 48
(*S*)-MeOPGlyNHCOMe	C_6D_6	−1 91		
(*R*)-MeOPGlyNHCOMe	C_6D_6	−2 06		−0 15
Ac-L-Ala-NHBn	$CDCl_3$		−2 36	
Ac-D-Ala-NHBn	$CDCl_3$		−1 36	−1 0
PhAc-L-Ala-NHMe	$CDCl_3$		−2 02	
PhAc-D-Ala-NHMe	$CDCl_3$		−1 91	−0 1
Ac-L-Ala-OBn	$CDCl_3$		−1 27	
Ac-D-Ala-OBn	$CDCl_3$		−0 86	−0 4[c]
Ac-L-Ala-OBn	C_6D_6		−3 46	
Ac-D-Ala-OBn	C_6D_6		−2 93	−0 5
Ac-L-Ala-L-Ala OBn	$CDCl_3$		−2 57	
Ac-D-Ala-L-Ala-OBn	$CDCl_3$		−1 67	−0 9
Ac-L-Ala-D-Ala-OBn	$CDCl_3$		−2 24	
Ac-D-Ala-D-Ala-OBn	$CDCl_3$		−1 48	−0 8
Ac-L-Ala-NH-t-butyl	$CDCl_3$		−2 35	
Ac-D-Ala-NH-t-butyl	$CDCl_3$		−1 04	−1 3[c]
Ac-L-Ala-NH-t-butyl	C_6D_6		−4 38	
Ac-D-Ala-NH-t-butyl	C_6D_6		−3 31	−1 1

Free energies of association were determined by NMR titration at 25°C [b] $\Delta\Delta G = \Delta G_S - \Delta G_R$ for (39a) or $\Delta G_1 - \Delta G_2$ for (39b) These figures are uncertain due to a low extent of saturation achieved in the titration

proposed that this chiral recognition is due to the three interactions shown in (41) The carboxylate undergoes hydrogen bonding with the guanidinium unit, the aromatic side-chain undergoes π-stacking with the naphthalene unit, and the ammonium group binds with the crown ether Unlike the L-enantiomers, the D-enantiomers of the amino-acids cannot undergo all three interactions simultaneously

Diederich and co-workers have discovered that binaphthyl derivatives (42a—d) will enantioselectively bind quinine (43)



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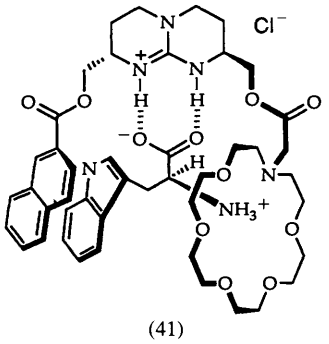

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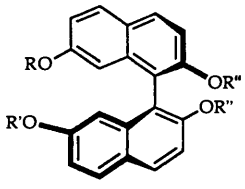
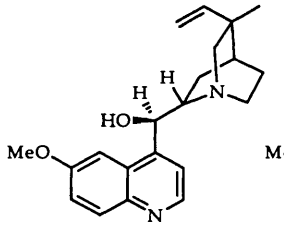
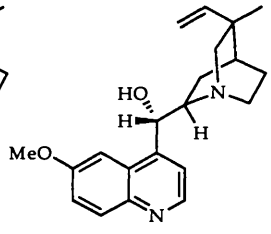


(42)	R	R'	R''
a	$PhCH_2$	$PhCH_2$	H
b	$PhCH_2$	$PhCH_2$	CH_3
c	H	H	CH_3
d	H	$PhCH_2$	CH_3



(43)



(44)

and quinidine (44) in the major groove The association constants are shown in Table 3 [32] When all of the hydroxyl groups on the binaphthyls are alkylated (42b), no binding is observed This indicates that hydrogen bonding is the principal attractive interaction involved, although π-stacking interactions between the aromatic rings may be involved as well

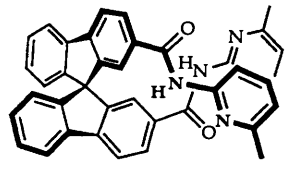
This discovery led them to design host (45), based on the 9,9'-spirobifluorene unit, which contains a more rigid, organized cleft than that of binaphthyl [33] Structure (45) exhibited strong binding and good enantioselectivity for a number of dicarboxylic acids [(47)—(55)], as shown in Table 4 A comparison with the binaphthyl host derivative (46), containing analogous functionality, demonstrated the importance of the conformational inflexibility of the spirobifluorene unit to its chiral recognition abilities

Hamilton and co-workers have designed a cleft molecule (56), based on the binaphthyl unit, which binds tartaric acid derivatives selectively [34] Fluorescence spectroscopy in CH_2Cl_2 gave association constants of 3.0×10^5 M^{-1} for D-(−)-dibenzoyl tartaric acid and 3.6×10^5 M^{-1} for L-(+)-dibenzoyl tartaric acid This gives a $\Delta\Delta G$ of 0.11 kcal mol^{-1} The proposed binding conformations are shown in (57) and (58) The enantioselectivity is believed to be due to unfavourable steric interactions between the benzoyl groups and the binaphthyl spacer in the D-(−)-

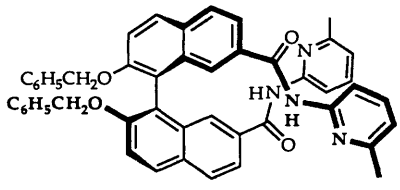
Table 3 Association constants[a] and $\Delta\Delta G$ values for hosts (42a—d) and guests (43) and (44)

Guest	Association constants, K_a (M^{-1}), for host		$\Delta\Delta G^b$ (kcal mol^{-1})
	(*R*)-(42a)	(*S*)-(42a)	
(43)	95	60	0.27
(44)	20	75	−0.74
	(*R*)-(42b)	(*S*)-(42b)	
(43)	—[c]	—[c]	—
(44)	—[c]	—[c]	—
	(*R*)-(42c)	(*S*)-(42c)	
(43)	1270	650	0.39
(44)	625	850	−0.18
	(*R*)-(42d)	(*S*)-(42d)	
(43)	775	140	0.99
(44)	105	550	−0.95

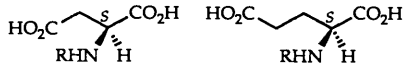
[a] Free energies of association were determined by NMR titration in $CDCl_3$ at 20 °C [b] $\Delta G = \Delta G_S - \Delta G_R$ [c] No measurable complexation was observed



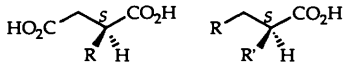
(45)



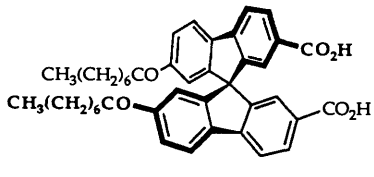
(46)



(47) R = $C_6H_5CH_2OCO$ (49) R = $C_6H_5CH_2OCO$
(48) R = n-BuOCO (50) R = n-BuOCO



(51) R = C_6H_5S (53) R = C_6H_5
(52) R = C_6H_5Se R'= Cbz



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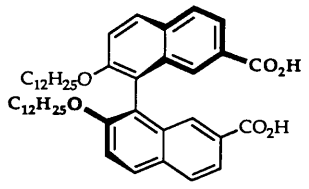
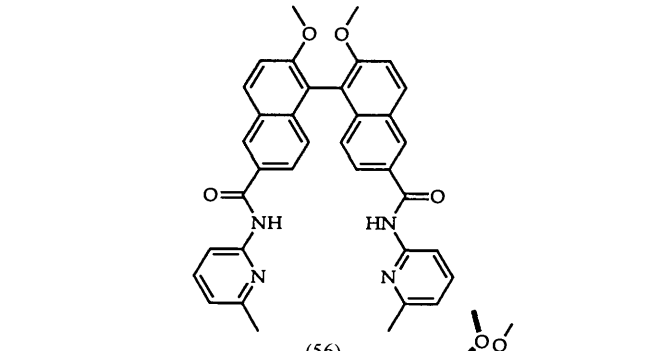


(55)

Table 4 Association constants[a] and $\Delta\Delta G$ values for hosts (45) and (46) and guests (47)—(55)

Guest	Association constants, K_a (M^{-1}), for host		$\Delta\Delta G^b$ (kcal mol^{-1})
	(*R*)-(45)	(*S*)-(45)	
(47)	820	4200	−0 9
(48)	1400	4800	−0 7
(49)	14000	3900	0 8
(50)	23000	10000	0 4
(51)	680	3400	−0 9
(52)	800	2200	−0 6
(53)	420	680	−0 3
(54)	490	11300	−1 8
	(*R*)-(46)	(*S*)-(46)	
(49)	20800	19400	0 1
(55)	8500	7200	0 1

Free energies of association were determined by NMR titration in $CDCl_3$ at 20°C [b] $\Delta\Delta G = \Delta G_S - \Delta G_R$



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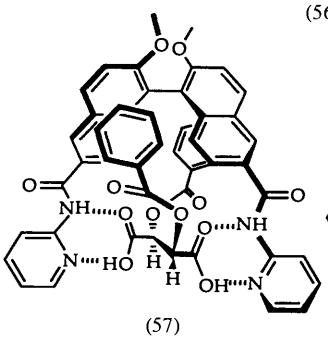

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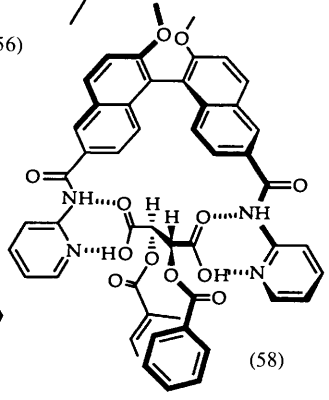
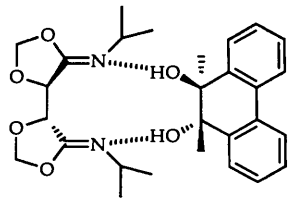


(58)

derivative For dipivaloyl tartaric acid derivatives, the association constants are $1\,01 \times 10^6$ M^{-1} for the D-(−)-enantiomer and $3\,2 \times 10^5$ M^{-1} for the L-(+)-enantiomer to give a $\Delta\Delta G$ of −0 67 kcal mol^{-1} The increased selectivity for the D-(−)-enantiomer is believed to be due to stabilizing π–Me interactions between the binaphthyl unit and the trimethyl acetate groups

Hara and co-workers have designed the host (*R*,*R*)-(59) to bind the diol (60) [35] The orientation of the hydrogen bonding sites forces the two diol enantiomers to bind with a different twist in their orientations The difference in the steric interactions for

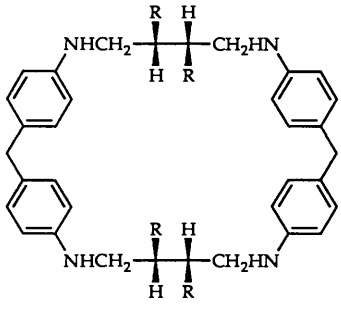


(*R*,*R*) (59) (*S*,*S*) (60)

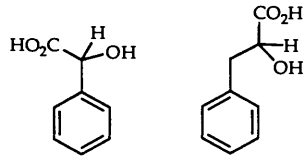
each orientation results in different strengths of binding The host (*R*,*R*)-(59) binds diol (*S*,*S*)-(60) with an association constant of 25 0 M^{-1}, and diol (*R*,*R*)-(60) with an association constant of 5 8 M^{-1} This corresponds to a $\Delta\Delta G$ of −0 87 kcal mol^{-1} between the two enantiomers

4.2 Lipophilic Binding Hosts

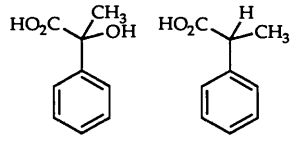
Since hydrogen bond interactions are less effective in aqueous media, π-stacking and hydrophobic interactions are often used to bind a substrate in water The relatively non-directed nature of these forces makes the design of enantioselective hosts more challenging since small changes in binding conformation will not necessarily result in large changes in binding strength These hosts usually tightly encapsulate their guests, making intimate contact over a large surface rather than at discrete points



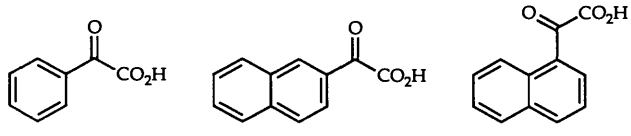
(61a) R = OCH_3
(61b) R = $OCH_2CH_2OCH_3$



(62) (63)



(64) (65)



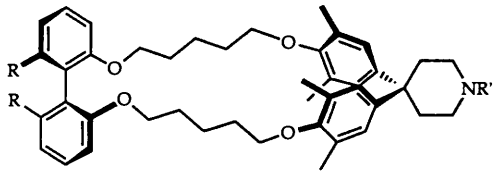
(66) (67) (68)

The first example of enantioselective recognition in aqueous media by a synthetic host was achieved by Koga and co-workers in 1984 [36] They used a cyclophane host (61a) consisting of two diphenylmethane skeletons bridged by two chiral C_4-chains derived from L-tartaric acid This was found to bind the aromatic carboxylic acids [(62)—(65)] in acidic D_2O(pD = 1 2) Although association constants were not determined, binding was evinced by large upfield shifts ($\Delta\delta$ up to −1 3 ppm) in the proton NMR signals of the guests Enantioselectivity was demonstrated by the signals of the two enantiomers being shifted to a different degree Further evidence of the enantioselectivity of these hosts was given when asymmetric reductions of achiral arylglyoxylic acids, (66)—(68), were performed on their inclusion complexes with hosts (61a) and (61b) using $NaBH_4$ [37] When the $NaBH_4$ reacts with the bound guests, it is believed that steric interactions with the host cause a preference for the reagent to approach from one face of the carbonyl over the other This gives rise to the reaction enantioselectivities shown in Table 5

Diederich and co-workers have been among the most prolific workers in this area, producing a number of chiral lipophilic

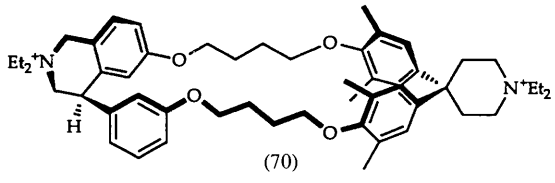
Table 5 Asymmetric reduction of arylglyoxylic acids

Host	Guest	e e (%)	Configuration
(61a)	(66)	2 4	*R*
(61a)	(67)	3 9	*R*
(61a)	(68)	9 7	*R*
(61b)	(68)	7 0	*R*

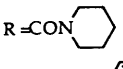
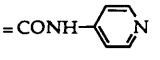
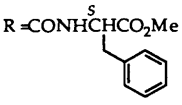


(69a) R = Me_2N, R' = Me
(69b) R = Et_2NCH_2 R' = Et

hosts Their first attempt was with hosts (69a and b), using the tetrasubstituted biphenyl unit as the source of chirality [38] These hosts failed to bind aromatic guests however, due to insufficient preorganization of the host cavities prior to complexation It was believed that the bridging aliphatic chains were free to approach each other, thus closing the cavity



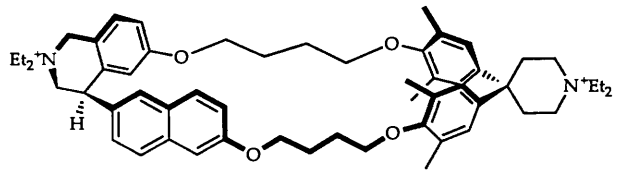
(70)

(71)
a R = CO_2H
b R = CO_2
c R = $CONH_2$
d R = CO_2Me
e R = 
f R = 
g R = 

The biphenyl unit was then replaced with a chiral source structurally related to the natural alkaloids latifine and cherylline, to give the host (70) [39 40] NMR studies in aqueous solutions with 40—50% MeOH demonstrated enantioselectivity by showing different chemical shifts between the enantiomers of both naproxen (71a) and its methyl ester (71d) A high degree of overlap between the signals of the host and the guests prevented an accurate determination of the association constants from being made However, very crude estimates were made, indicating association constants of approximately 50 M^{-1} for (71a), and 300 M^{-1} for (71d) The low association constants observed are believed to be due to the narrowness of the cavity provided by the chiral spacer

To alleviate this difficulty, the host was improved by replacing the phenyl ring of the chiral spacer with a naphthyl unit to provide a host (72) with a wider cavity [41] This host provides stronger binding to naproxen derivatives and demonstrates a moderate degree of enantioselectivity as shown in Table 6

A further improvement was made by using binaphthyl derivatives as chiral sources to give hosts (73) and (74) [37 32 42] The

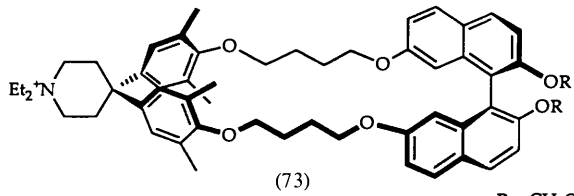


(72)

Table 6 Association constants[a] and $\Delta\Delta G$ values for host (72) and various naproxene derivatives

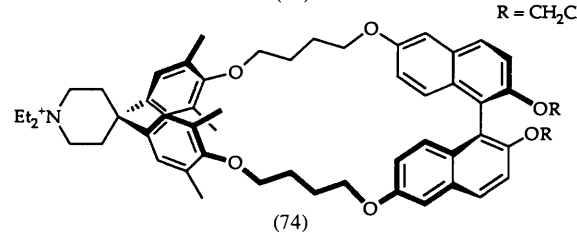
Guest	Association constants, K_a (M^{-1}), for host (*R*)-(72)	(*S*)-(72)	$\Delta\Delta G^b$ (kcal mol^{-1})
(71a)[c]	930	810	0 08
(71c)	450	420	0 04
(71d)	1130	1070	0 03
(71e)	1210	900	0 17
(71f)	730	470	0 26
(71g)[d]	230	200	0 08

Free energies of association were determined by NMR titration in D_2O/CD_3OD (60 40) at 20°C [b] $\Delta\Delta G = \Delta G_S - \Delta G_R$ [c] In 0 01 M D_2O CD_3OD (50 50) [d] In 0 01 M DCl/CD_3 OD (60 40)



(73)

R = $CH_2CH_2N^+Et_3$



(74)

'major groove' of the binaphthyl spacers was found to provide wide enough cavities for the inclusion of aromatic guests while retaining chiral discrimination These receptors were found to give good binding and enantioselection of the naproxen derivatives (71a—f) (Table 7)

In the anticipation that hosts containing two chiral spacers would give greater enantioselection than those containing one chiral and one achiral spacer, a number of hosts [(75)—(77)] were synthesized which contained two chiral binaphthyl spacers linked by two C_4-chains [43] These hosts were found to give very poor enantioselection (Table 8) This is believed to be due to the high degree of conformational flexibility available to these hosts

A highly rigid host (78), composed of a Troger's base and a diphenylmethane unit linked by two ethenoanthracene moieties, was reported by Wilcox and co-workers [44 46] This is one of the few hosts that provide enantio- and diastereo-selection of neutral aliphatic and alicyclic substrates Determined by NMR studies in aqueous media (pD = 6 8), enantioselection has been observed for menthol (79),[46] 3,3-dimethylcyclohexanol (80),[47] and citronellol (81) [48] Substantial diastereoselection has also been observed between (−)-menthol (79), (+)-isomenthol (82),[46 48] and (+)-neomenthol (83),[47] and between *cis*- and *trans*-4-t-butylcyclohexanol (84) [49] These conclusions are based on the observation of differing chemical shifts between the enantiomers and the calculation of differing apparent associa-

Table 7 Association constants[a] and $\Delta\Delta G$ values for hosts (73) and (74) with various naproxene derivatives

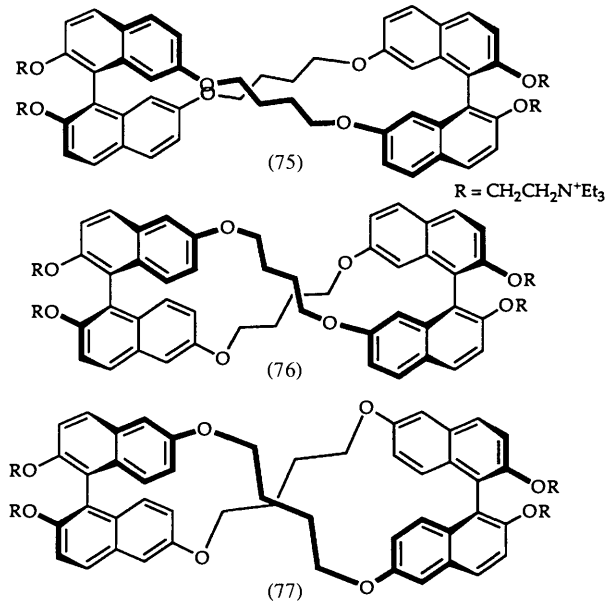
Guest	Association constants, K_a (M^{-1}), for host		$\Delta\Delta G^b$ (kcal mol^{-1})
	(*R*)-(73)	(*S*)-(73)	
(*S*)-(71a)	2105	2540	0 16
(*S*)-(71b)[d]	1040	1335	0 15
(*S*)-(71c)	775	1010	0 15
(*S*)-(71d)	2075	3110	0 23
(*S*)-(71e)	1760	2840	0 28
(*S*)-(71f)	1405	2490	0 33
	(*R*)-(74)		
(*S*)-(71f)	395		
(*S*)-(71f)	560		0 20

[a] Free energies of association were determined by NMR titration in D_2O/CD_3OD (60 40) at 20°C [b] $\Delta\Delta G = \Delta G_S - \Delta G_R$ In 0 1 M DCl/CD_3OD (60 40) [c] In 0 01 M K_2CO_3/CD_3OD (60 40)

Table 8 Association constants[a] and $\Delta\Delta G$ values for hosts (75), (76), and (77) with naproxene derivative (74f)

Hosts	Association constants, K_a (M^{-1}), for host		$\Delta\Delta G^b$ (kcal mol $^{-1}$)
	(*R*)-(74f)	(*S*)-(74f)	
(75)	—[c]	—[c]	—
(76)	320	375	− 0 09
(77)	435	455	~ 0

Free energies of association were determined by NMR titration in D_2O/CD_3OD (60 40) at 20°C [b] $\Delta\Delta G = \Delta G_S - \Delta G_R$ [c] No measurable complexation was observed



tion constants for enantiomeric and diastereomeric solutes Determination of precise association constants has been confounded by the observation of slightly different apparent association constants for different protons on a single guest This perturbation is likely to be due to the effect of a small amount of higher order (2 1 host guest) binding

Most lipophilic host molecules rely on π-stacking rather than hydrophobic interactions to achieve binding Since host (78) binds aliphatic and alicyclic guests, π-stacking interactions are not expected, and binding is believed to be achieved primarily by hydrophobic interactions Intermolecular interactions involving attractive forces between molecules, such as hydrogen bonding or π-stacking, are enthalpically favourable ($\Delta H < 0$) and entropically disfavourable ($\Delta S < 0$) According to the equation $\Delta G = \Delta H - T\Delta S$, the binding strength of host molecules which rely on such interactions should decrease as the temperature is increased Hydrophobic solute interactions are enthalpically disfavourable ($\Delta H > 0$) and entropically favourable ($\Delta S > 0$) Therefore, the binding strength of host molecules which rely on these interactions should increase as temperature is increased For example, for the hydrogen-bonded complex (86), prepared by Adrian and Wilcox,[50] the binding strengths dropped precipitously as the temperature was increased In dry $CDCl_3$, the association constants were 24000 M^{-1} at 283 K, 9400 M^{-1} at 293 K, 4800 M^{-1} at 303 K, 2100 M^{-1} at 313 K, and 1000 M^{-1} at 323 K A van't Hoff plot of this data revealed that $\Delta H = -14\ 3$ kcal mol^{-1} and $\Delta S = -30$ cal $mol^{-1}K$ For a complex based on π-stacking interactions, such as that between host (92f) and isoquinoline, prepared by Dougherty and co-workers,[51] the association constants again dropped steeply as the temperature increased The van't Hoff plot revealed that $\Delta H = -11$ kcal mol^{-1} and $\Delta S = -17$ cal $mol^{-1}K$ Binding studies with host (78) and (−)-menthol (79) were performed at various temperatures, and the association constants for one of the protons were found to be 3400 (+ 700, − 500) M^{-1} at 296 K, 4400 (+ 600, − 500) M^{-1} at 308 K, 4200 (+ 400, − 300) M^{-1} at 318 K, and 4500 (+ 1300, − 900) M^{-1} at 328 K [47] Different association constants were observed at these temperatures for other protons The observed differences in association constants calculated for various guest protons indicate that this system is perturbed by small amounts of higher order binding Because of this, and because the change in association constants over the observed temperature range is small compared with the uncertainties in the association constants, accurate determination of ΔH and ΔS *via* a van't Hoff plot is not possible It is significant however, that these association constants do not drop as the temperature is increased Instead, they seem to rise slightly Similar behaviour was shown by all of the guest protons observed This indicates that $\Delta H > 0$ and $\Delta S > 0$, and supports the hypothesis that binding in this case is achieved primarily by hydrophobic interactions

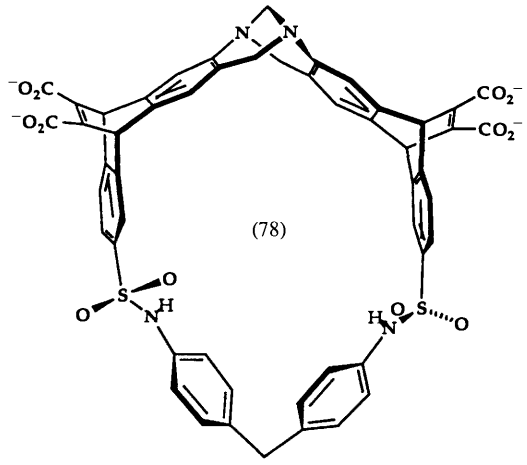
Another host (85) has also been synthesized which replaces the diphenyl methane unit with another ethenoanthracene unit [52] Preliminary results indicate that this host exhibits both stronger binding and greater enantioselectivity than host (78)

Murakami *et al* have designed a cage-type cyclophane (87) using L- and D-valine residues as chiral sources [53] This host has been shown to enantioselectively bind the steroid hormones α-estradiol (88), β-estradiol (89), and estratriol (90) as shown in Table 9 The chemical shifts induced by complexation indicate that it is the aromatic moieties of the steroids that are bound within the cavity This is further supported by the observation that testosterone (91), which does not contain an aromatic moiety, does not bind to host (87)

Dougherty and co-workers have also created a series of chiral hosts (92a—g) base on two linked ethenoanthracene units [54] These have been used to bind neutral achiral aromatic guests and to enantioselectively bind chiral cationic guests containing trimethylammonium substituents No results have been reported, however, in regard to their enantioselectivity for neutral chiral guests

4.3 Constrictive Binding Hosts

Another class of host molecules exists which, rather than relying on attractive interactions with the guests, utilizes what has been termed 'constrictive binding' [55] These hosts consist of rigid, hollow armatures containing portals which provide access to the



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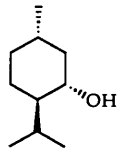
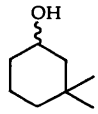


(-)-(79)



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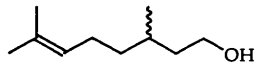

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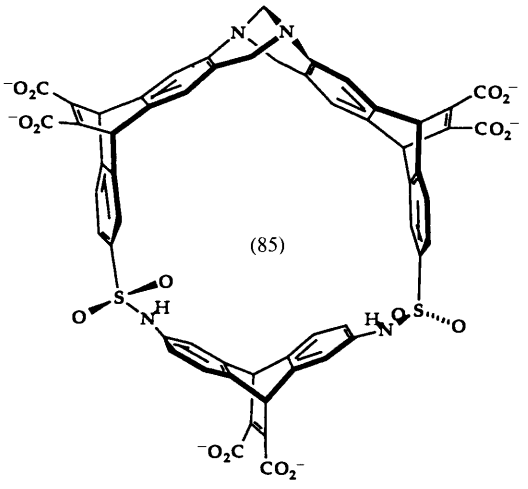

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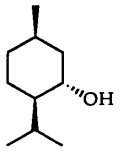
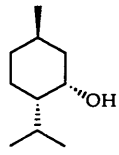
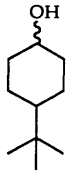


(+)-(82)



(+)-(83)



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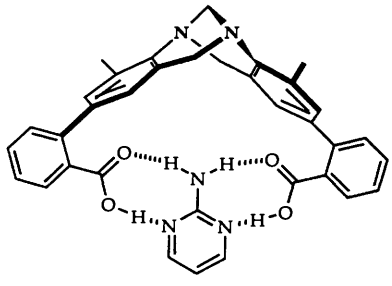

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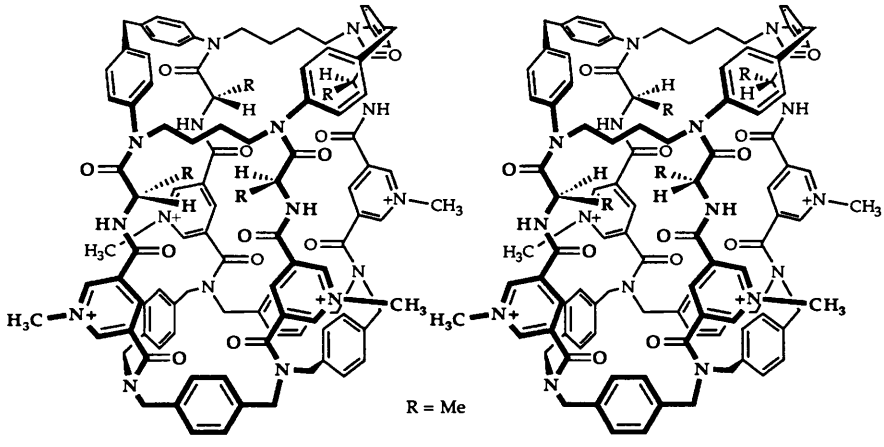
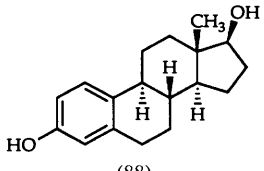


R = Me

(+)-(87) (-)-(87)



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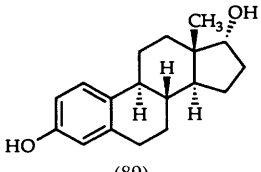

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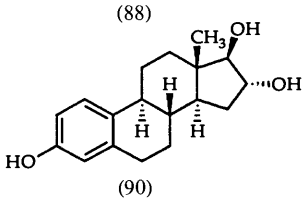

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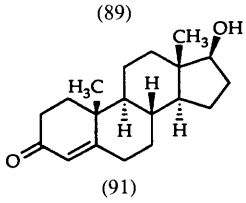


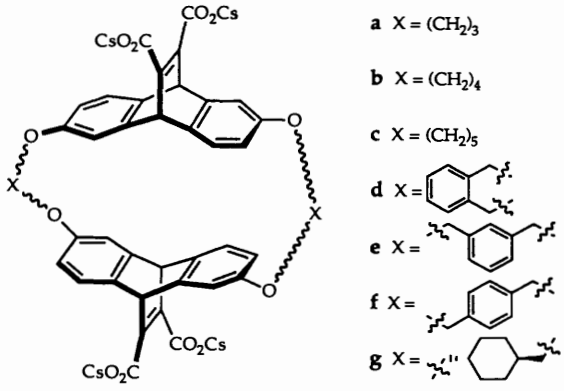
(91)

Table 9 Association constants[a] and $\Delta\Delta G$ values for host (87) with steroids (88)—(91)

Guests	Association constants, K_a (M^{-1}), for host (+)—(87)	(−)—(87)	$\Delta\Delta G^b$ (kcal mol^{-1})
(88)	460	1300	− 0 62
(89)	760	700	0 05
(90)	360	520	− 0 22
(91)	—[c]	—[c]	—

[a] Free energies of association were determined by NMR titration in D_2O/CD_3OD (75 25) at 27 °C [b] $\Delta\Delta G$ = ΔG (−)-enantiomer − ΔG (+) enantiomer [c] No measurable complexation was observed

(92)



interior of the hosts The relative size and shape of these portals, compared to those of the guests, imposes steric constraints which the guests must thermally overcome in order to enter or leave the hosts

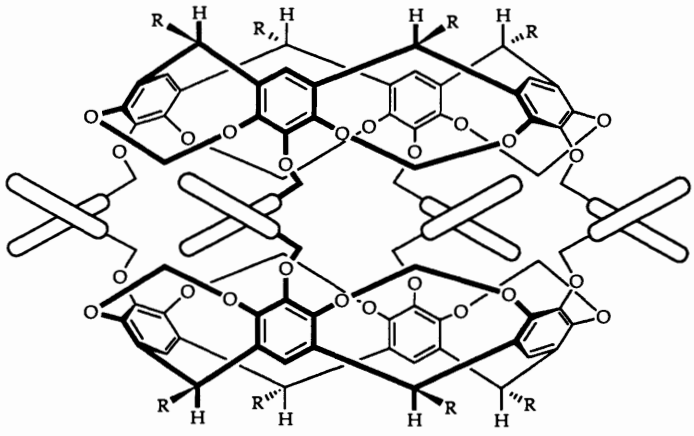
Cram and co-workers have developed a constrictive host (93) with chiral portals by linking two cavitands with four binaphthyl spacers [56] Host–guest complexes were formed by heating the host in neat guest, cooling, and isolating the complex The complex was then dissolved in $CDCl_3$ at 23 °C, and the rate of guest release was measured by ^{1}H-NMR

From the complexes of enantiomerically pure (*R*) and (*S*) host (93), and (*S*)-$BrCH_2CH(CH_3)CH_2CH_3$, the first-order rate constants for guest release were determined to be $4\,4 \times 10^{-2} h^{-1}$ for the (*R*)-(*S*) diastereomer, and $6\,2 \times 10^{-3} h^{-1}$ for the (*S*)-(*S*) diastereomer This gave $k_{RS}/k_{SS} = 7$, and $\Delta\Delta G = 1\,1$ kcal mol $^{-1}$ at 23 °C

Enantiomerically pure (*S*)-host (93) and racemic $BrCH_2CH_2CHBrCH_3$ gave a mixture of diastereomeric complexes in ratios ranging from 1 5 1 to 2 1, indicating a $\Delta\Delta G$ of association of approximately 0 3 kcal mol^{-1} at 100 °C The dissociation rate constants were $k_{fast} = 3\,0 \times 10^{-1}$ h^{-1} and $k_{slow} = 5\,8 \times 10^{-2} h^{-1}$ This gave $k_{fast}/k_{slow} = 5$ and $\Delta\Delta G = 1\,0$ kcal mol $^{-1}$ at 23 °C The less thermodynamically stable diastereomer gave the faster rate

In the same manner, enantiomerically pure (*S*)-host (93) and racemic $BrCH_2CHBrCH_2CH_3$ gave a diastereomeric ratio of 2 1 The dissociation rate constants were $k_{fast} = 1\,21 \times 10^{-2} h^{-1}$ and $k_{slow} = 1\,3 \times 10^{-3}$ h^{-1} This gave $k_{fast}/k_{slow} = 9$, and $\Delta\Delta G = 1\,3$ kcal mol^{-1} at 23 °C In this case, the more thermodynamically stable diastereomer gave the faster rate

Collet and co-workers have also created a host (94) which appears to utilize constrictive binding [57] This host was complexed with racemic bromochlorofluoromethane (95) in $CDCl_3$, and the association constants of the diastereomeric complexes were determined by ^{1}H-NMR at 59 °C These were found to be 0 30 M^{-1} for the (+)-(95)·(+)-(94) diastereomer and 0 22 M^{-1} for the (−)-(95)·(+)-(94) diastereomer to give a $\Delta\Delta G$ of 0 21 kcal mol^{-1}



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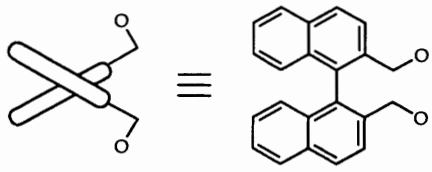
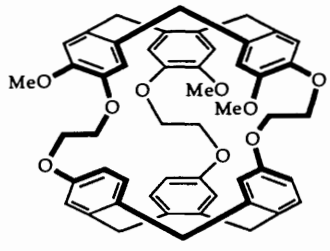




(94)

5 Concluding Comments

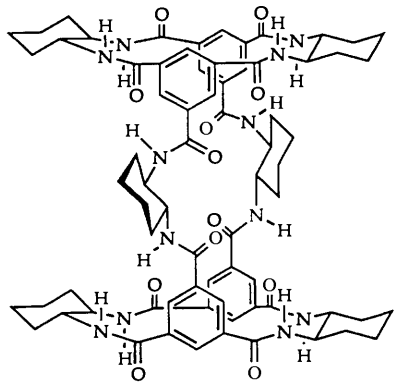
The field of molecular recognition is moving forward at an exciting pace Progress is being made along several paths The acceleration of chemical reactions through a template effect based on non-covalent interactions has been demonstrated in a totally synthetic system [58] New self-replicating systems (molecules that are catalysts for their own synthesis) have recently been developed [59] Experiments in crystal design for new materials production are being pursued [60]

Chemists have always sought new knowledge to support the development, refinement, and improvement of chemical technologies The obvious applications of enantioselective and diastereoselective receptors in separation and analysis are being vigorously pursued in many laboratories Most of the technological applications of enantioselective and diastereoselective synthetic receptors are yet to be invented The practical importance of shape-selective binding will be magnified when shape selectivity can be combined with catalytic capability Examples from the biological world provide some idea of the fantastic level of self-organization and control that can be based on shape-selective binding and catalysis Experiments described in this chapter provide the foundation for further advances in this promising new field

6 Addendum

After submission of this review, Still and co-workers published a report[61] on a unique peptide-binding host (96) which can be synthesized in one step It is highly enantioselective, exhibiting differences of free energy of binding between enantiomeric pairs of up to 3 0 kcal mol^{-1}, as shown in Table 10 This is the largest enantioselectivity so far reported The host binds simple pep-

tides through four intermolecular hydrogen bonds With larger peptides, the host seems to be able to use outlying amides to form hydrogen bonds with up to three amino acid residues



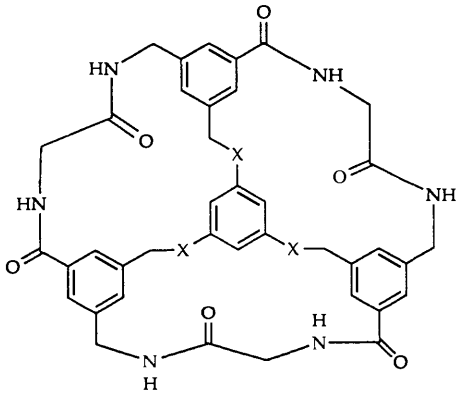
(96)

Table 10 Free energies of association[a] for host (96) and various peptides

Guest Peptide	ΔG (kcal mol^{-1}) of binding for peptide (L)	(D)	$\Delta\Delta G^b$ (kcal mol^{-1})
N-Ac-Gly-NHMe	−1 9		
N-Ac-Ala-NHMe	−3 5	−2 2	−1 3
N-Ac-Val-NHMe	−5 0	−2 4	−2 6
N-Ac-Ile-NHMe	−4 3	−2 4	−1 9
N-Ac-Leu-NHMe	−3 4	−2 4	−1 0
N-Ac-PGly[c]-NHMe	−5 9	−2 9	−3 0
N-Ac-Phe-NHMe	NC[d]	−2 0	> +2 0
N-Oc[e]-Tyr-NHMe	NC		
N-Ac-Ser-NHMe	−3 5	−3 4	−0 1
N-Ac-HSer[f]-NHMe	−5 1	−3 7	−1 4
N-Ac-Thr-NHMe	−3 5	−2 9	−0 6
N-Boc-Val-NHMe	−2 8	−1 7	−1 1
N-Boc-Val-NH_2	−4 9	−3 7	−1 2
N-Boc-Gly-Val-NHMe	−6 2	−3 2	−3 0
N-Boc-Gly-Val-Gly-NHBn	< −7 2	−4 6	< −2 6

[a] Free energies of association were determined by NMR titration of 0 5 mM (96) in $CDCl_3$ at 25 °C [b] $\Delta\Delta G = \Delta G_L - \Delta G_D$ PGly, phenylglycine [d] NC, no complexation detected [e] Oc, octanoyl [f] HSer, homoserine

Still and co-workers have also used hosts (97) and (98) to bind simple peptides [62] These basket-shaped hosts are C_3 symmetric, and exist largely in a single family of closely related conformations They also exhibit extremely high enantioselectivity, as shown in Table 11



(97) X = S
(98) X = O

Table 11 Free energies of association[a] for hosts (97) and (98) and various peptides

Peptides	ΔG (kcal mol^{-1}) of binding for (97)	(98)	$\Delta\Delta G^b$ (kcal mol^{-1}) for (97)	(98)
N-Boc-D-Ala-NHMe	−1 7	−2 1		
N-Boc-L-Ala-NHMe	−3 9	−3 8	−2 2	−1 7
N-Boc-L-Ala-NHBn	−1 4			
N-Boc-L-Ala-NHtBu	NC[c]			
N-Boc-D-Val-NHMe	−1 5	−1 5		
N-Boc-L-Ala-NHMe	−4 4	−4 0	−2 9	−2 5
N-Boc-D-Leu-NHMe	−1 5	−1 6		
N-Boc-L-Leu-NHMe	−4 1	−3 8	−2 6	−2 2
N-Boc-D-Ser-NHMe	−3 8	−4 4		
N-Boc-L-Ser-NHMe	< −6 1	< −6 2	< −2 3	< −1 8
N-Boc-L-Ser(OBn)-NHMe	−3 1			
N-Boc-D-Thr-NHMe	−3 2	−3 6		
N-Boc-L-Thr-NHMe	< −6 2	lg[d]	< −3 0	
N-Ac-D-Ala-NHMe	−2 7			
N-Ac-L-Ala-NHMe	−3 9		−1 2	
N-Ac-D-Ala-NHtBu	−2 0			
N-Ac-L-Ala-NHtBu	−3 0		−1 0	

Free energies of association were determined by NMR titration of 0 5 mM (97) or (98) in $CDCl_3$ at 25 °C [b] $\Delta\Delta G = \Delta G_L - \Delta G_D$ NC no complexation detected [d] lg too large to measure accurately

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