MOLECULAR RECOGNITION

1. Receptor–Substrate-/Host–Guest-Chemistry

Molecular recognition is a central point. It may be said that without molecular recognition, there would be no life in this world. Vital biochemical processes such as enzyme action, molecular transport, genetic information, processing and protein assembly all involve molecular recognition as an essential action (1–3). Understanding of its principles is still a problem although first elucidation of the rules that govern molecular recognition dates back to the late nineteenth century (4). Strictly speaking, in 1894 Emil Fischer, a farsighted chemist, came up with his brilliant "lock-and-key" idea. In his famous paper (5) he proposed that enzyme and substrate can be compared to lock and key getting selectivity between molecules involved. Moreover, and this occurred even earlier, it was Paul Ehrlich who recognized that molecules do not act if they do not bind, thus, introducing the concept of receptor (6). Finally binding or fixation requires interaction, affinity between the partners that may be related to the idea of coordination introduced by Alfred Werner (7).

According to these basic concepts, molecular recognition implies complementary lock-and-key type fit between molecules. The lock is the molecular receptor and the key is the substrate that is recognized and selected to give a defined receptor–substrate complex, a coordination compound or a supermolecule. Hence molecular recognition is one of the three main pillars, fixation, coordination, and recognition, that lay foundation of what is now called supramolecular chemistry (8–11).

Behind this new direction of supramolecular chemistry, the chemistry beyond the molecule, is a highly interdisciplinary field of science covering the

chemical, physical, and biological features of chemical species of greater complexity than molecules themselves that are held together and organized by means of intermolecular (nonbinding) interactions (12). The chemistry of molecular recognition is also the core of host–guest chemistry which is a sub-discipline or a particular aspect of supramolecular chemistry mostly involving inclusion and complex formation (13) (see also INCLUSION COMPOUNDS).

2. Principles of Receptor Design

2.1. Information Storage and Read Out. Picking up the thread of the introduction, molecular recognition is defined by the energy and the information involved in the binding and selection of substrates by a given receptor molecule that may also involve a specific function (14). Mere binding is not recognition, although it is often taken as such. Instead, one may say that recognition is binding with a purpose, like receptors are ligands with a purpose. It implies a pattern recognition process through a structurally well-defined set of intermolecular interactions. Molecular recognition, thus, deals with the molecular storage and supramolecular read out of molecular information (9).

Information may be stored in the architecture of the receptor, in its binding sites, and in the ligand layer surrounding the bound substrate such as specified in Table 1. It is read out at the rate of formation and dissociation of the receptor–substrate complex (14). The success of this approach to molecular recognition lies in establishing a precise complementarity between the associating partners, ie, optimal information content of a receptor with respect to a given substrate.

2.2. Complementarity. To a first approximation, complementarity should take two forms (Fig. 1). Firstly, the shape and size of the receptor cavity must complement the form of the substrate. Secondly, there must be a chemical

Table 1. **Structural Parameters for Storage of Information in a Chemical Receptor**

Receptor	Parameter
architecture	size
	shape
	connectivity
	cyclic order
	conformation
	chirality
	dynamics
binding sites	electronic properties (charge, polarity, polarisability, van der Waals attraction and repulsion)
	size
	shape
	number
	arrangement
	reactivity (protoniziable, deprotonizable, reducible, oxidizable)
surrounding ligand layer	thickness
	overall polarity (lipophilic, hydrophilic)
	specific polarity (exo/endo-lipo/polarophilic)

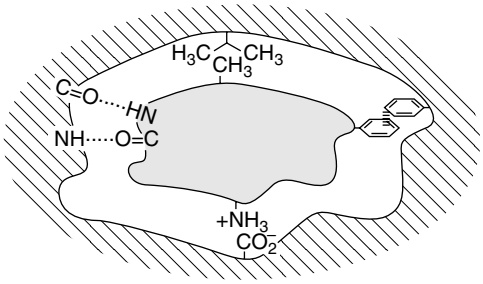


Fig. 1. Schematic representation of a receptor–substrate (host–guest) complex involving cavity inclusion of the substrate and the formation of different types of weak supramolecular interactions between receptor (hatched) and substrate (dotted).

complementarity between the binding groups lining the interior of the cavity and the external chemical features of the substrate (15).

The weak intermolecular forces that are principally involved in stabilizing receptor-substrate interactions and involved in molecular recognition processes (16) are summarized in Table 2. Examples are shown in Figure 1.

Most effective differentiation of the receptor between substrates will occur when multiple interactions are involved in the recognition process. The more binding regions (contact area) present, the stronger and more selective will be the recognition (17). This is the case for receptor molecules that contain intramolecular cavities, clefts or pockets into which the substrate may fit (Fig. 1).

2.3. Reorganization and Preorganization. On principle there are two different modes of receptor behavior illustrated in Figure 2. One of them, already evoked, is represented by the so-called lock-and-key image (Fig. 2**a**), involving complementary fit concept between rigid substrate and rigid receptor or rigid guest and rigid host relating to conformational flexibility of the molecular constituents forming the receptor–substrate (host–guest) complex (4). Receptors of this type are expected to present very efficient recognition between complementary partners, ie, both high stability and high selectivity of the receptor–substrate complex. The advantage of complementary receptor preorganization comes from minimizing the unfavorable entropy involved in substrate binding (see below).

However, in most biological system there is a degree of flexibility in the receptor (2). The approach of the substrate leads to conformational changes and an organization of the binding site around it. With this induced fit mechanism

Table 2. **Types of Interactions in Molecular Recognition**

hydrogen bonding between basic and acidic centers
electrostatic attraction between anionic and cationic centers
metal-ligand interaction
dipole–dipole interaction
π-stacking and charge-transfer interaction between aromatic residues in the receptor and delocalized regions of the substrate
van der Waals attraction between hydrophobic regions on the two components
covalent bonds, that can be reversibly formed and broken (eg, disulfides, borate esters).

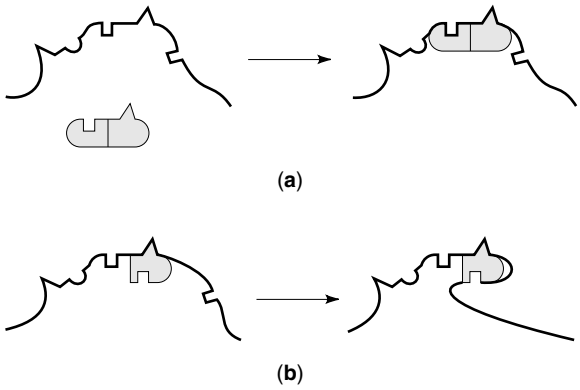


Fig. 2. Principal mechanisms of formation of a receptor–substrate complex: (**a**) Fischer's rigid "lock-and-key" model; (**b**) "induced fit" model showing conformational changes of the receptor (solid line) upon substrate binding.

of binding (Fig. 2**b**), a higher entropy price is paid but there are several advantages (18). A flexible receptor will permit a more wrap around interception or even complete encapsulation with the substrate involving many more potential binding interactions. This may lead to high selectivity of binding involving the amplification of molecular recognition interactions illustrated in Figure 3 (19).

In case of the rigid lock-and-key type receptor forming five hydrogen bonds plus two extended electrostatic attractions (Fig. 3**a**), one mismatched hydrogen bond will result in only a small reduction in overall binding free energy $4.18 - 8.36$ kJ mol^{-1} ($1 - 2$ kcal mol^{-1}) out of $\sim$41.8 kJ mol^{-1} ($\sim$10 kcal mol^{-1}). The small difference in association constants (K_s) that would result ($\sim$two orders of magnitude) is not sufficient, eg, for the differentiation of chemically similar substrates commonly encountered with biological systems (1). One solution would be using a flexible version of the receptor (Fig. 3**b**) that will profit

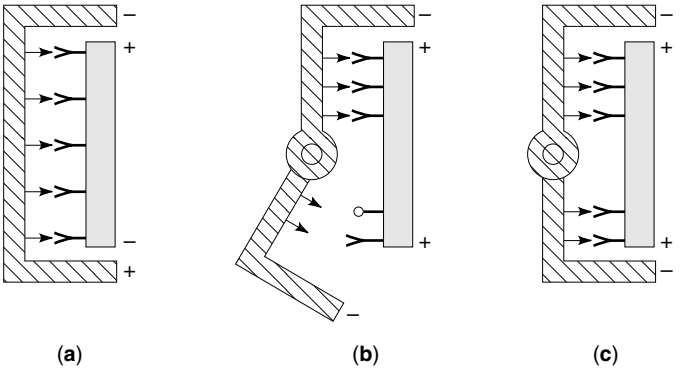


Fig. 3. Schematic approach illustrating amplification of molecular recognition effects of (**a**) matched rigid, (**b**) mismatched rigid, and (**c**) flexible type of receptor–substrate assemblies (19).

from the amplification of molecular recognition interaction. Here a single mismatched hydrogen bond due to a repulsive interaction forces the receptor into a nonproductive binding conformation leaving two hydrogen bonding and an electrostatic site distant from the substrate. The difference in binding is, thus, amplified from a single hydrogen bond to almost half the binding interactions relative to the matched case in Figure 3**c,** which is profitable for selectivity.

However, reduced stability of the receptor–substrate complex as such involving a flexible receptor is the other side of the coin, since part of the binding energy is used up in the change of conformation of the receptor. This is the point amounting to the so-called principle of preorganization which can be expressed as follows: "the smaller the changes in organization of receptor and substrate or host and guest required for complex formation, the stronger is the binding" (20). An illustration of this approach is given in Figure 4 considering a systematic series of well-known synthetic receptors (crown compounds and analogues, see also INCLUSION COMPOUNDS) that owe their binding properties to varying degrees of preorganization, ie, organization of their binding sites (donor atoms) prior to complexation (21).

Podands (Fig. 4**a**) are acyclic collections of binding sites held together by appropriate spacer units (22,23). During the complexation act to form a podate

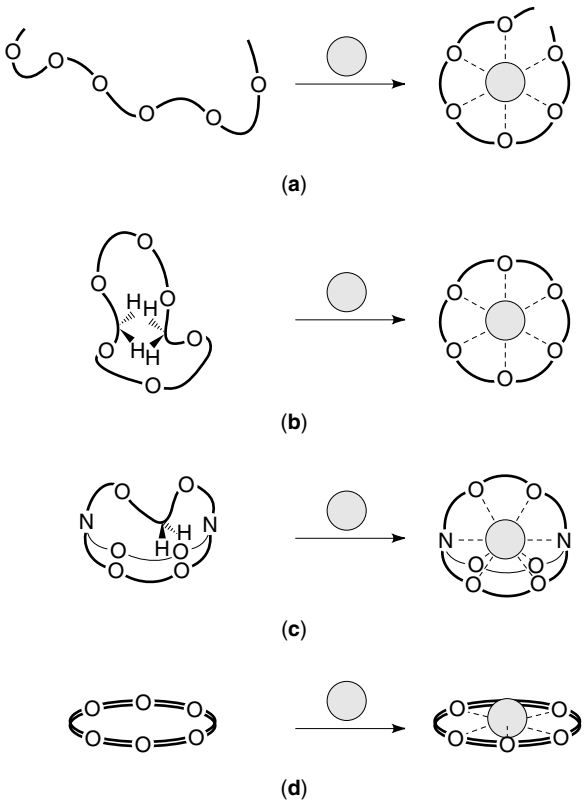


Fig. 4. Recognition and preorganization of hosts (receptors) on complex formation (21).

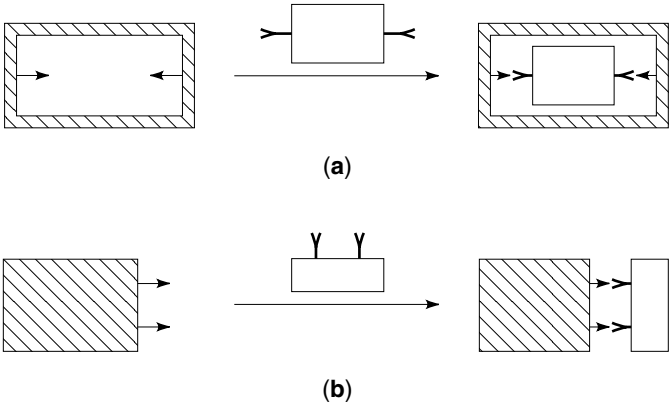


Fig. 5. Diagram of (**a**) endo- and (**b**) exo-receptor recognition of substrates (▨).

(podaplex), many degrees of conformational freedom must be frozen out. Crowns and coronands (Fig. 4**b**) are cyclic collections of binding sites and are less flexible than podands (13,24). Nevertheless, they posses a variety of conformations, many of which fill their own potential cavities with their own spacer units. Cryptands (Fig. 5**c**), which are bridged crown analogues, naturally have a smaller number of nonbinding conformations, and therefore, require less expenditure of reorganization on inclusion formation than crowns (25,26). The so-called spherands (27,28) (Fig. 4**d**) are at the end of the unfolded progression of receptor structures with regard to the parameter of preorganization (20,21). Hence they are characterized as completely preorganized receptor systems possessing an enforced cavity with perfect octahedral arrangement of six donor oxygens and cavity diameter to be complementary to Li^+ and Na^+ in both an electronic and steric sense, giving rise to extremely high stability constants for complexes (spheraplexes) with these cations ($K_sLi^+ > 7{\cdot}10^{16}$, $K_sNa^+ = 1.2{\cdot}10^{14}$; in $CDCl_3$ sat. with D_2O at 25 °C) unlike K^+ and larger cations (cf Table 3) that are not complexed (20,28). From the kinetic point of view the facts are different and the order is reverse, ie, the rigid highly preorganized spherands are slow, as contrasted with the flexible barely preorganized podands that are fast both in formation and decomposition of the receptor–substrate (host–guest) complex (20,21).

Table 3. **Comparison of Cation and Cavity Diameters**

Cation	Cation diameter,[a] Å	Crown ether	Cavity diameter,[a] Å
Li^+	1.36	12-crown-4 (**1a**)	1.2–1.5
Mg^{2+}	1.56		
Na^+	1.90	15-crown-5 (**1b**)	1.7–2.2
Ca^{2+}	2.12		
Sr^{2+}	2.54	18-crown-6 (**1c**)	2.6–3.2
K^+	2.66		
Ba^{2+}	2.86		
Rb^+	2.98		
Cs^+	3.38	21-crown-7 (**1d**)	3.4–4.3

[a] = 0.1 nm.

Hence, the balance between rigidity and flexibility is of particular importance for the binding and the dynamic properties of a receptor. It is, thus, a decisive structural design parameter of the receptor depending on the use. For instance, processes of exchange regulation, cooperativity and allostery connected with molecular recognition require a built-in flexibility so that the receptor may adapt and respond to changes unlike rigid receptors (14,29).

2.4. Topology. This parameter may have reference to either the receptor as an individual molecular structure or to the receptor–substrate complex on a higher level of organization that is directly related to the mode and efficiency of molecular recognition (14,30).

It has already been stressed that a concave receptor is a favorable case. Under these circumstances the receptor cavity is lined with binding sites directed toward the bound species (see Fig. 1). This corresponds to Cram's definition of a receptor (host) molecule providing binding sites that are convergent, as contrasted with the bound substrate (guest) featuring divergent complementary sites, ie, the substrate is more or less completely surrounded by the receptor forming an inclusion complex (20,31). This widely used principle of convergence defines a convergent or endo-supramolecular chemistry (host–guest chemistry) with endo-receptors (endo-hosts) effecting endo-recognition (Fig. 5**a**) (9).

The opposite procedure consists in making use of an external receptor surface rather than an internal cavity as substrate receiving site. This amounts to the passage from a convergent endo-supramolecular chemistry to a divergent or exo-supramolecular chemistry, and from endo- to exo-receptors (Fig. 5**b**) (9). Here receptor–substrate binding occurs by surface-to-surface interaction which may be termed affixation as contrasted with inclusion. Exo-recognition with strong and selective binding, in particular, requires a large enough contact area and a sufficient number of complementary interactions along the interface. Such a mode of molecular recognition also finds biological analogies, for instance at the antibody–antigen interface of immunological importance (32). Metalloexoreceptor aggregation, molecular recognition at organic and inorganic monolayers, films and solid surfaces bearing recognition groups, as well as the design of supramolecular solid architectures and materials, are other important instances of the exo-recognition principle discussed in more detail below.

Apart from the basic classification in convergent endo- and divergent exoreceptors, molecular receptors (hosts) of extremely varied structural types have been developed (30) including the acyclic podands, the macrocyclic crown ethers, coronands or torands, the macropolycyclic cryptands and speleands, the spherands, cavitands and carcerands, the calixarenes and cryptophanes, the clathrands, the helicands and other organization framework species (12). Each of these trivial names refers to a particular aspect of the structure involving the overall receptor topology, that is connectivity, dimensionality and cyclic order. Examples of compounds are illustrated elsewhere in this article (see also INCLUSION COMPOUNDS) while a selection of possible topologies are shown in Figure 6, from a linear receptor (**a**) to spherical (**i**) or cylindrical (**j**) tricyclic structures following the classification of graphs (14). Moreover, all these types of receptors may possess a single receptor unit to recognize and bind a single substrate, eg, (**d**) or contain more than one discrete binding subunit (**h**) being characteristic of monotopic and oligo-/polytopic receptors, respectively. The size and the shape of the binding

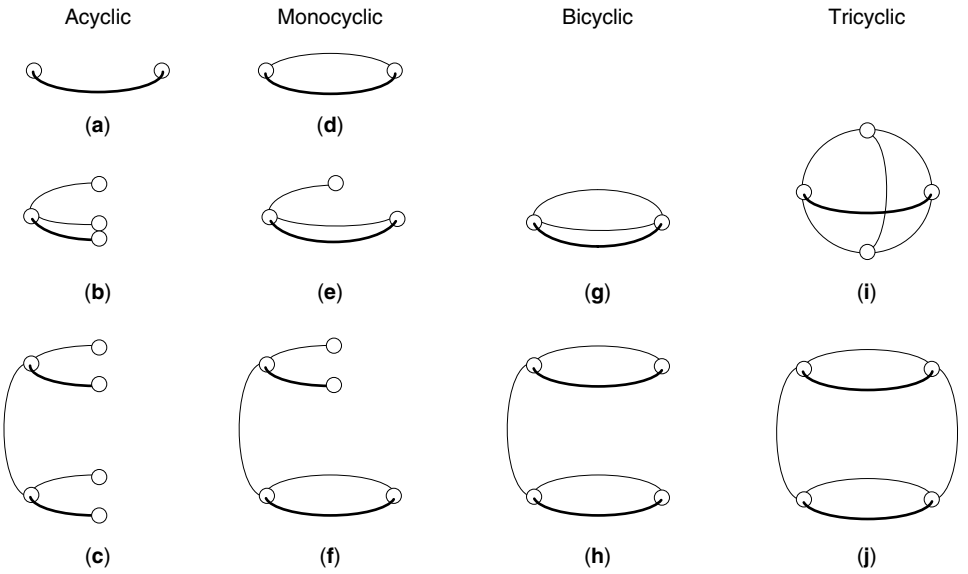


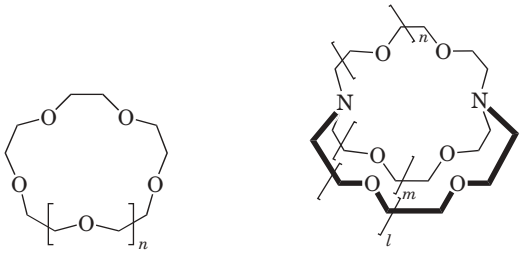
Fig. 6. Topological structure types of receptors (hosts) (14).

cavity that they define and their rigidity or flexibility are determined by the nature of the structural subunits making up the branches of the graphical representations in Figure 6. In this respect they serve the same purpose for conveying properties of molecular recognition, mostly based on geometrical discrimination.

3. Simple Modes of Molecular Recognition

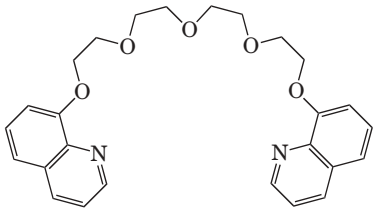
Substrates involved in molecular recognition may feature a particular shape, size, state of charge, chemical affinity or optical specification (19,30,33–36). In general most of these parameters share. Nevertheless there may be dominating features of a certain substrate molecule to be used by a complementary receptor in the recognition process (9).

3.1. Size and Shape Dominated Substrate Recognition. Perhaps the simplest recognition process is that of a spherical substrate, in its most elementary form a ball-shaped metal ion of defined diameter. Supramolecular chemistry in itself started with this problem, in particular having the effort for recognition and binding of alkali and alkaline-earth cations (37). Numerous studies have been performed that are reported in many papers and summarized in reviews and books (12) showing that three main classes of receptors providing spherical recognition property may be distinguished (38). They are (*1*) macrocyclic polyethers, the well-known crown ethers and their derivatives (24); (*2*) the macropolycyclic cryptands (25,26); and (*3*) the acyclic analogues of crown compounds and cryptands usually designated as podands (22,23). Prototypical compounds for each substance class are given by compounds (**1**)–(**3**) (Fig. 7). They all possess a spherical or quasispherical negatively polarized cavity prepared for the accommodation of alkali- and alkaline-earth metal ions that have complementary

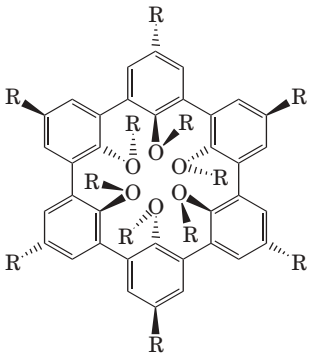


(**1**) (**a**) $n = 0$ 12-crown-4
(**b**) $n = 1$ 15-crown-5
(**c**) $n = 2$ 18-crown 6
(**d**) $n = 3$ 21-crown-7

(**2**) (**a**) $l = m = n = 0$ [1.1.1]
(**b**) $l = 1, m = n = 0$ [2.1.1]
(**c**) $l = m = 1, n = 0$ [2.2.1]
(**d**) $l = m = n = 1$ [2.2.2]

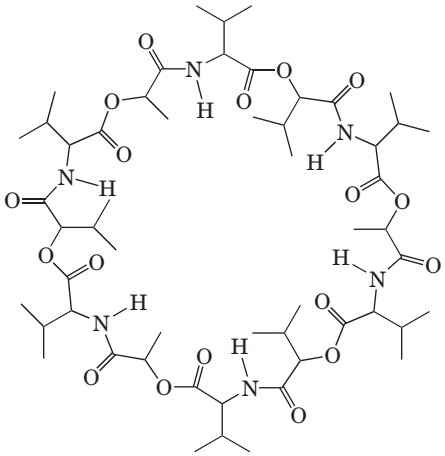


(**3**)



R = CH_3

(**4**)



(**5**)

Fig. 7. Crown type and analogous receptor molecules of different varieties; (**1**) crown ethers; (**2**) cryptands; (**3**) a podand; (**4**) a spherand; and (**5**) the natural depsipeptide valinomycin.

size, giving rise to a feature termed as spherical recognition (9). Coronates, cryptates or podates are the names of the respective inclusion complexes (39).

The match between crown cavity diameter and cation diameter is obvious from Table 3 showing that, eg, Li^+ and 12-crown-4 (**1a**) or K^+, respectively Ba^{2+} and 18-crown-6 (**1c**) correspond. Similar are the cryptands of gradually increasing cavity size [2.1.1], [2.2.1] and [2.2.2] for Li^+, Na^+ and Sr^{2+} or K^+ and Ba^{2+}, while the small cavity of [1.1.1] fits H^+. The example of such a matched cryptate where K^+ is accommodated into the cavity of [2.2.2] is illustrated in Figure 8**a** (25). Although acyclic podands do not provide a permanent cavity, they may create one by encircling a spherical cation with the length of the receptor molecular thread being the controlling parameter (22,40). Nevertheless, from what has already been said, low preorganization and topology of the podands handicap the substrate recognition which is increasingly higher in the circular

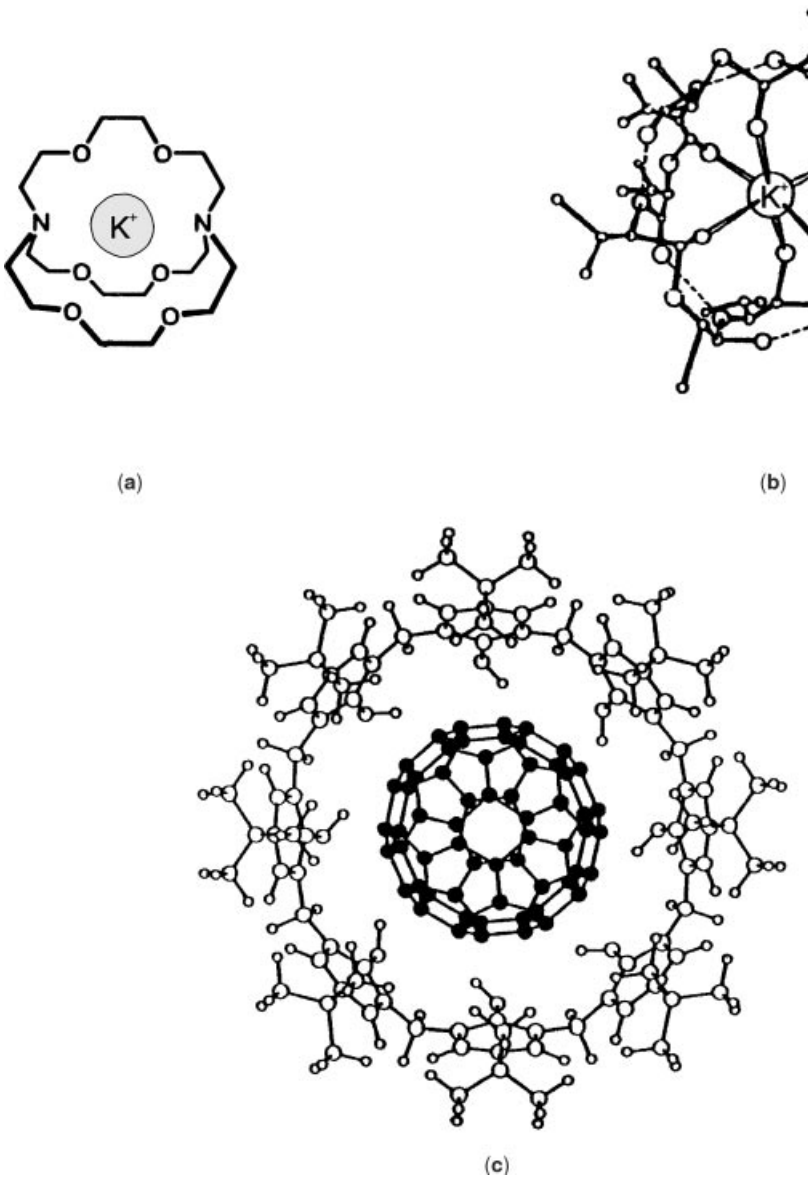


Fig. 8. Spherical recognition: (**a**) K^+ cryptate of [2.2.2] (**2d**); (**b**) K^+ complex of valinomycin (**5**); and (**c**) inclusion compound of C_{60} into *tert*-butylcalix[8]arene.

crown and spheroidal cryptand case, but is most pronounced for the spherand type of receptor (eg, **4**) also mentioned before.

Alkali and alkaline-earth cation recognition is also affected rather efficiently by other macrocyclic receptors that have been synthesized (21) such as the cryptospherands (an amalgamation of cryptand and spherand topology) (20,31) and lariat ethers (41), the latter is characterized by a crown ether ring that has attached extra podand arms for feeling and lock in of the substrate.

Moreover, natural macrocycles displaying antibiotic properties are also very efficient in the recognition of alkali metal ions (42). For instance, valinomycin (**5**) gives a strong and selective complex in which a K^+ ion is included in the macrocyclic cavity in octahedral environment of six carbonyl oxygens (Fig. 8**b**) (43).

In a word, all these receptors are more or less able to discriminate against cations that are either smaller or larger than their cavity (44). However, in a strict sense, discrimination of metal-ion spheres does not concern with molecular recognition but selection of the carbon ball C_{60} certainly does. In fact, the fullerene C_{60} has been included into the cavity of octa-*tert*-butylcalix[8]arene (Fig. 8**c**) shutting out C_{70} and making a very convenient and efficient C_{60} purification possible without any expensive apparatus (45).

Recognition of a tetrahedral substrate geometry requires the construction of a receptor molecule with a tetrahedral recognition site (9). This may be realized by positioning four suitable binding sites at the corners of a tetrahedron and incorporating them into a bridged molecular framework such as shown with compound (**6**) (Fig. 9**a**) (25,38,46). In fact, the tetrahedral NH_4^+ cation is very firmly held inside the cavity of the tricyclic cryptand (**6**), forming the ammonium cryptate (Fig. 9**b**) (47). This cryptate presents a high degree of receptor–substrate complementarity in that the ammonium ion fits into the cavity of (**6**) and is held by a tetrahedral array of hydrogen bonds including also electrostatic interactions with the oxygen atoms (48). Unsymmetrical derivatives of (**6**) display notably perturbed NH_4^+ binding, with a marked loss in recognition behavior (49).

Recognition of a primary ammonium ion, by analogy, is achieved by making use of a symmetrical triazacoronand enabling a trigonal recognition process in its

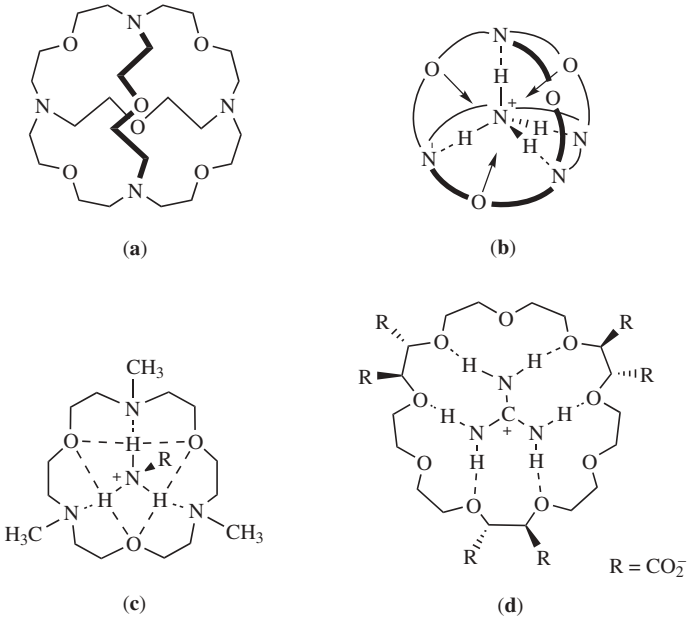


Fig. 9. Representative examples of **6** (**a, b**) tetrahedral; (**c**) trigonal; and (**d**) circular recognition.

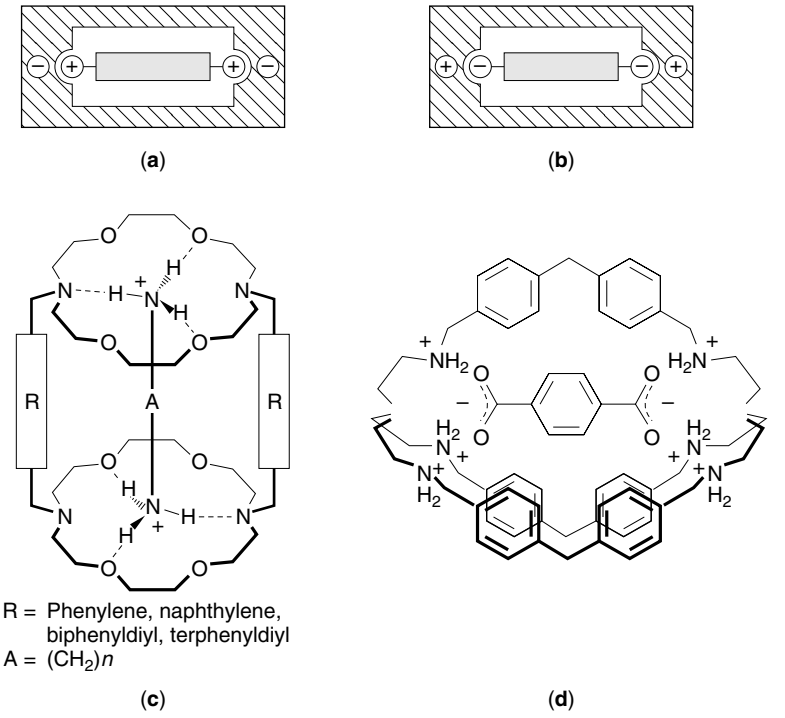
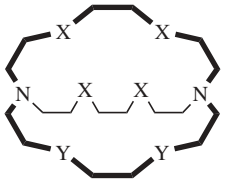


Fig. 10. Linear recognition: diagrammatic representation of the recognition of linear dicationic (**a**) and dianionic (**b**) substrates; (**c, d**) typical examples of receptor–substrate complexes.

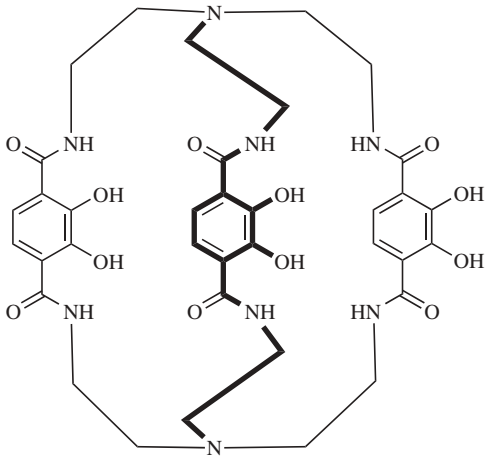
inclusion complex (Fig. 9**c**) (50). A recognition site for secondary ammonium groups is provided by the diaza analogue of 12-crown-4 [cf (**1a**)] (51). It binds via two hydrogen bonds (52). On the other hand, the derivative of a 27-membered crown compound yielded a particular stable inclusion complex with the guanidinium cation that is bound through an array of six hydrogen bonds suggesting an almost circular recognition mode (Fig. 9**d**) (53,54).

Linear recognition is mainly a subject of molecular length recognition (9). For that reason preferential substrates bear two recognizable functional groups at a distance corresponding to a ditopic receptor molecule (Fig. 10**a**) (55). An example is given by the cylindrical macrotricyclic cryptand that yields cryptates with terminal diammonium cations $H_3N^+-(CH_2)_n-N^+H_3$ of matching molecular length (Fig. 10**c**) (56). A complementary substrate, eg, relating to the receptor with R = naphthalene–2, 6–diyl in Figure 10**c**, would be the 1,5-pentane diammonium cation [A = $(CH_2)_5$]. In the resulting complex, the substrate is located in the central cavity and anchored by its two NH_3^+ groups in the macrocyclic binding sites (57).

3.2. Charge Attraction Dominated Recognition. Thus far, for recognition sizes and shapes of the substrate have been the focus. Nevertheless, charge attraction between the substrate and the receptor has also played a part since cations such as metal ions or ammonium ions were complexed by negatively polarized cavities. But metal ions involved hard alkali and alkaline-earth



(7)



(8)

Fig. 11. Receptor molecules (cryptands) having hetero (nonoxygen) donor atoms (**7**) or endo-functional acidic sites (**8**) in the framework.

cations rather than weaker transition metal ions. Replacing the oxygen sites of crown compounds and cryptands with nitrogen (58) and sulfur atoms (59,60) yields receptors [eg, (**7**), Fig. 11] that show marked preference for transition-metal ions (61) and may allow high selective recognition of toxic heavy-metal ions such as cadmium, lead or mercury according to the hard and soft acid and base (HSAB) principle (62). Others containing internally directed functionalized units such as in the triscatechol derivative (**8**, Fig. 11) form very strong and selective complexes with Fe^{3+} or actinide and lanthanide ions (63,64) while a similar receptor with hard endocarboxylic acid groups is efficient for hard Ca^{2+} and Mg^{2+} ions showing again responsibility of a charge density effect in the receptor–substrate recognition (65). Thus, recognition of hard alkali and alkaline-earth metal ions is determined by coulombic attraction whereas the weak transition-metal ions are mainly controlled by geometrical parameters of orbital overlap.

By analogy, recognition of an anionic substrate requires an electron-deficient receptor cavity including positively charged or neutral electron-deficient groups that may serve as interaction sites for anion binding (9,30). Ammonium and guanidinium units, which form $N^+ - H\cdots X^-$ bonds, have mainly been used (66), but electron-deficient boron, tin, mercury or metal ion centers in complexes also interact with anions (67). Apart from this demand, anionic substrates have another specific feature in that they are large compared with cations. Moreover they possess a range of geometries: spherical (eg, halides), linear (eg, N_3^-, CN^-OCN^-), planar (eg, NO_3^-, $RCOO^-$) or tetrahedral (eg, SO_4^{2-}, ClO_4^-, phosphates). Polyammonium macropolycycles have been studied most extensively as receptor molecules for anion recognition (68). When (**6**) (Fig. 9**a**) is tetraprotonated it binds Cl^- very strongly and very selectively compared with Br^- and other types of anions giving the size complementary chloride cryptate, in which the included anion is bound by four $N^+ - H\cdots Cl^-$ hydrogen bonds

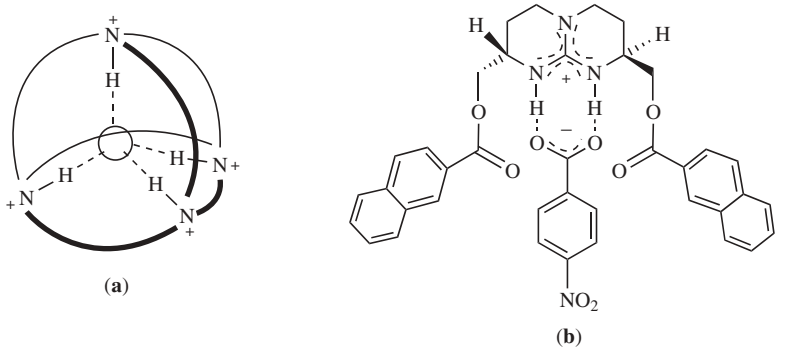


Fig. 12. (**a**) Spherical anion (Cl^-); and (**b**) carboxylate anion recognition.

(Fig. 12**a**) making spherical recognition of the chloride ion possible (69). Quaternary ammonium derivatives of oxygen-free macrotricycles of type (**6**) bind spherical anions as well (70), and more recently acyclic quaternary polypyridinium and polybipyridinium receptors for chloride and bromide recognition have also been reported (71). Linear recognition is displayed by the hexaprotonated form of ellipsoidal bis-tren type cryptands which bind with length discrimination various polyatomic anions and extend the recognition of anionic substrates beyond the spherical halides such as triatomic anion N_3^- (72) or dicarboxylate ions (73) via a pattern schematically shown in Figure 10**b** or illustrated for a case of dicarboxylate recognition in Figure 10**d**. Anion recognition has also made significant progress by means of a receptor type that features a guanidinium group (66). This particular group is of special interest for the recognition and binding of carboxylate and phosphate functions and related species since it may form two chelating H-bonds with the anionic units. An example is given in Figure 12**b** (74).

3.3. Hydrogen Bond Dominated Recognition. Recognition of bioactive compounds is largely determined by the use of hydrogen bonding between polar sites (75). Here substrate recognition results from the formation of specific hydrogen bonding pattern between complementary subunits, in a way reminiscent of base pairing in nucleic acids (76). Hence hydrogen bonding has also been determined an important parameter for the design of artificial receptors (19,30,35,77,78). In fact, a great many of the above receptors and substrates where ammonium and anionic groups are involved base on this interaction mode. A more simplified version of hydrogen bond dominated receptors is seen with 2-aminopyridine derivatives, mostly of amide type (19). They can form specific hydrogen bonds to carboxylic acids such as illustrated in Figure 13**a** showing a respective receptor substrate complex between a picoline diamide receptor and complementary glutaric acid substrate that binds selectively via a length discrimination against dicarboxylic acids of larger and smaller chain length (79). Vice versa, dicarboxylic acid-type receptors are also efficient in the recognition of 2-aminopyridines, respectively of 2-aminopyrimidine (Fig. 13**b**) (80).

An alternative approach to dicarboxylic acid recognition has been developed by using a receptor cleft based on a rigid spacer and two Kemp's triacid binding sites specified in Figure 13**c** (81–83). In this case, the principal binding force is a double carboxylic acid dimer interaction leading to both strong and selective

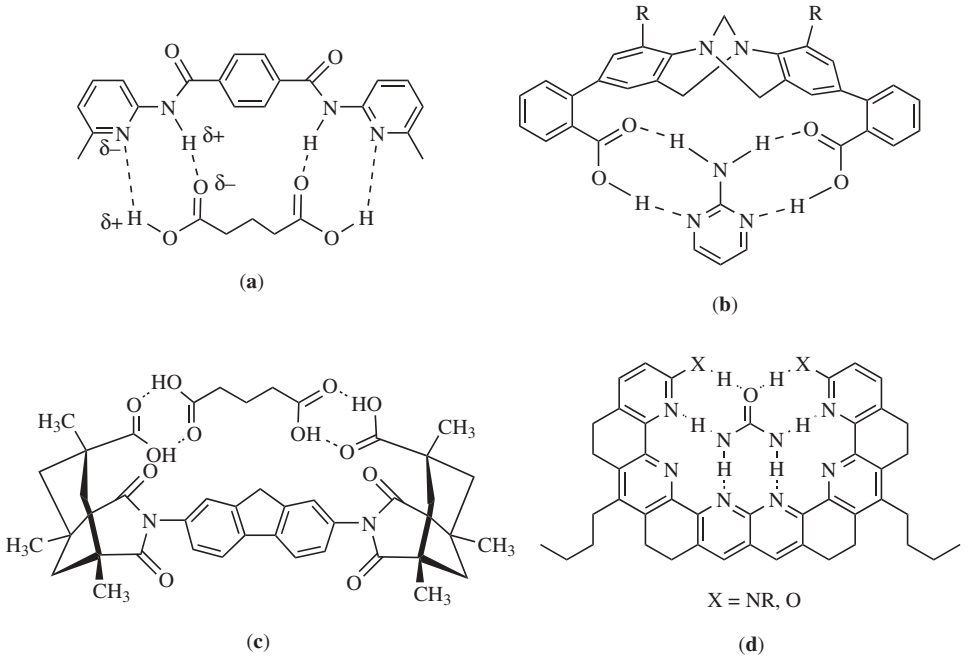


Fig. 13. Hydrogen bond dominated substrate recognition of: (**a**), (**c**) dicarboxylic acids; (**b**) 2-aminopyrimidine; and (**d**) urea.

binding to carboxylic acids of complementary shape and size, ie, glutaric acid (84). Another obvious cleft-type receptor showing both a rigid molecular framework and complementary orientation of hydrogen bonding (85) to allow, eg, the efficient recognition and binding of urea is illustrated in Figure 13**d** (86). Although the receptor clefts that use carefully designed and rigid components to hold hydrogen bonding groups at a fixed distance apart are very common in this field, macropolycycles comprising similar functions offer an alternative albeit more synthetically challenging solution to the same problem, discussed more detailed below where the recognition of particular substrate molecules is dealed with.

3.4. π-Stacking and Charge-Transfer Dominated Substrate Recognition. Nature's strategy for the recognition of substrates featuring a flat aromatic framework (planar recognition) affords another recognition element, namely π−π stacking interactions between aromatic rings, ie, aromatic groups of receptor and substrate that meet a parallel face-to-face orientation, apart from hydrogen bonding being also typical of the nucleotide recognition (77). A very simple example showing the principles of π−π stacking supported substrate recognition is illustrated in Figure 14**a** (87). The flat heterocyclic substrate, uracil derivative, fits in face-to-face mode into the conformationally stepped receptor macroring containing a napththalene π-stacking unit and being bound via a system of extra hydrogen bonds to a diamidopyridine unit. The association constant for the analogous receptor molecule without the π-stacking unit is more than four times lower. The role of the π-stacking subunit in the above receptor clearly

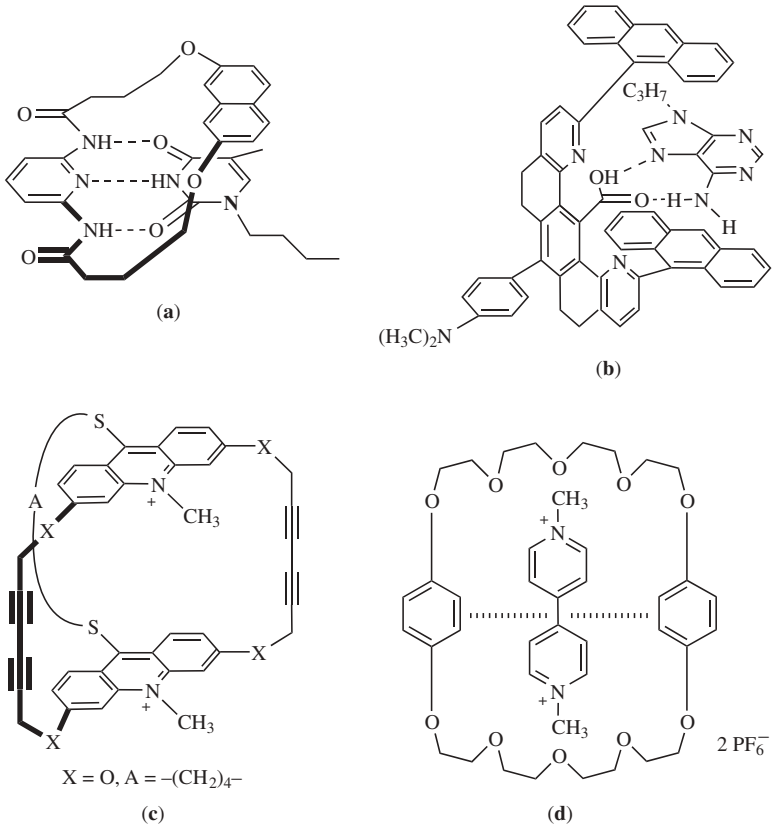


Fig. 14. π-Stacking and charge-transfer dominated recognition of flat aromatic–heteroaromatic substrates (formation of intercalates).

indicates that doubling the π-stacking contribution should lead to substantial improvement of recognition behavior and increasement of binding energy. This has led to a molecular tweezer design strategy to flank a hydrogen bonding carboxylic acid by two π-stacking anthracene units corresponding to the receptor–substrate relationship demonstrated in Figure 14**b** (88).

In a way, π–π stacking and charge transfer type of recognition have something in common. Examples making facts obvious are presented in Figure 14**c** and 14**d.** The macrobicyclic intercaland of Figure 14**c** and related receptors have been found to recognize flat shaped substrates through π–π stacking and bind them to form a molecular cryptate, in particular if electron donating substrate species are involved to allow charge-transfer interaction, such as planar molecular anions or nucleic acids (89). Similarly, large ring electron donor aromatic crown ethers were designed that yield charge-transfer type intercalation complexes with paraquats (Fig. 14**d**) (90). Vica versa, macrocyclic bipyridinoquates form charge-transfer supported intercalation complexes with flat aromatic substrates having electron-donating substituents (91).

3.5. Lipophilic Interaction Dominated Substrate Recognition. Making recognition through lipophilic interaction possible require receptors

presenting large and more or less rigidly connected architectures of macrocyclic or cage-like nature (92). Here only some illustrative examples can be given (see also INCLUSION COMPOUNDS), referring the reader to specific reviews of this vast subject (8–12).

The naturally occurring cyclodextrins having endo-lipophilic cone-shape are perhaps the most important and also the first receptor molecules whose selective inclusion properties toward lipophilic organic molecules were recognized (93,94). They comprise a family of cyclic oligosaccharides, composed of 6,7, and 8 glucose units in its most familiar representatives (α,β, and γ-cyclodextrin, respectively) providing endo-lipophilic and exo-hydrophilic cone-shaped molecular cylinders of increasing size (Fig. 15**a**). Cyclodextrins form size and shape

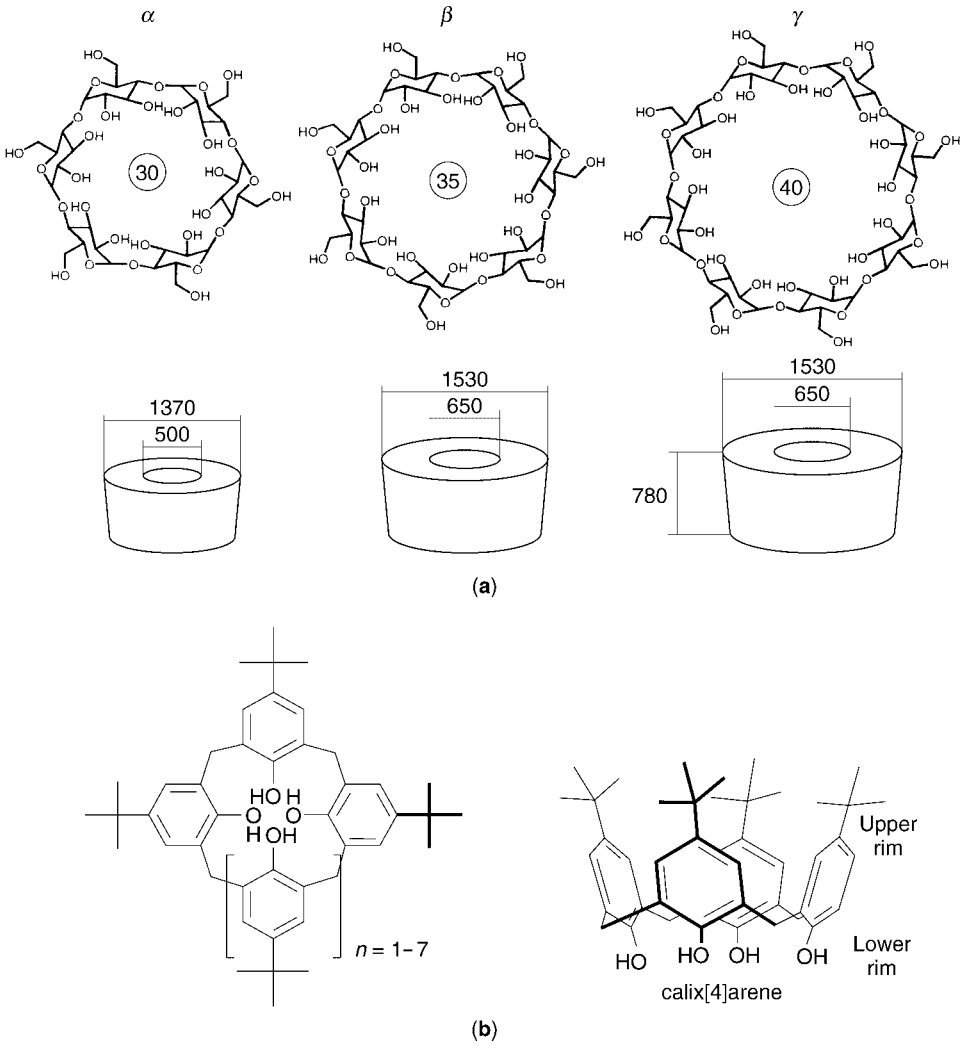


Fig. 15. Prototype examples of (**a**) cyclodextrins and (**b**) calixarenes, showing conformational structures and dimensions.

selective inclusion compounds with a wide variety of substrates including benzene derivatives, paraffins, and noble gases (95).

Calixarenes (from the Latin *calix*) may be understood as artificial receptor analogues of the natural cyclodextrins (96,97). In its prototypical form they feature a macrocyclic metacyclophane framework bearing protonizable hydroxy groups made from condensation of *p*-substituted phenols with formaldehyde (Fig. 15**b**). Dependent on the ring size, benzene derivatives are the substrates most commonly included into the calix cavity (98), but other interesting substrates such as C_{60} have also been accommodated (Fig. 8**c**) (45).

As mentioned, calixarenes fall into the cyclophane-type of compounds that has emerged the central class of synthetic receptors in molecular recognition involving all kinds of ortho-, meta- and para-bridged aromatic macrocycles and oligomacrocycles, ie, pocket, open vessel, and macrocage receptors (99,100). A beautiful construction of this type are the cryptophanes, an example of which is shown in Fig. 16**a** (101,102). Cryptophanes are of much interest in particular for their ability to recognize and bind derivatives of methane that match the cavity. Although substrates are rather cut off outside here, the most extreme case of imprisonment of substrates is provided by the carceplexes (103). They are the inclusion complexes of carcerands (104). A prototype example is illustrated in Figure 16**b.** These containers have a virtually closed molecular surface indicating that carceplexes are formed during shell closure of two hemisphere components (cavitands) templated around the substrate (31,105,106). They also found that high structural recognition is involved in this capture, and the shell closure to give empty carcerands do not occur. Once substrates have been trapped in the cavity they can be released again only by destruction of the

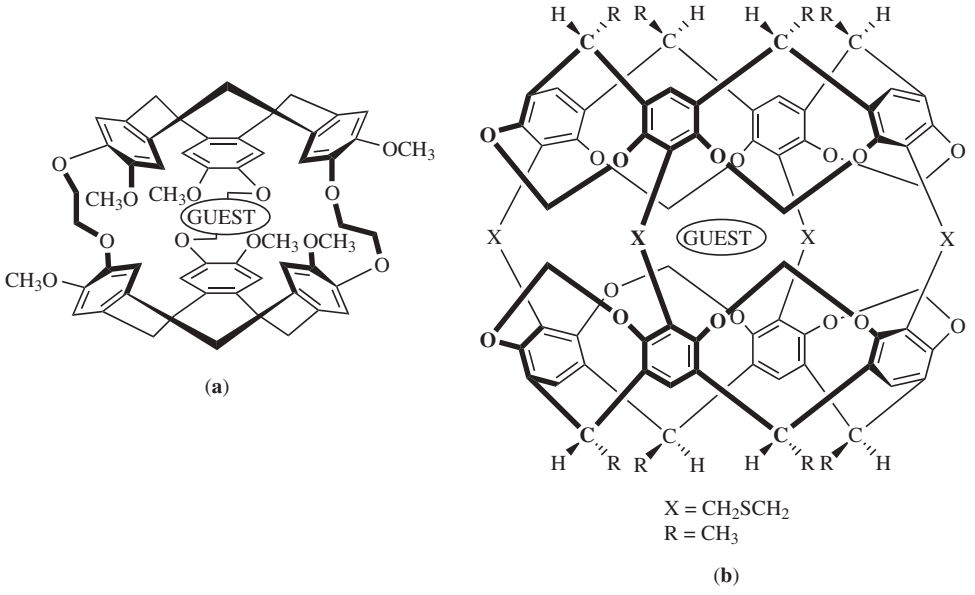


Fig. 16. (**a**) Inclusion complex of a cryptophane; and (**b**) a carceplex (carcerand inclusion complex).

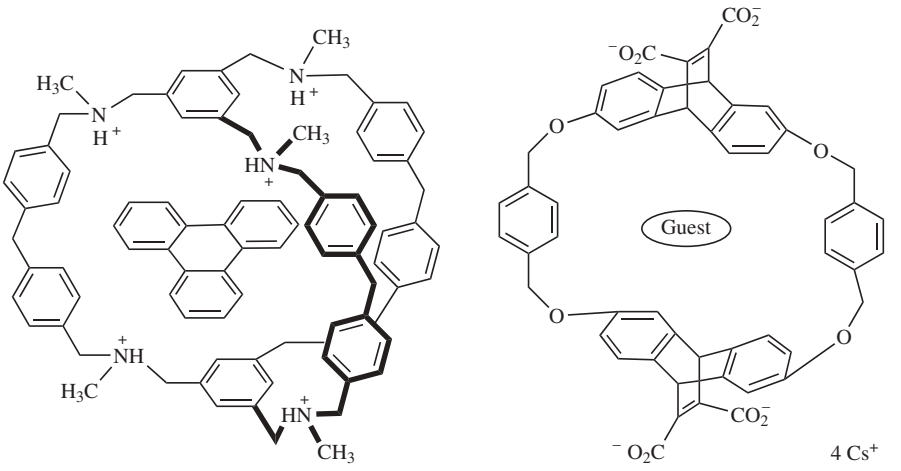


Fig. 17. Inclusion complexes of endo-hydrophobic–exopolarophilic receptors involving charges of different nature.

carcerand framework. Hemicarcerands are like carcerands except that by conformational modifications they can generate portals which join the inner phase of the receptor with the outer phase making an equilibrium of the substrate between in and out possible (103–106).

While the previous receptors are typically used in organic solvents, except for the cyclodextrins, there are special cases of cyclophane receptors supplied with peripheral charges (ammonium units) (107–112) or ionizable groups (carboxylate functions) (113,114) (Fig. 17) to allow substrate recognition, as in nature, in an aqueous medium, profiting from the solvophobic effects of water (115).

4. Multiple and Multisite, Coreceptor- and Coupled-System Substrate Recognition

Once recognition units for specific groups and individual features of a substrate have been identified, one may consider combining several of them within the same receptor. Thus far, though not carefully directed, the previous receptors in many cases, and as pointed out already possess this property of nonindividual interaction modes. More carefully directed, this leads to multiple and multisite recognition depending on the design of binding subunits which may cooperate for the simultaneous complexation of several substrates or of a multiply bound polyfunctional species to yield polynuclear complexes (homo- or heteronuclear) and mononuclear polyhapto-type complexes, respectively (116). Moreover, one may distinguish co-receptor systems for which the binding of several substrates is commutative and cascade systems, for which the substrate binding steps are noncommutative but follow a given sequence (9).

A typical example of the multiply binding type of molecular recognition of a polyfunctional species is demonstrated in Figure 18 (117). Owing to the different

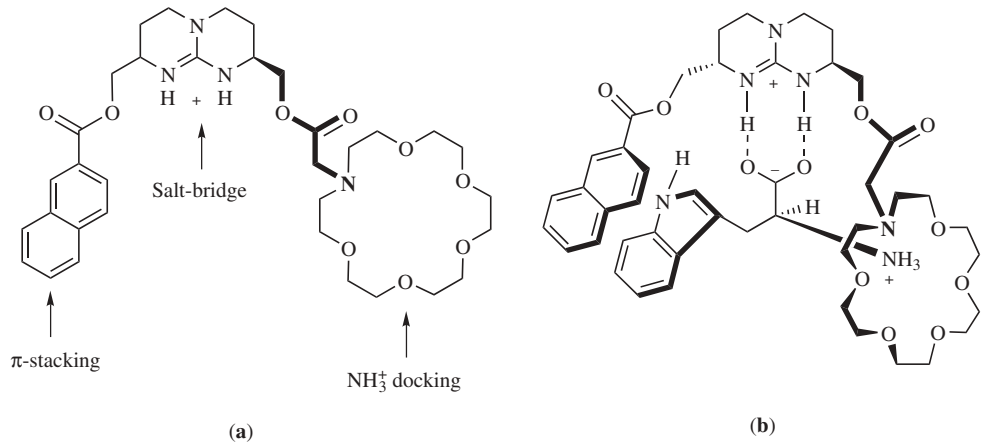


Fig. 18. (**a**) A bicycloguanidinium receptor; and (**b**) its three-point association to the zwitterionic α-amino acid trypthophan (118).

binding sites that are an electron deficient guandinium group, a negatively polarized macroring and a naphthalene π-stacking unit, the receptor shown in Figure 18**a** should allow simultaneous interaction with, eg, the carboxylate, the ammonium and the aromatic groups of a substrate that is an aromatic zwitterionic amino acid (tryptophan) such as illustrated in the receptor–substrate complex of Figure 18**b** (66,118).

Numerous receptors comprising other multiply docking units and binding sites have been synthesized (19,35,77,117–120) including, eg, the speleands that in its frame comprise a negatively polarized macroring and an apolar but rigid shaping component for the size selective recognition of a primary ammonium cation (121).

The macrocyclic hexaimine structure of Figure 19**a** forms a homodinuclear cryptate with Cu(I) (122), whereas crown ether boron receptors (Fig. 19**b**) have been applied for the simultaneous and selective recognition of complementary cation–anion species such as potassium and fluoride (123) or ammonium and alkoxide ions (124) to yield a heterodinuclear complex (120).

Metalloreceptors based on a designed cationic inclusion complex as the specific accommodation site for the recognition of an uncharged guest molecule is another useful development (119,125). Metallomacrocycles of salen-type containing a complexed uranyl cation are most common here (126). The triple porphyrin receptor shown in Figure 19**c** is a more complex example of this strategy that operates in double recognition mode when forming complexes with zinc and 2,4,6-tri-4-pyridyl-*s*-triazine matching size and geometry of the tritopic metalloreceptor (127).

Receptor systems for the combined and commutative recognition of differently sized cation species (eg, K^+ and Li^+, Fig. 20**b**) have also been designed (128). They may follow the first step of the diagram in Figure 20**a** while recognition of the previous metalloreceptors is noncommutative with substrate binding in a given sequence typical of cascade complexation (Fig. 20**a**) (129). Here complexes are formed by first binding metal ions, which then serve as interaction

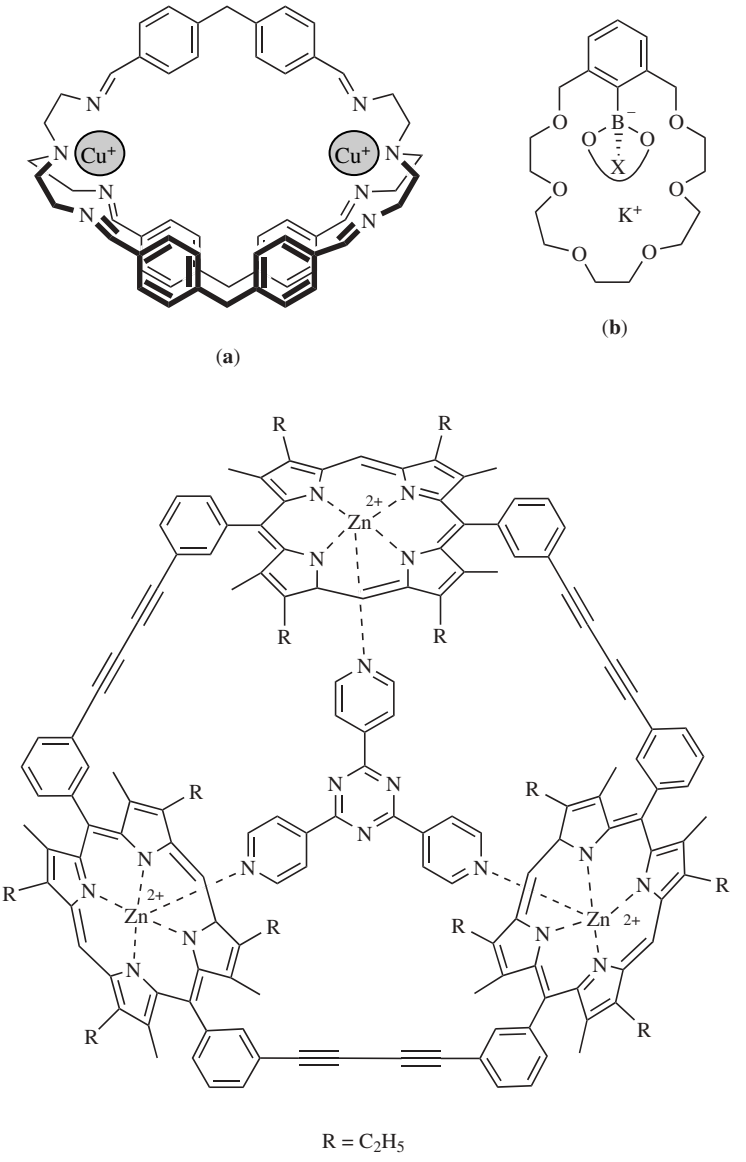


Fig. 19. Multiple and multisite substrate recognition: (**a**) a homo dinuclear (dicationic) and (**b**) a heterodinuclear (cation and anion) inclusion complex: (**c**) a trihapto-type inclusion complex of a triple porphyrin receptor.

sites for another substrate. Such is also the case for the dinuclear copper complex of Figure 20**c** containing a bridging imidazolato group related to the copper proteins (130).

Allosteric coupling results when occupation of a given receptor site leads to a change in the recognition and binding features of the other sites (cf Fig. 20**b**) making binding easier or more difficult (positive or negative cooperativity) (9,34). The allosteric effect plays a major role in the regulation of the activity of an

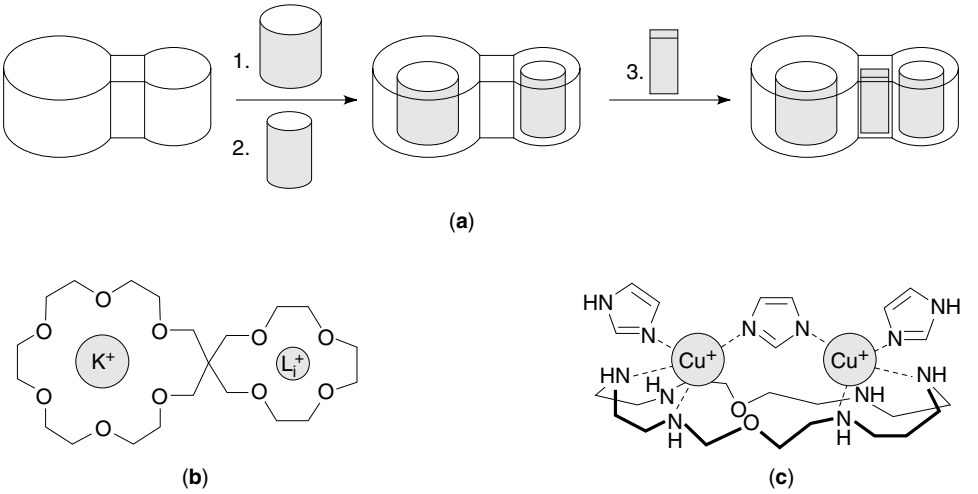


Fig. 20. (**a**) Schematic illustration of the formation of a cascade complex; (**b**) a heterodinuclear cation complex of a diloop crown receptor; and (**c**) a typical cascade complex.

enzyme involving conformational changes included by the binding of an effector (131). This kind of cooperativity has also been studied in synthetic receptors (132,133). An obvious approach to achieve such systems is based on the clapperboard construction schematized in Figure 21**a** comprising two binding sizes of types A and B, respectively, inside and at the ends (34,134). Binding of M (eg, a metal ion) enhances the ability for the inclusion of L (eg, a lipophilic organic substrate). A similar case of allostery is illustrated in Figure 21**b** where the thymine derivative binding using hydrogen bond and π-stacking interactions is increased by a factor of 4–6 upon sodium ion uptake by the oligoethylene glycol ether part of the receptor system (135).

5. Chiral Recognition

Enantiomers are perhaps the substrate type most difficult to distinguish. As is well known, they are stereochemical species that have exactly the same structure except for their mirror image (chirality) relationship (33) (see also CHIRAL SEPARATIONS). This causes a problem. On the other hand, chiral (enantiomer) recognition in complexation is one of the most important means by which receptor sites of biological systems such as in genes or enzymes act and regulate (2). From the principle point of view, recognition of a substrate enantiomer from racemic mixture (50:50 % mixture of enantiomers) requires an enantiomeric optically resolved receptor structure in order to make possible two diastereomeric receptor–substrate complexes allowing differentiation (Fig. 22**a**) (136).

Following this line, a great variety of optically resolved (optically active) crown compounds were prepared for the resolution of racemic cationic substrates, eg, chiral primary ammonium salts, protonated α-aminoalcohols and α-amino acid derivatives, through complexation (137–139). Among the highest

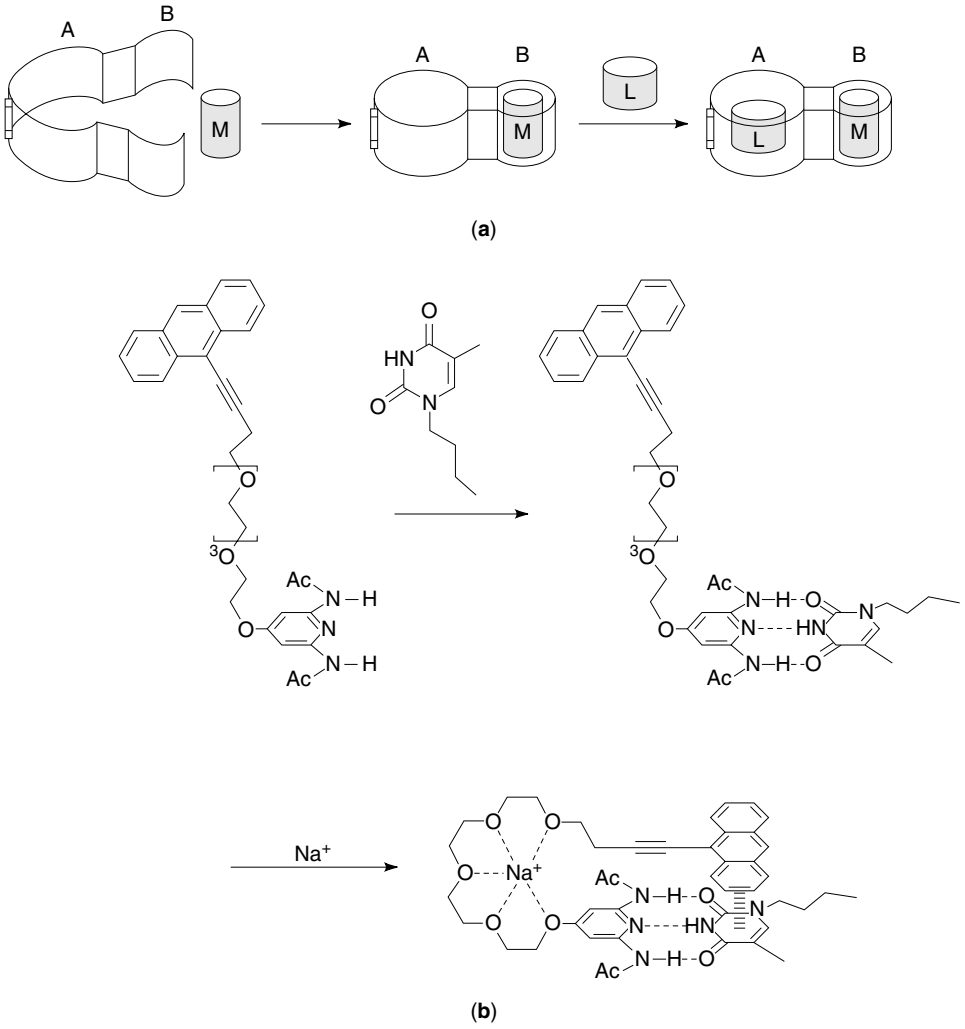


Fig. 21. (**a**) Diagrammatical representation of an allosteric receptor mechanism; (**b**) allosteric binding of a thymine derivative promoted on K^+ uptake (34).

enantiomer recognition properties for chiral ammonium ions were obtained with crown ethers having one or two 1,1-binaphthyl chiral barriers in the framework (Fig. 23**a**) (27,37,140). Others contain a spirobifluorene chiral subunit (141) or are derived from terpenoids, amino acids, and hydroxy acids that make use of the natural pool of chiral compounds (138). Typical examples for the latter classes of receptors are shown in Figure 23**b, c** where natural α-D-glucose (142) or tartaric acid (143) are the chiral sources. A further important family of chiral receptors derived from natural glucose are the cyclodextrins (Fig. 15**a**) (93–95). Moreover, most of these receptors (cf. Fig. 23**a–c**) are carefully designed systems in that they contain at least one C_2 axis of symmetry (dissymmetric compound type), a tactic that makes the receptors nonsided with respect to perching substrates, eg, ammonium guests (136). Beyond that C_3 symmetric receptor

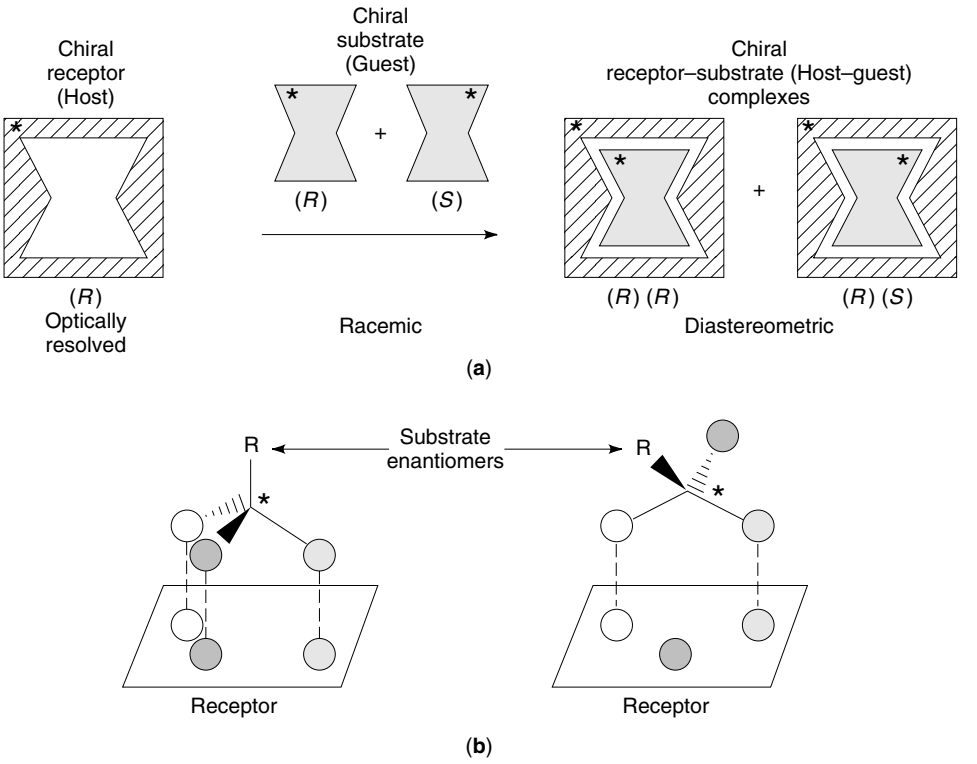


Fig. 22. Principle of chiral receptor–substrate recognition: (**a**) formation of diastereomeric inclusion complexes; (**b**) three-point interaction model.

molecules have also been used to advantage in chiral recognition such as the cryptophane in Figure 16**a** (101,102) or the basket shaped chiral host presented in Figure 23**d** (144). Although besides chiral ammonium ions amides are the substrate class of compounds to be very efficiently resolved by the majority of receptors, particular enantiomer recognition properties including steroid hormones have also been reported (145). The cryptophane is typical of the chiral resolution of methane derivatives (eg, CHFClBr) (146) and the basket-shaped host of Figure 23**d** exhibits extremely high enantioselectivity for various peptides (144).

Interpretation of these results are in keeping with the complementarity between chiral receptor and chiral substrate as sketched in Figure 22 (notice the orientation of the stars) and visualized in Figure 18**b.** This figure shows that the zwitterionic amino acid tryptophan of natural configuration (*S*) ideally complements the three sites of the chiral (optically resolved) receptor cleft, while the optical antipode of tryptophan (*R*-configurated enantiomer) is less suited for binding (117). These facts express what is generally called the three-point interaction principle (136,147) illustrating fit or misfit of chiral receptor substrate recognition (Fig. 22**b**).

For more details on this topic see References (138,139,148); for more illustrations on the chiral fit concept see also INCLUSION COMPOUNDS.

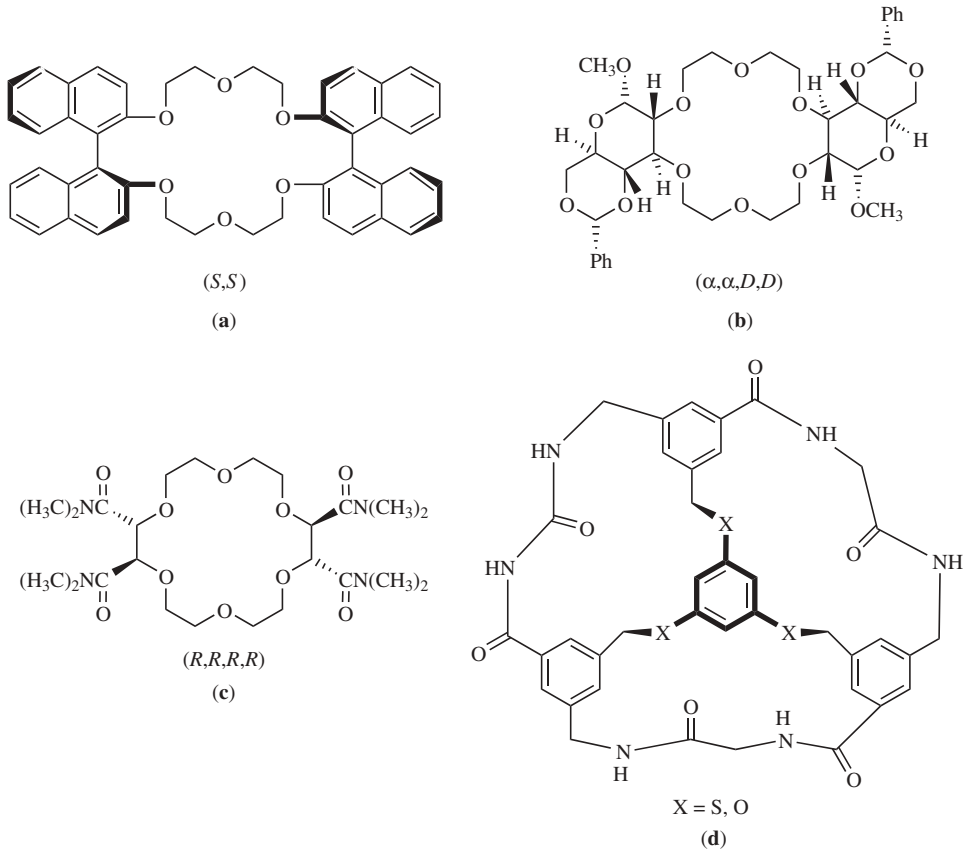


Fig. 23. Prototypical receptor molecules for chiral (enantioselective) substrate recognition.

6. Artificial Receptors for Particular Substrate Recognition

The recognition of substrates from many different compound classes has been discussed. Nevertheless, some particular substrates remain that are biorelevant species or play central roles as drugs. Barbiturates are such an important family of drugs and are the target for molecular recognition (19,77). According to their structure, the barbiturate moiety essentially fuses two imide groups within a six-membered ring. Thus, two diaminopyridine units correctly positioned in a macrocyclic ring should bind to all six of the accessible hydrogen bonding sites in barbiturates, as shown in Figure 24**a** (149). A crystal structure of a respective receptor–substrate complex has been performed that comes up to the expectations (19,77).

The structural and synthetic relationships shared between barbiturates and urea, which is another substrate of high physiological interest, suggest that the above receptor strategy could be modified for the selective complexation of urea. The designed modification for urea recognition involves replacement of the H-bond donating pyridine-6-amido groups in the previous barbiturate

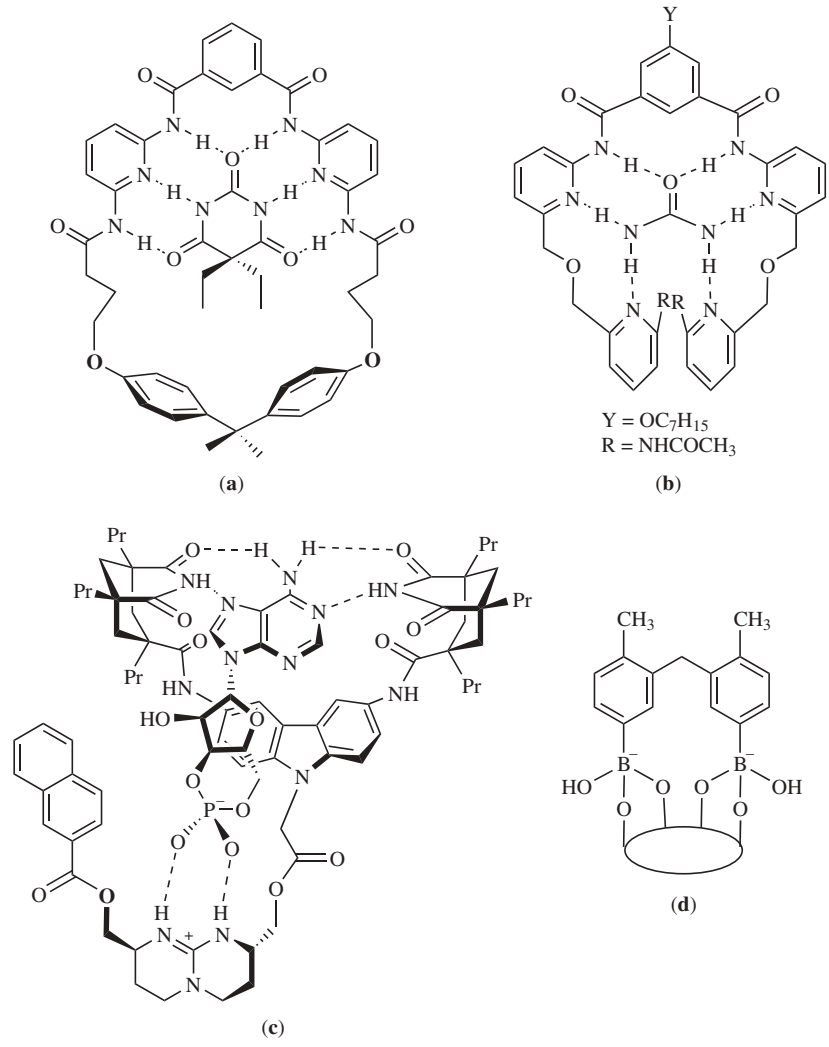


Fig. 24. Receptor substrate complexes involving particular substrate recognition.

receptor by two H-bond accepting groups that differ by 120° in alignment to the substrate. Such an arrangement of binding groups exists in the receptor molecule for urea illustrated in Figure 24**b** (19,77). An approach using an acyclic, but rigid hydrogen bond heteroaromatic framework such as the naphthiridine derivative presented in Figure 13**d** has also been developed (86), and last but not least the above metalloreceptor strategy based on a metal center (eg, UO_2) as an electrophilic binding site for the carbonyl oxygen of urea included in a macrocyclic receptor was successfully applied (119,125,126). A modification of the rigid heterocyclic cleft-type receptor mentioned above (cf Fig. 13**d**) has also yielded good results in the recognition of uric acid, the key product of the purine metabolism (150).

Nature's strategy for the recognition of nucleic acid bases offers an ideal example of directional and orientational dependence of simultaneous hydrogen bonding and aromatic stacking interactions to make advantage for an artificial receptor design of nucleic acid bases. A taste of it has already been given in Figures 14**a** (87) and 14**b** (88) illustrating effective recognition of an uracil and adenine derivative, respectively (19,77). In addition, receptors where two such sites are linked through a spacer element attenting to the recognition of multiple nucleic acid base derivatives have also been carried out successfully (77,151).

Nucleotides, the building blocks of DNA and RNA strands, beside a polyphosphate chain and ribose or deoxyribose also contain a nucleobase. According to this importance, efforts have been directed toward the problem of phosphate recognition and the development of artificial receptors capable of distinguishing nucleotides with respect to both the nucleobase and the phosphate chain (66,118). A tricky solution of the problem is presented in Figure 24**c,** taking advantage of the phosphate affinities of a bicycloguanidinium cation and the well-established chelating capacity of a molecular cleft featuring two converging imide functions (152).

Boronic acid–diol covalent interactions creating five- or six-membered rings reversibly form in aqueous media, thus, providing an important tool in the recognition of saccharides (153–155). Moreover, many monosaccharides possess at least two binding sites (diol area) which differ from other monosaccharides. Based on this strategy a number of small saccharide selective receptor molecules with conformationally well-defined distance and orientation between two boronic acid functionalities have been designed. An example is given in Figure 24**d** (156). D-Glucose yields a relatively strong 1:1 complex at pH 11.3, whereas complexes with galactose, talose, maltose, cellobiose, and lactose are weaker. The complex with glucose is believed to involve bonds to the C1–C2 and C4–C6 diols as sketched in Figure 24**d.** Chiral recognition of saccharides along this line using chirally modified diboronic acid receptors have also been realized (157). A second main category of saccharide receptors are typical of bowl-shaped molecules belonging to the resorcinarenes (158) (see INCLUSION COMPOUNDS) and other more recent examples (153). What is more, there are good expectations for the development of artificial adrenalin (159) and peptide receptors (160).

However, all the receptors hitherto discussed are monomolecular species which possess a monomolecular cavity, pocket, cleft, groove or combination of it including the recognition sites to yield a molecular receptor–substrate complex. They can be assembled and preserved in solution although there are dependences (see below). By way of contrast, molecular recognition demonstrated in the following comes from multimolecular assembly and organization of a nonsolution phase such as polymer materials and crystals.

7. Molecular Recognition in Polymers and Solids

If a polymer is prepared in the presence of molecules, the "print molecules" which are extracted after polymerization, the remaining polymer may contain cavities, prints, or footprints that can recognize the print molecule (161). Actually, the cast relates to the matrix molecule like lock and key of Emil Fischer's

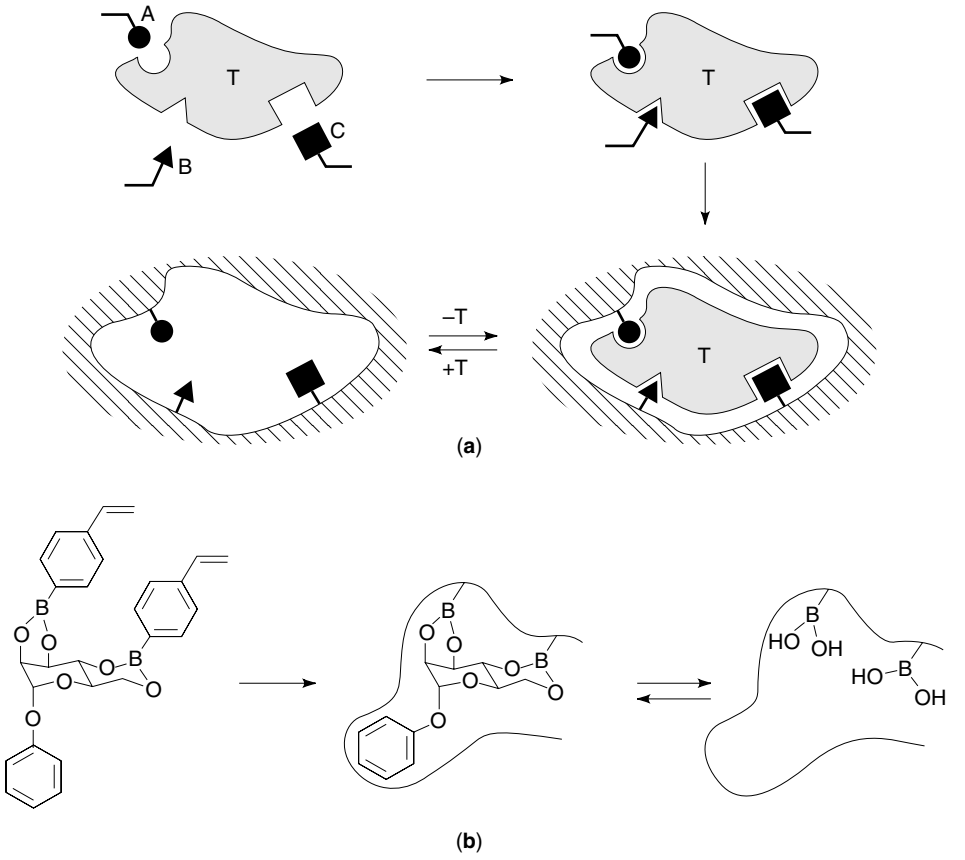


Fig. 25. Schematic representation of imprinting: (**a**) cross-linking polymerization in the presence of a template (T) to obtain cavities of specific shape and a defined spatial arrangement of functional groups (binding sites, A–C); (**b**) cross-linked polymer prepared from the template monomer and ethylene dimethacrylate with and without the templates (161).

long-known principle (5) (see Fig. 1). A scheme of this clever imprinting technique is illustrated in Figure 25**a,** and a relevant example of imprinted polymer is shown in Figure 25**b.** The template monomer of Figure 25**b** is a compound in which two polymerizable moieties of vinylphenylboronic acid have been bound to phenyl α-D-manopyranoside as the print molecule. A 1:9 ratio of the monomer and ethylene dimethacrylate were copolymerized in an inert solvent to yield a macroporous polymer of which the template is split off providing chiral cavities each bearing a pair of boronic acid groups. Polymers of this type have excellent ability for recognition of the template molecule, also in the given enantiomer configuration when subjected to its racemate.

By analogy, a great many of other functionalized styrenes, including carboxylic acids, amino acids, Schiff bases, or specific compounds, eg, L-DOPA, have successfully been applied as print templates. Moreover, it has also been shown that silica gel can be imprinted with similar templates, and that the

resulting gel has specific recognition sites determined by the print molecule (162–164).

In a sense, molecular recognition using hollow organic crystals, in particular clathrate structures (165), is similar although the interactions forming the framework are noncovalent but weak interactions (16). For the same reason typical multinuclear crystalline inclusion compounds and clathrates are not stable in solution, but decompose unlike the monomolecular inclusions and more stable receptor–substrate complexes (165). Nevertheless molecular recognition behavior of crystalline inclusion compounds is both various dependent on the structure that can be cavity-, layer- or channel-type (167), and in many cases highly selective including chiroselectivity (168).

A packing motif giving a general idea of such an efficient chiral recognition machinery that uses the crystalline inclusion phenomenon is illustrated in Figure 26 (169). The optically active receptor molecule (Fig. 26**a**), a bulky derivative of lactic acid, chiroselectively yields a crystalline inclusion compound with (*R*)-configurated 3-methylcyclohexanone (Fig. 26**b**), refusing the steric mirror image (*S*-configuration) of the substrate, whereas the correctly configurated substrate (*R*) ideally matches the intermolecular lattice space (Fig. 26**c**). Along this line a number of bulky crystalline hosts have been designed capable of chiral substrate recognition, eg, of alcohols, phenyloxirane, sulfoxides and lactones, to say nothing of more simple constitutional isomer recognition and of the recognition of other chemically different species (165,167,170). However, it would mean doubling of information to go into details here since this particular topic is extensively covered under the subjects extra molecular cavity and lattice type inclusion compounds (see INCLUSION COMPOUNDS).

Microporous inorganic materials dominated historically by the zeolites and alumosilicates, and the great variety of more recent nonoxide and coordination framework materials should also be mentioned here (171–174) but not discussed in detail. This type of molecular recognition is usually known as molecular sieving.

8. Molecular Recognition at Interfaces and Surface Monolayers

There are three advantages to study molecular recognitionon surfaces and interfaces (monolayers, films, membranes or solids) (175): (*1*) rigid receptor sites can be designed; (*2*) the synthetic chemistry may be simplified; (*3*) the surface can be attached to transducers which makes analysis easier and may transform the molecular recognition interface to a chemical sensor. And, which is also a typical fact, this kind of molecular recognition involves outside directed interaction sites, ie, exo-receptor function (9) (see Fig. 5**b**).

To begin with, molecular recognition of crystal interfaces make possible the control of crystal growth processes in that suitably designed auxiliary molecules act as promoters or inhibitors of crystal nucleation inducing, for instance, the resolution of enantiomers or the crystallization of desired polymorphs and crystal habits (176). As an example (Fig. 27), crystals of achiral glycine, due to their enantiopolar arrangement, may differentiate between (*R*)- and (*S*)-amino acids when being used as additives (177). Thus an α-amino acid additive such as

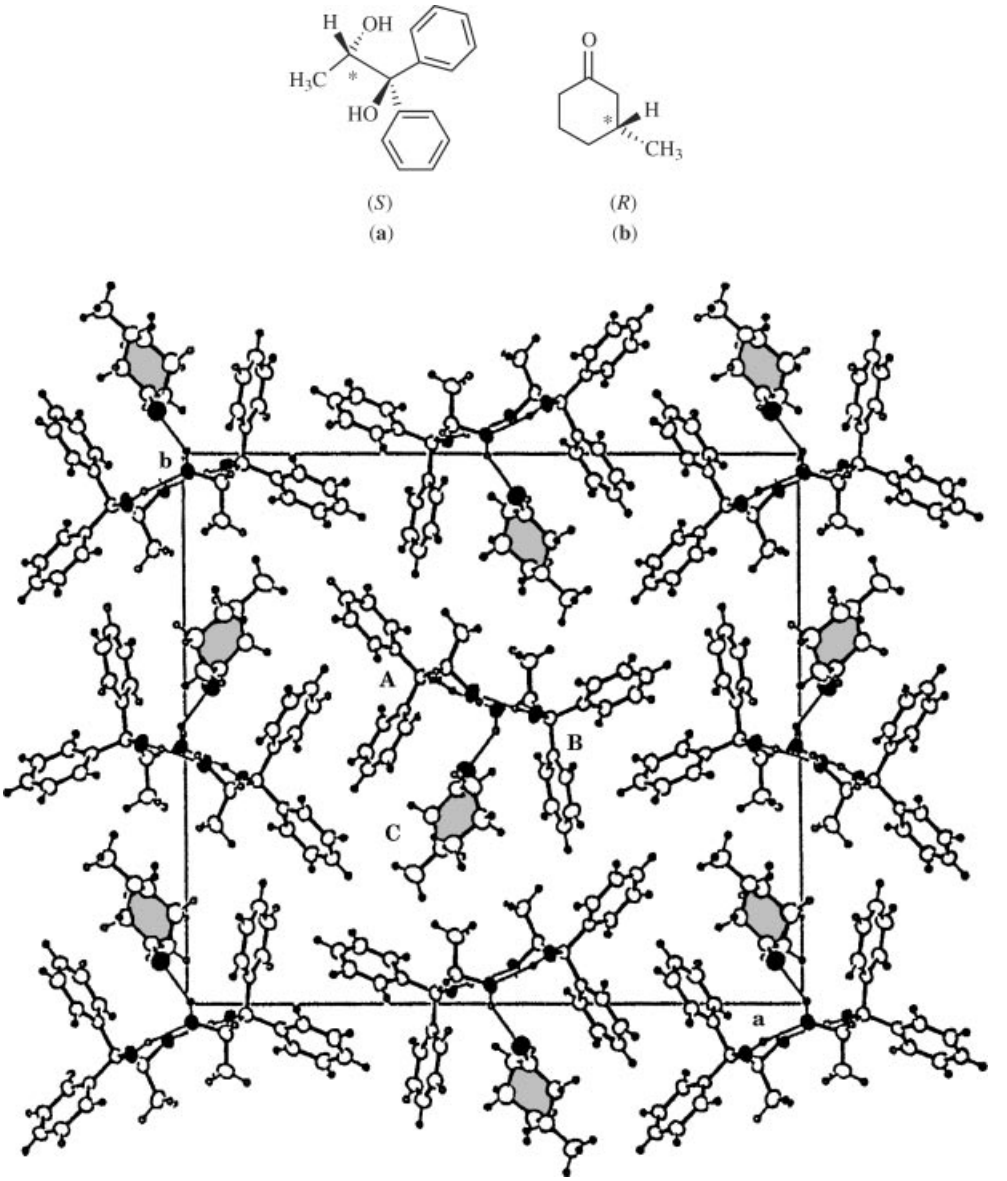


Fig. 26. Clathrate receptor chemistry: (**a**) a chiroselective crystalline host compound (clathrand); (**b**) a typical guest molecule to be included in the specified configuration; and (**c**) the crystal structure of the respective clathrate (A and B denote host and C the guest species) (169).

alanine of configuration (*R*) capable of replacing a glycine molecule will block crystal growth only at one of the two enantiopolar crystal faces, the (*pro-R*)-face [(010)-face in Fig. 27**b**]. An (*S*)-amino acid practises the same effect on the (*pro-S*)-face of the glycine crystal [(010)-face], and [(0$\bar{1}$0)-face], and addition of racemic (*R,S*)-amino acid suppresses growth at both enantiopolar faces (Fig. 27**c**). In consequence, the crystal of glycine changes its habit from a symmetric

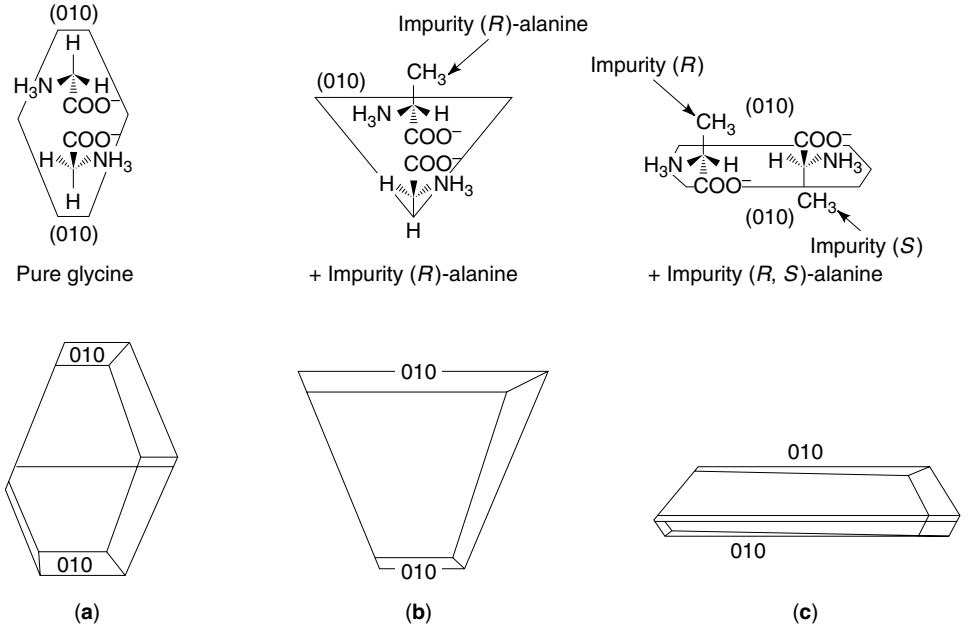


Fig. 27. Recognition at crystal interfaces and its role in the engineering of crystal morphology and configurational assignment of molecules (176,177).

bipyramide to either two asymmetric mirror-image pyramids or a platelet making engineered crystal habits possible (178) (Fig. 27). These impurity crystals having large and hydrophobic planes orientedly swim at the air–water surface which can be applied toward the resolution of further amino acids and for the direct and relative assignment of the absolute configuration of chiral molecules and crystals using stereochemical correlations (179).

Following another direction, it has previously been shown that alkanethiols spontaneously adsorb to Au from dilute solutions of ethanol and other nonaqueous solvents, and that the resulting self-assembling monolayers (SAMs) assume a close-packed overlayer structure on Au (111) and other textured Au surfaces, being quite robust in aqueous solutions and vapor-phase ambients (180). This mode of self-assembly chemistry has been used to synthesize monolayer assemblies that function as molecular recognition interfaces based on the presence of recognizer end groups (181). Thus one-component SAMs formed of *n*-alkanethiols having extra carboxylic acid functionalized end groups specifically adsorb vapor-phase acid-terminated molecules via H-bonding (Fig. 28) or vapor-phase amine-terminated molecules via proton-transfer interaction, exhibiting chemical complementorship (182). It has also been demonstrated that two-component SAMs, which consist of inert *n*-alkanethiol framework molecules and defect inducing template molecules, can discriminate between solution-phase probe molecules based on their geometrical properties, similar to the imprinting technique discussed before (see Fig. 25**a**) but on the two-dimensional level only (182). In order to create analogous molecular recognition property on an oxide surface, a silica overlayer was prepared on tin oxide by the chemical vapor deposition of

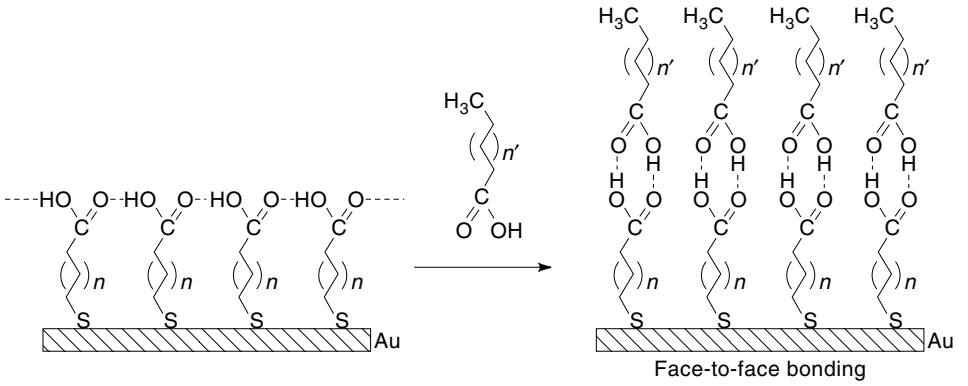


Fig. 28. Self-assembly monolayer to function as molecular recognition interface (182).

silicon alkoxide using preadsorbed benzoate anions as template molecules, which were then removed to yield vacancies in the overlayer capable of size recognition of the probe molecules (183).

In an obvious example of molecular recognition at the air–water interface, the receptor consists of an organized monolayer formed from amphiphiles that have complementary binding sites (184). For example, the double-chain triazine amphiphile illustrated in Figure 29 (185) was employed for the formation of a monolayer receptor at the air–water interface which specifically interacts with barbituric acid dissolved in the water subphase, creating a supramolecular strand, in close analogy to solid-state and solution structures formed of the hydrogen-bonded components (186,187). The stabilization conferred on the monolayer by its networking with barbituric acid made its imaging by atomic force microscopy (afm) possible, while the noncomplexed monolayer is destroyed by the scanning tip of the afm (185). Vice versa, amphiphilic derivatives of

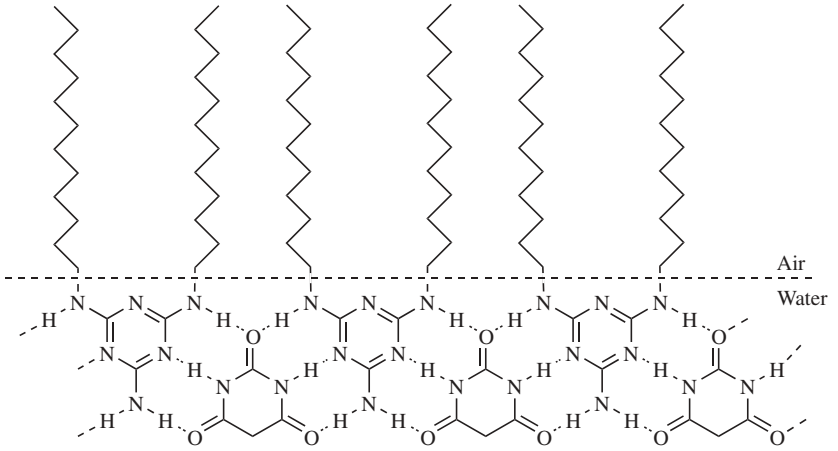


Fig. 29. Molecular recognition of an organized assembly at the air–water interface (184).

barbituric acid form a monolayer receptor at the air–water interface interacting with complementary substrates such as 1,4,6-triaminopyridine, melamine and urea (188). The recognition reaction that occurred was investigated by measuring the pressure-surface area isotherms and by using uv-visible spectroscopy. For this latter reason some of the recognizer amphiphiles contain the azobenzene chromophore in its framework (189). Various monolayer self-assembled systems developed primarily for the recognition of nucleobases, dipeptides and sugars at the air–water interface including amphiphilic recorcinarene receptors have also been studied (184). Furthermore, monolayer receptors originating from long-chain derivatives of Kemp's acid (see Fig. 13**c**) were employed for the molecular recognition of amino acids and various nitrogen aromatic compounds (190).

In another example, involving vesicles as organizing entities, molecular recognition occurred between mixed vesicles bearing recognizable moieties. Interaction occurs between the mixed vesicles, which leads to the formation of larger aggregates attributable to the interaction of their recognizable moieties located at the external interface of the vesicles (191).

For the investigation of molecular recognition in micelles, adenine derivatives and positively charged (thyminylalkyl)ammonium salts such as shown in Figure 30 were prepared, which were solubilized in sodium dodecyl sulfate (SDS) solutions. Nmr studies have shown that binding occurs in a 1:1 molar ratio in the interior of the micelles as illustrated in Figure 30 (192).

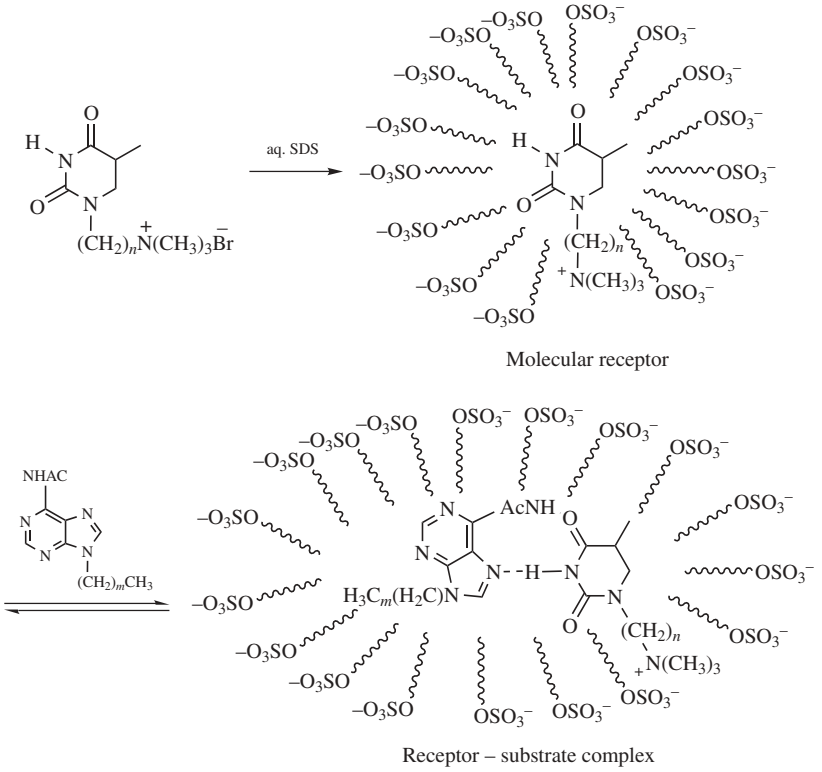


Fig. 30. Molecular recognition in micellar systems (184).

In summary, one may say that the air–water inface is much larger, smoother, and more organized than the interfaces of aqueous micelles and bilayers, which in turn are larger and more organized than those of molecular pairs in bulk water. Thus the binding affinity in general is increased by a factor of 10^2–10^4 each time one proceeds from bulk water to microscopic interfaces of micelles or bilayers and finally to air–water macroscopic interfaces having obvious bearing on the recognition property (184).

9. Self-Recognition

This mode of molecular recognition, on principle, is defined as the recognition of like from unlike or self from unself-molecules, embodied in the spontaneous selection and preferential assembly of like components in a mixture (9).

So far this article has been concerned with interactions among chemically different species which is true for most of the chemical recognition processes including supramolecular and biomolecular processes. With crystals it is usually the other way around. Although some crystals, co-crystals, crystalline complexes, and crystalline inclusion compounds (see above, and INCLUSION COMPOUNDS), are built from more than one kind of molecule and are exceptions, most crystals are built from identical (or enantiomeric) copies of the same molecule. Thus, a usual one-component crystal is a macro-supramolecular assembly (193) where one should more properly speak of molecular self-recognition. This is not a fact contradictory to the basic principles of molecular recognition, discussed at the beginning, since naturally the case might occur in which the two complementary structures happen to be identical in dealing with a self-complementary relationship. So, even when all the molecules are identical (or enantiomeric), an acceptor part of one molecule can interact with a donor part of a second, and the acceptor part of the second can interact in exactly the same manner with the donor part of a third, and so on, giving rise to periodicity of the crystal and to the limited number of space groups used in molecular crystals (194). For instance, it is very uncommon for molecules in a crystal structure to be related by rotation axis or mirror planes, because identical parts of molecules avoid one another, except for molecular sites having a so-called self-complementary donor–acceptor group (195). Self-complementary groups such as the carboxylic acid, the amide, the urea function or its combinations form finite, one-dimensional tape, two-dimensional layer, or three-dimensional motifs of organic molecules mostly obtained from hydrogen bonding. Representative examples are given in Figure 31 (196).

In solution, highly ordered structures created via self-recognition and self-assembly of a programmed H-bonding molecular component are also possible (197) such as the hexameric pseudo supermacrocycle of a designed DNA base hybrid shown in Figure 32 (198), to say nothing of the self-assembly of organic Langmuir and Langmuir-Blodgett films (199) where self-recognition at the air–water interface is of vital importance as well (see Fig. 29).

With respect to inorganic self-recognition and self-assembly this would involve preferential binding of like metal ions by like ligands in a mixture of ligands and ions (9). Indeed, selective formation of double-helicates was obtained from mixtures of oligo-bipyridine strands in the presence of suitable metal ions,

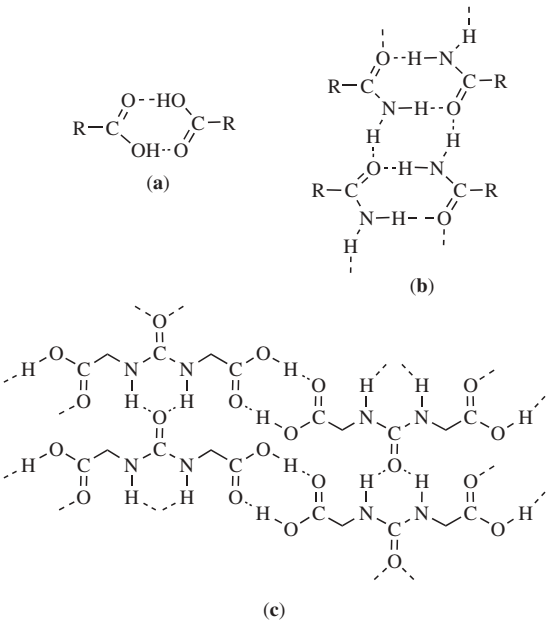


Fig. 31. Supramolecular (hydrogen-bonded) motifs of self-complementary molecules (196).

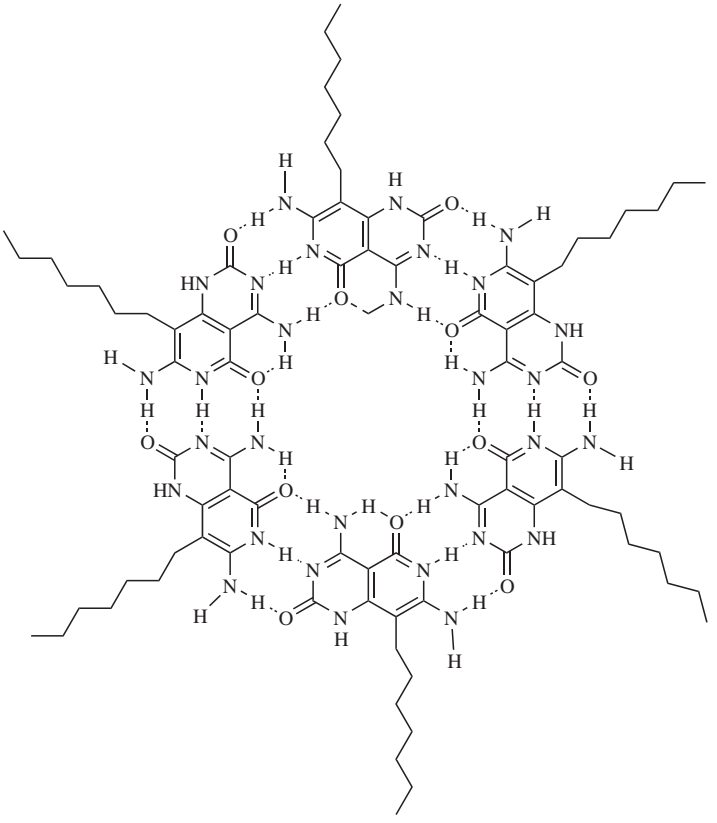


Fig. 32. Hexameric self-assembled supermolecule involving self-recognition (198).

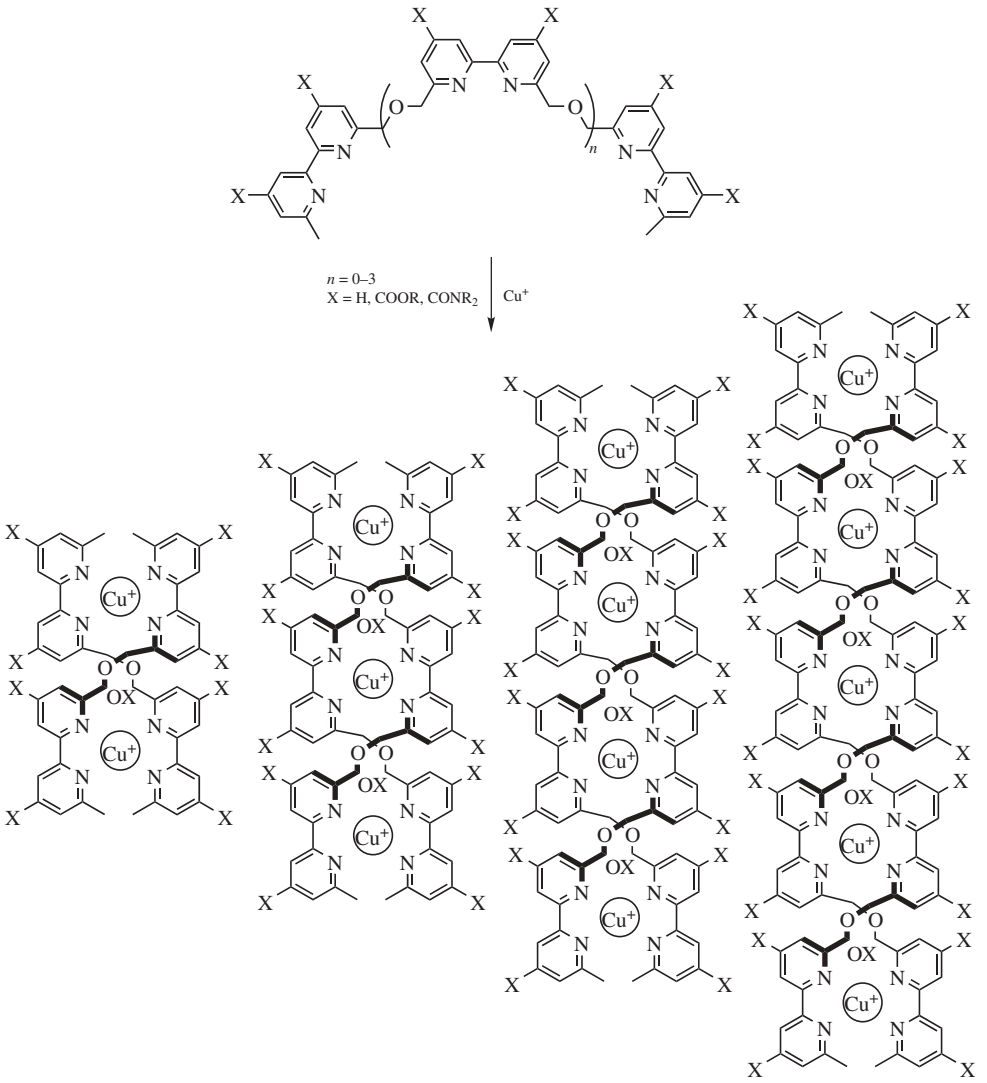


Fig. 33. Self-recognition in the self-assembly of double helixes (9,200).

eg, Cu^{+}, without significant crossover, ie, the desired helicates are generated with self-recognition (Fig. 33) (200). Similar self-recognized triple-helicates have also been obtained from bis-catechols and Ga(III) (201).

A particular point of interest included in these helical complexes concerns the chirality. The helicates obtained from the achiral strands are a racemic mixture of left- and right-handed double helices (Fig. 34) (202). This special mode of recognition where homochiral supramolecular entities, as a consequence of homochiral self-recognition, result from racemic components is known as optical self-resolution (203). It appears in certain cases from racemic solutions or melts (spontaneous resolution) and is often quoted as one of the possible sources of optical resolution in the biological world. On the other hand, the more commonly

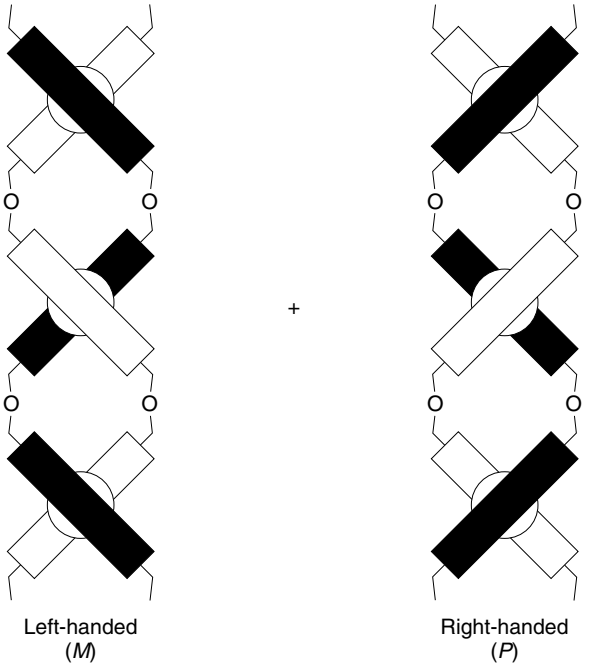


Fig. 34. Enantiomeric double-stranded helixes corresponding to Figure 33 (9,202).

found process of heterochiral self-recognition gives rise to a racemic supramolecular assembly of enantio pairs (204).

10. Conclusion

Although molecular recognition, the programmed molecular interaction or binding with a purpose, is difficult to put into numerical values, its fundamental importance in natural sciences with special points of emphasis in molecular biology (1–3) and supramolecular chemistry (8–12) is clear now. Of course, one may say that molecular recognition as itself is old hat, considering the early lock-and-key principle of Emil Fischer (5) mentioned at the beginning. Nevertheless, molecular recognition has also proved the main portal to enter into the new fascinating technological developments that supramolecular sciences have made available and may further open in the future (205).ValinomycinED: Unknown ppn ED: Unknown vl

CITED PUBLICATIONS

1. M. I. Page, *The Chemistry of Enzyme Action*, Elsevier, Amsterdam, 1984.
2. E. C. Hulme, *Receptor Biochemistry*, Oxford University Press, New York, 1990.
3. S. M. Roberts, ed., *Molecular Recognition—Chemical and Biochemical Problems*, The Royal Society of Chemistry, Cambridge, 1989.

4. J.-P. Behr, ed., *The Lock and Key Principle, Perspectives in Supramolecular Chemistry*, Vol. **1**, Wiley, Chichester, 1994.
5. E. Fischer, Ber. Dtsch. Chem. Ges. **27**, 2985 (1894); see also F. W. Lichtenthaler, Angew. Chem. **106**, 2456 (1994); *Angew. Chem. Int. Ed. Engl.* **33**, 2364 (1994).
6. P. Ehrlich, *Studies on Immunity*, Wiley, New York, 1906.
7. A. Werner, Z. Anorg. Chem. **3**, 267 (1893).
8. F. Vögtle, *Supramolecular Chemistry—An Introduction*, Wiley, Chichester, 1993.
9. J.-M. Lehn, *Supramolecular Chemistry*, VCH, Weinheim, 1995.
10. E. Weber, ed., *Supramolecular Chemistry I—Directed Synthesis and Molecular Recognition, Top, Curr. Chem.*, Vol. **165**, Springer, Berlin-Heidelberg, 1993.
11. E. Weber, ed., *Supramolecular Chemistry II—Host Design and Molecular Recognition, Top. Curr. Chem.*, Vol. **175**, Springer, Berlin-Heidelberg, 1995.
12. J. L. Atwood, J. E. Davies, D. D. MacNicol and F. Vögtle, eds., *Comprehensive Supramolecular Chemistry*, Vols. **1**–**10**, Elsevier, Oxford, 1996.
13. F. Vögtle and E. Weber, eds., *Host-Guest Complex Chemistry—Macrocycles*, Springer, Berlin-Heidelberg, 1985.
14. J.-M. Lehn, Struct. Bonding **16**, 1 (1973).
15. H.-J. Schneider, T. Blatter, U. Cuber, R. Juneja, T. Schiestel, U. Schneider, I. Theis, and P. Zimmermann, in H.-J. Schneider, T. Blatter, U. Cuber, R. Juneja, T. Schiestel, U. Schneider, I. Theis, and P. Zimmermann, eds., *Frontiers in Supramolecular Chemistry and Photochemistry*, VCH, Weinheim, 1991, p. 29.
16. M. Mascal, Contempor. Org. Syn., 31 (1994); see also G. R. Desiraju, Angew. Chem. **107**, 2541 (1995); Angew. Chem. Int. Ed. Engl. **34**, 2311 (1995).
17. H.-J. Schneider, Chem. Soc. Rev., 227 (1994).
18. D. E. Koshland, Jr., Angew. Chem. **106**, 2468 (1994); Angew. Chem. Int. Ed. Engl. **33**, 2375 (1994).
19. D. Hamilton, in H. Dugas, ed., *Bioorganic Chemistry Frontiers*, Vol. **2**, Springer, Berlin-Heidelberg, 1991, p. 115.
20. D. J. Cram, Angew. Chem. **100**, 1041 (1988); Angew. Chem. Int. Ed. Engl. **27**, 1009 (1988).
21. E. Weber in S. Patai and Z. Rappoport, eds., *Crown Ethers and Analogs*, Wiley, Chichester, 1989, p. 305.
22. F. Vögtle and E. Weber, Angew. Chem. **91**, 813 (1979); Angew. Chem. Int. Ed. Engl. **18**, 753 (1979).
23. G. W. Gokel and O. Murillo, in Ref. 12, Vol. **1**, p. 1.
24. G. W. Gokel, *Crown Ethers and Cryptands, Monographs in Supramolecular Chemistry*, Vol. **3**, The Royal Society of Chemistry, Cambridge, 1991.
25. J. M. Lehn, *Acc. Chem. Res.* **11**, 49 (1978).
26. B. Dietrich, P. Viout, and J. M. Lehn, *Macrocyclic Chemistry*, VCH, Weinheim, 1993.
27. D. J. Cram and K. N. Trueblood, in F. Vögtle, ed., *Host Guest Complex Chemistry I, Top. Curr. Chem.*, Vol. **98**, Springer, Berlin-Heidelberg, 1981, p. 43; see also D. J. Cram and K. N. Trueblood, in Ref. 13, p. 125.
28. D. J. Cram, Angew. Chem. **98**, 1941 (1986); Angew. Chem. Int. Ed. Engl. **25**, 1039 (1986).
29. J.-M. Lehn, Angew. Chem. **100**, 91 (1988); Angew. Chem. Int. Ed. Engl. **27**, 89 (1988).
30. E. Weber and F. Vögtle, in Ref. **12**, Vol. **2**, p. 1.
31. D. J. Cram, *From Design to Discovery*, American Chemical Society, Washington, D.C., 1990.
32. A. G. Amit, R. A. Marinzza, S. E. V. Phillips, and R. J. Poljak, *Science* **233**, 747 (1986).
33. S. Hauptmann and G. Mann, *Stereochemie*, HTB Spektrum Akademischer Verlag, Heidelberg, 1996, p. 291.

34. H.-J. Schneider and A. K. Mohammad-Ali, in Ref. 12, Vol. **2**, p. 69.
35. A. R. van Doorn, W. Verboom and D. N. Reinhoudt, in G. W. Gokel, ed., *Advances in Supramolecular Chemistry*, Vol. **3**, JAI Press, Greenwich, 1993, p. 159.
36. B. König, *J. Prakt. Chem.* **337**, 339 (1995).
37. C. J. Pedersen, *Angew. Chem.* **100**, 1053 (1988); *Angew. Chem. Int. Ed. Engl.* **27**, 1021 (1988).
38. E. Weber and F. Vögtle, in Ref. 13, p. 1.
39. E. Weber and H.-P. Josel, *J. Incl. Phenom.* **1**, 79 (1983).
40. R. Hilgenfeld and W. Saenger, in F. Vögtle, ed., *Host-Guest Complex Chemistry II, Top. Curr. Chem.* Vol. **101**, Springer, Berlin-Heidelberg, 1982, p. 1; see also, R. Hilgenfeld and W. Saenger, in Ref. 13, p. 43.
41. G. W. Gokel and O. F. Schall, in Ref. 12, Vol. **1**, p. 97.
42. M. Dobler, *Ionophores and Their Structures*, Wiley, New York, 1981.
43. M. R. Truter, *Struct. Bonding* **16**, 71 (1973).
44. Y. Inoue and G. W. Gokel, eds., *Cation Binding by Macrocycles*, Marcel Dekker, New York, 1990.
45. T. Suzuki, K. Nakashima, and S. Shinkai, *Chem. Lett.*, 699 (1994); see also T. Anderson, K. Nilson, M. Sundahl, G. Wetsman, and O. Wennerström, *J. Chem. Soc., Chem. Commun.*, 604 (1992).
46. J.-M. Lehn, *Pure Appl. Chem.* **49**, 857 (1977).
47. E. Graf and J.-M. Lehn, *J. Am. Chem. Soc.* **97**, 5022 (1975).
48. E. Graf and J.-M. Lehn, *Helv. Chim. Acta* **64**, 1040 (1981).
49. E. Graf, J.-P. Kintzinger, J.-M. Lehn, and J. LeMoigne, *J. Am. Chem. Soc.* **104**, 1672 (1982).
50. J.-M. Lehn and P. Vierling, *Tetrahedron Lett.* **21**, 1323 (1980).
51. J. C. Metcalfe, J. F. Stoddart and G. Jones, *J. Am. Chem. Soc.* **99**, 8317 (1977).
52. J. Krane and O. Aune, *Acta Chem. Scand.* **B 34**, 397 (1980).
53. J.-M. Lehn, P. Vierling, and R. C. Hayward, *J. Chem. Soc., Chem. Commun.*, 296 (1979).
54. J. W. H. M. Uiterwijk, S. Harkema, J. Geevers, and D. N. Reinhoudt, *J. Chem. Soc., Chem. Commun.*, 220 (1982).
55. I. O. Sutherland, in G. W. Gokel, ed., *Advances in Supramolecular Chemistry*, Vol. **1**, JAI Press, Greenwich, 1990, p. 65.
56. I. O. Sutherland, *J. Incl. Phenom.* **7**, 213 (1989).
57. C. Pascard, C. Riche, M. Cesario, F. Kotzyba-Hibert, and J.-M. Lehn, *J. Chem. Soc., Chem. Commun.*, 557, (1982).
58. J. S. Bradshaw, K. E. Krakowiak, and R. M. Izatt, *Azo-Crown Macrocyles*, Wiley, New York, 1993.
59. J. S. Bradshaw and J. Y. K. Hui, *J. Heterocycl. Chem.* **11**, 649 (1974).
60. S. R. Cooper, *Acc. Chem. Res.* **21**, 141, (1988).
61. S. R. Cooper, ed., *Crown Compounds: Toward Future Applications*, VCH, Weinheim, 1992.
62. T. L. Ho, *Hard and Soft Acids and Bases Principle in Organic Chemistry*, Academic Press, New York, 1977.
63. K. N. Raymond, *Coord. Chem. Rev.* **105**, 135 (1990).
64. F. Ebmeyer and F. Vögtle, in H. Dugas, ed., *Bioorganic Chemistry Frontiers*, Vol. **1**, Springer, Berlin-Heidelberg, 1990, p. 143.
65. K. Gloe, H. Stephan, O. Heitzsch, H. Bukowsky, E. Uhlemann, R. Pollex, and E. Weber, *J. Chem. Soc., Chem. Commun.*, 1955 (1994).
66. C. Seel, A. Galán, and J. de Mendoza, in Ref. 11, p. 101.
67. H. E. Katz, in H. E. Katz, eds., *Inclusion Compounds*, Vol. **4**, Oxford University Press, Oxford, 1991, p. 391.

68. F. P. Schmidtchen, in F. P. Schmidtchen, eds., *Biomimetic and Bioorganic Chemistry II, Top. Curr. Chem.*, Vol. **130**, Springer, Berlin-Heidelberg, 1986, p. 101.
69. E. Graf and J.-M. Lehn. *J. Am. Chem. Soc.* **98**, 6403 (1976).
70. F. Schmidtchen and G. Müller, *J. Chem. Soc., Chem. Commun.*, 1115 (1984).
71. P. D. Beer, N. C. Fletcher, A. Grieve, J. W. Wheeler, C. P. Moore, and T. Wear, *J. Chem. Soc., Perkin Trans 2*, 1545 (1996).
72. B. Dietrich, J. Guilhem, J.-M. Lehn, C. Pascard, and E. Sonveaux, *Helv. Chim. Acta.* **67**, 91 (1984).
73. W. M. Hosseini and J.-M. Lehn, *Helv. Chim. Acta* **69**, 587 (1986); J.-M. Lehn, R. Méric, J.-P. Vigneron, I. Bkouche-Waksman, and C. Pascard, *J. Chem. Soc., Chem. Commun.*, 62 (1991).
74. A. M. Echavarren, A. Galán, J. de Mendoza, A. Salmerón, and J.-M. Lehn, *J. Am. Chem. Soc.* **111**, 4994 (1989).
75. G. A. Jeffrey and W. Saenger, *Hydrogen Bonding in Biological Structures*, Springer, Berlin-Heidelberg, 1991.
76. J. D. Watson and F. H. C. Crick, *Nature* **171**, 737 (1953).
77. A. D. Hamilton, in G. W. Gokel, ed., *Advances in Supramolecular Chemistry*, Vol. **1**, JAI Press, Greenwich, 1990, p. 1.
78. D. A. Bell and E. V. Anslyn, in Ref. 12, Vol. **2**, p. 439.
79. F. Garcia-Tellado, S. Goswami, S.-G. Chang, S. J. Geib, and A. D. J. Hamilton, *J. Am. Chem. Soc.* **112**, 7393 (1990).
80. J. C. Adrian and Jr., C. S. Wilcox, *J. Am. Chem. Soc.* **111**, 8055 (1989).
81. J. Rebek, Jr., *Science (Washington DC)* **235**, 1437 (1987).
82. J. Rebek, Jr., *J. Mol. Recogn.* **1**, 1 (1988).
83. J. Rebek, Jr., in E. Weber, ed., *Molecular Inclusion and Molecular Recognition—Clathrates II, Top. Curr. Chem.* Vol. 149, Springer, Berlin-Heidelberg, 1988, p. 189.
84. J. Rebek, Jr., D. Nemeth, P. Ballester, and F.-T. Lin, *J. Am. Chem. Soc.* **109**, 3474 (1987).
85. T. W. Bell, P. J. Cragg, M. G. B. Drew, A. Firestone, A. D.-I. Kwok, J. Liu, R. T. Ludwig, and A. T. Papoulis, *Pure Appl. Chem.* **65**, 361 (1993).
86. T. W. Bell and J. Liu, *J. Am. Chem. Soc.* **110**, 3673 (1988).
87. A. D. Hamilton and D. Van Engen, *J. Am. Chem. Soc.* **109**, 5035 (1987).
88. S. C. Zimmerman, in Ref. 10, p. 71.
89. M.-P. Teulade-Fichou, J.-P. Vigneron, and J.-M. Lehn, *Supramol. Chem.* **5**, 139 (1995).
90. B. Odell, M. V. Reddington, A. M. Z. Slawin, N. Spencer, J. F. Stoddart, and D. J. Williams, *Angew. Chem.* **100**, 1605 (1988); *Angew. Chem. Int. Ed. Engl.* **27**, 1547 (1988).
91. B. L. Allwood, N. Spencer, H.-Shahriari-Zavareh, J. F. Stoddart, and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1064 (1987).
92. C. S. Wilcox, N. M. Glagovich, and T. H. Webb, in C. S. Wilcox, N. M. Glagovich, and T. H. Webb, eds., *Structure, Dynamics, and Reactivity in Aqueous Solutions*, ACS Symposium Series **568**, American Chemical Society, Washington DC, 1994, p. 282.
93. M. L. Bender and M. Komiyama, *Cyclodextrin Chemistry*, Springer, New York, 1978.
94. J. Szejtli, *Cyclodextrin Technology*, Kluwer, Dordrecht, 1988.
95. Ref. 12, Vol. **3**.
96. C. D. Gutsche, *Calixarenes, Monographs in Supramolecular Chemistry*, Vol. **1**, The Royal Society of Chemistry, Cambridge, 1989.
97. J. Vicens and V. Böhmer, eds., *Calixarenes—A Versatile Class of Macrocyclic Compounds*, Kluwer, Dordrecht, 1991.
98. A. Pochini and R. Ungaro, in Ref. 12, Vol. **2**, p. 103.
99. F. Diederich, *Cyclophanes, Monographs in Supramolecular Chemistry*, Vol. **2**, The Royal Society of Chemistry, Cambridge, 1991.

100. Ref. 12, Vol. **2**.
101. A. Collet, in Ref. 10, p. 103.
102. A. Collet, in Ref. 12, Vol. **2**, p. 325.
103. J. C. Sherman, *Tetrahedron*, **51**, 3395 (1995).
104. D. J. Cram, *Nature* **356**, 29 (1992).
105. D. J. Cram and J. M. Cram, *Container Molecules and Their Guests, Monographs in Supramolecular Chemistry*, Vol. **4**, The Royal Society of Chemistry, Cambridge, 1994.
106. P. Timmerman, W. Verboom and D. N. Reinhoudt, *Tetrahedron* **52**, 2663 (1996).
107. Y. Mirakami, J. Kikuchi, and T. Ohno, in G. W. Gokel, ed., *Advances in Supramolecular Chemistry*, Vol. **1**, JAI Press, Greenwich, 1990, p. 109.
108. Y. Murakami and O. Hayashida, in Ref. 12, Vol. **2**, p. 419.
109. J. Franke and F. Vögtle, in J. Franke and F. Vögtle, eds., *Biomimetic and Bioorganic Chemistry II, Top. Curr. Chem.*, Vol. **132**, Springer, Berlin-Heidelberg, 1986, p. 135.
110. F. Diederich, *Angew. Chem.* **100**, 372 (1988); *Angew. Chem. Int. Ed. Engl.* **27**, 362 (1988).
111. F. Diederich, *J. Chem. Educ.* **67**, 813 (1990).
112. H. J. Schneider, *Angew. Chem.* **103**, 1419 (1991); *Angew. Chem. Int. Ed. Engl.* **30**, 1417 (1991).
113. D. A. Dougherty, in Ref. 12, Vol. **2**, p. 195.
114. F. Vögtle, C. Seel, and P.-M. Windscheif, in Ref. 12, Vol. **2**, p. 211.
115. D. B. Smithrud, E. M. Sanford, I. Chao, S. B. Ferguson, D. R. Carcanague, J. D. Evanseck, K. N. Houk and F. Diederich, *Pure Appl. Chem.* **62**, 2227 (1990).
116. J. SD. Brodbelt and C.-C. Liou, *Pure Appl. Chem.* **65**, 409 (1993).
117. A. Galán, D. Andreu, A. M. Echavarren, P. Prados, and J. de Mendoza, *J. Am. Chem. Soc.* **114**, 1511 (1992).
118. C. Seel and J. de Mondoza, in Ref. 12, Vol. **1**, p. 519.
119. W. Verboom and D. N. Reinhoudt, in Ref. 12, Vol. **2**, p. 495.
120. M. T. Reetz, in Ref. 12, Vol. **2**, p. 553.
121. J. Canceill, A. Collet, J. Gabard, F. Kotzyba-Hibert, and J.-M. Lehn, *Helv. Chim. Acta* **65**, 1894 (1982).
122. J. Jazwinski, J.-M. Lehn, D. Lilienbaum, R. Ziessel, J. Guilhem, and C. Pascard, *J. Chem. Soc., Chem. Commun.*, 1691 (1987).
123. M. T. Reetz, C. M. Niemeyer, and K. Harms, *Angew. Chem.* **103**, 1515 (1991); *Angew. Chem. Int. Ed. Engl.* **30**, 1472 (1991).
124. M. T. Reetz, C. M. Niemeyer, and K. Harms, *Angew. Chem.* **103**, 1517 (1991); *Angew. Chem. Int. Ed. Engl.* **30**, 1474 (1991).
125. F. C. J. M. van Veggel, W. Verboom, and D. N. Reinhoudt, *Chem. Rev.* **94**, 279 (1994).
126. D. M. Rudkevich, W. T. S. Huck, F. D. J. M. van Veggel, and D. N. Reinhoudt, in L. Fabbrizzi and P. Poggi, eds., *Transition Metals in Supramolecular Chemistry*, Kluwer, Dordrecht, 1994, p. 329.
127. S. Anderson, H. L. Anderson, and J. K. M. Sanders, *Acc. Chem. Res.* **26**, 469 (1993).
128. E. Weber, *J. Org. Chem.* **47**, 3478 (1982).
129. J.-M. Lehn, *Pure Appl. Chem.* **52**, 2441 (1980).
130. P. K. Coughlin, J. C. Dewan, S. J. Lippard, E. I. Watanabe, and J.-M. Lehn, *J. Am. Chem. Soc.* **101**, 265 (1979).
131. J. Monod, J.-P. Changeux, and F. Jacob, *J. Mol. Biol.* **6**, 306 (1963).
132. J. Rebek, Jr., *Acc. Chem. Res.* **17**, 258 (1984).
133. J. C. Rodriguez-Ubis, O. Juanes, and E. Brunet, *Tetrahedron Lett.* **35**, 1295 (1994).
134. H.-J. Schneider and D. Ruf, *Angew. Chem.* **102**, 1192 (1990); *Angew. Chem. Int. Ed. Engl.* **29**, 1159 (1990).
135. M. Inonye, T. Konishi, and K. Isagawa, *J. Am. Chem. Soc.* **115**, 8091 (1993).

136. E. L. Eliel, S. H. Wilen, and L. N. Mander, *Stereochemistry of organic compounds*, Wiley, New York, 1994.
137. D. J. Cram and J. M. Cram. *Acc. Chem. Res.* **11**, 8 (1978).
138. J. F. Stoddart, *Chem. Soc. Rev.* **8**, 85 (1979); see also, J. F. Stoddart, in E. L. Eliel and S. H. Wilen, eds., *Topics in Stereochemistry*, Vol. **17**, Wiley, New York, 1987, p. 207.
139. M. Pietraszkiewicz and N. Spencer, *J. Coord. Chem.* **27**, 115 (1992).
140. D. J. Cram, R. C. Helgeson, L. R. Sousa, J. M. Timko, M. Newkome, P. Moreau, F. De Jong, G. W. Gokel, D. H. Hoffman, L. A. Domeier, S. C. Peacock, K. Madan, and L. Kaplan, *Pure Appl. Chem.* **43**, 327 (1975).
141. V. Prelog, *Pure Appl. Chem.* **50**, 893 (1978).
142. J. F. Stoddart, in J. F. Stoddart, eds., *Progress in Macrocyclic Chemistry*, Vol. **2**, Wiley, New York, 1981, p. 173.
143. J. P. Behr, J. M. Girodeau, R. C. Hayward, J.-M. Lehn, and J.-P. Sauvage, *Helv. Chim. Acta* **63**, 2096 (1980).
144. J.-I. Hong, S. K. Namgong, A. Bernardi, and W. C. Still, *J. Am. Chem. Soc.* **113**, 5111 (1991).
145. Y. Murakami, O. Hayashida, T. Ito, and Y. Hisaeda, *Chem. Lett.*, 497 (1992).
146. H. Grosenick, V. Schurig, J. Costante, and A. Collet, *Tetrahedron: Asymmetry* **6**, 87 (1995).
147. T. D. Booth, D. Wahnon, and I. Wainer, *Chirality* **9**, 96 (1997); see also, V. Davankov, *Chirality* **9**, 99 (1997).
148. T. H. Webb and C. S. Wilcox, *Chem. Soc. Rev.*, 383 (1993).
149. S. K. Chang and A. D. Hamilton, *J. Am. Chem. Soc.* **110**, 1318 (1988).
150. T. R. Kelly and M. P. Maguire, *J. Am. Chem. Soc.* **109**, 6549 (1987).
151. A. D. Hamilton and D. Little, *J. Chem. Soc., Chem. Commun.*, 297 (1990).
152. G. Deslongchamps, A. Galán, J. de Mendoza, and J. Rebek, Jr., *Angew. Chem.* **104**, 58 (1992); *Angew. Chem. Int. Ed. Engl.* **31**, 61 (1992).
153. J. Haseltine and T. J. Doýle, in *Organic Synthesis: Theory and Applications*, Vol. 3, JAI Press, Greenwich, 1996, p. 85.
154. T. D. James, K. R. A. S. Sandanayake, and S. Shinkai, *Angew. Chem.* **108**, 2039 (1996); *Angew. Chem. Int. Ed. Engl.* **35**, 1910 (1996).
155. T. D. James, P. Linnane, and S. Shinkai, *J. Chem. Soc., Chem. Commun.*, 282 (1996).
156. Y. Shiomi, M. Saisho, K. Tsukagoshi, and S. Shinkai, *J. Chem. Soc., Perkin Trans. 1*, 2111 (1993).
157. T. D. James, K. R. A. S. Sandanayake, and S. Shinkai, *Nature* **374**, 345 (1995).
158. Y. Aoyama, in Ref. 12, Vol. **2**, p. 279; see also, K. Kobayashi, Y. Asakawa, Y. Kikuchi, H. Toi, and Y. Aoyama, *J. Am. Chem. Soc.* **115**, 2648 (1993).
159. T. Schrader, *Angew. Chem.* **108**, 2816 (1996); *Angew. Chem. Int. Ed. Engl.* **35**, 2649 (1996).
160. H.-J. Schneider, *Angew. Chem.* **105**, 890 (1993); *Angew. Chem. Int. Ed. Engl.* **32**, 848 (1993).
161. G. Wulff, W. Vesper, R. Grobe-Einsler, and A. Sarhan, *Makromol. Chem.* **178**, 2799 (1977); see also G. Wulff, in J. S. Siegel, ed., *Supramolecular Stereochemistry*, Kluwer, Dordrecht, 1995, p. 13.
162. G. Vlatakis, L. I. Andersson, R. Müller, and K. Moosbach, *Nature* **361**, 645 (1993).
163. J. H. G. Steinke, I. R. Dunkin, and D. C. Sherrington, *Advances in Polymer Science* **123**, 81 (1995).
164. G. Wulff, *Angew. Chem.* **107**, 1958 (1995); *Angew. Chem. Int. Ed. Engl.* **34**, 1812 (1995); see also, G. Wulff, in W. T. Ford, ed., *Polymeric Reagents and Catalysts, ACS Symposium Series*, Vol. **308**, American Chemical Society, Washington, D.C., 1986, p. 186.

165. E. Weber, ed., *Molecular Inclusion and Molecular Recognition—Clathrates I and II, Top. Curr. Chem.*, Vols. **140** and **149**, Springer, Berlin-Heidelberg, 1987 and 1988.
166. E. Weber, in Ref. 165, Vol. **140**, p. 1.
167. J. L. Atwood, J. E. D. Davies and D. D. MacNicol, eds., *Inclusion Compounds*, Vol. **1**–**3**, Academic Press, Inc., London, 1984; Vols. **4**–**5**, Oxford University Press, Oxford, 1991.
168. F. Toda, in Ref. 12, Vol. 6, p. 465; see also, F. Toda, in Ref. 165, Vol. 140, p. 43 and D. Worsch and F. Vögtle, in Ref. 165, Vol. **140**, p. 21.
169. E. Weber, C. Wimmer, A. L. Llamas-Saiz, and C. Foces-Foces, *J. Chem. Soc. Chem. Commun.*, 733 (1992); see also, E. Weber and C. Wimmer, *Chirality* **5**, 331 (1993).
170. Ref. 12, Vol. 6.
171. C. L. Bowes and G. A. Ozin, *Adv. Mater.* **8**, 13 (1996).
172. T. Bein, ed., *Supramolecular Architecture, ACS Symposium Series*, Vol. **499**, American Chemical Society, Washington, DC, 1992.
173. A. Müller, H. Reuter and S. Dillinger, *Angew. Chem.* **107**, 2505 (1995); *Angew. Chem. Int. Ed. Engl.* **34**, 2311 (1995).
174. I. Dance, in G. R. Desiraju, ed., *The Crystals as a Supramolecular Entity, Perspectives in Supramolecular Chemistry*, Vol. **2**, Wiley, Chichester, 1996.
175. J.-H. Fuhrhop and J. Köning, *Membranes and Molecular Assemblies: The Synkinetic Approach, Monographs in Supramolecular Chemistry*, Vol. **5**, The Royal Society of Chemistry, Cambridge, 1994.
176. L. Addadi, Z. Berkovitch-Yellin, I. Weissbuch, J. van Mill, L. J. Shimon, M. Lahav, and L. Leiserowitz, *Angew. Chem.* **97**, 476 (1985); *Angew. Chem. Int. Ed. Engl.* **24**, 466 (1985); see also I. Weissbuch, R. Popovitz-Biro, L. Leiserowitz, and M. Lahav, in Ref. 4, p. 173.
177. I. Weissbuch, L. Addadi, Z. Berkovitch-Yellin, E. Gati, S. Weinstein, M. Lahav, and L. Leiserowitz, *J. Am. Chem. Soc.* **105**, 6615 (1983).
178. Z. Berkowitch-Yellin, *J. Am. Chem. Soc.* **107**, 8239 (1985).
179. I. Weissbuch, L. Addadi, L. Leiserowitz, and M. Lahav, *J. Am. Chem. Soc.* **110**, 561 (1988).
180. E. Delamarche, B. Michel, H. A. Biebuyck, and C. Gerber, *Adv. Mater.* **8**, 719 (1996).
181. L. H. Dubois and R. G. Nuzzo, *Annu. Rev. Phys. Chem.* **43**, 437 (1992).
182. R. M. Crooks, O. Chailapakul, C. B. Ross, L. Sun and J. K. Schoer, in R. M. Crooks, O. Chailapakul, C. B. Ross, L. Sun, adn J. K. Schoer, eds., *Interfacial Design and Chemical Sensing, ACS Symposium Series*, Vol. **561**, American Chemical Society, Washington, D.C., 1994, p. 104.
183. N. Kodakari, N. Katada, and M. Niwa, *Chem. Vap. Deposition*, **3**, 59 (1997).
184. C. M. Paleos and D. Tsiourvas, *Adv. Mater.* **9**, 695 (1997).
185. H. Koyano, K. Yoshihara, K. Ariga, T. Kunitake, Y. Oishi, O. Kawano, M. Kuramori, and K. Suchiro, *J. Chem. Soc., Chem. Commun.* 1769 (1996).
186. J.-M. Lehn, M. Mascal, A. DeCian, and J. Fischer, *J. Chem. Soc., Chem. Commun.*, 479 (1990).
187. C. T. Seto, J. P. Mathias, and G. M. Whitesides, *J. Am. Chem. Soc.* **115**, 1321 (1993).
188. R. Ahuji, P.-L. Caruso, D. Möbius, W. Paulus, H. Ringsdorf, and G. Wildburg, *Angew. Chem.* **32**, 1082 (1993); *Angew. Chem. Int. Ed. Engl.* **32**, 1033 (1993).
189. K. Kurihara, K. Ohto, Y. Honda, and T. Kunitake, *J. Am. Chem. Soc.* **113**, 5077 (1991).
190. Y. Ikeura, K. Kurihara, and T. Kunitake, *J. Am. Chem. Soc.* **113**, 7342 (1991).
191. C. M. Paleos, Z. Sideratou, and D. Tsiourvas, *J. Phys. Chem.* **100**, 13 898 (1996).
192. J. S. Nowick, J. S. Chen, and G. Noronha, *J. Am. Chem. Soc.* **115**, 7636 (1993).
193. J. D. Dunitz, in G. R. Desiraju, ed., *The Crystal as a Supramolecular Entity, Perspectives in Supramolecular Chemistry*, Vol. **2**, p. 1; see also, C. Pascard, in G. Tsoucaris

and co-eds., *Crystallography of Supramolecular Compounds*, Kluwer, Dordrecht, 1996, p. 127.
194. A. I. Kitaigorodskii, *Molecular Crystals and Molecules*, Academic Press, New York, 1973; see also, C. P. Brock and J. D. Dunitz, *Chem. Mater.* **6**, 1118 (1994).
195. M. Simard, D. Su and J. D. Wuest, *J. Am. Chem. Soc.* **113**, 4696 (1991); see also, J. Rebek, *Acc. Chem. Res.* **17**, 258 (1984) and E. Fan, C. Vicent, S. J. Geib, and A. D. Hamilton, *Chem. Mater.* **6**, 1113 (1994).
196. J. C. MacDonald and G. M. Whitesides, *Chem. Rev.* **94**, 2383 (1994).
197. J. Rebek, Jr., *Acta Chem. Scand.* **50**, 707 (1996).
198. M. Mascal, N. M. Hecht, R. Warmuth, M. H. Moore, and J. P. Turkenburg, *Angew. Chem.* **108**, 2348 (1996); *Angew. Chem. Int. Ed. Engl.* **35**, 2204 (1996).
199. A. Ulmann, *Ultrathin Organic Films*, Academic Press, Boston, 1991.
200. R. Krämer, J.-M. Lehn, and A. Marquis-Rigault, *Proc. Natl. Acad. Sci. USA* **90**, 5394 (1993).
201. D. L. Caulder and K. N. Raymond, *Angew. Chem.* **109**, 1508 (1997); *Angew. Chem. Int. Ed. Engl.* **36**, 1440 (1997).
202. J.-M. Lehn and A. Rigault, *Angew. Chem.* **100**, 1121 (1988); *Angew. Chem. Int. Ed. Engl.* **27**, 1095 (1988).
203. A. Collet, in Ref. 12, Vol. **10**, p. 113.
204. J. Jacques, A. Collet, and S. H. Wilen, *Enantiomers, Racemates, and Resolutions*, Wiley, New York, 1981.
205. J.-M. Lehn, in Ref. 4, p. 307.

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