Molecular recognition: designed crystalline inclusion complexes of carboxylic hosts

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Recently there has been a gradual drift of organic chemists into research relevant to biology. This has resulted in a rich array of sophisticated model systems. Ultimately, such models are intended to imitate the specific recognition of substrates. The lattice-type inclusions are expected to be particularly useful in this respect. This paper explains the basic ideas of a new strategy for directed lattice inclusion called "coordination-assisted clathrate formation." Besides matching sizes and shapes, this strategy makes extensive use of functional group interactions between a host and a guest molecule, allowing molecular recognition in the solid state. In particular, the carboxylic group is demonstrated as a sensitive site of host molecules for interaction (multicontact binding) with guest molecules of different H-bond donor and/or acceptor strength involving alcohols, carboxamides, dimethyl sulfoxide and carboxylic acids. Hosts refer to molecules of different geometric shapes (scissor-type, roof-shaped and small-ring acids). We will look at structural aspects of the H-bonded supramolecular aggregates formed between host and guest that are responsible for the mutual recognition properties.

Keywords: molecular recognition; crystalline inclusion complexes; carboxylic hosts, X-ray crystal structures; H-bonding

Molecular recognition is fundamental for biotic processes.[1] It is also important in bioorganic and abiotic chemistry.[2] The field is growing rapidly.[3] Many topics are involved — catalysis, compound transport and separation, regulation, enzyme mimicry, host-guest systems, new materials, and so on. Thus, there is great potential in applications.[4,5]

GENERAL APPROACH

Each molecule has a specific surface that is characterized by size, shape and functional sites.[6] These properties should apply to molecular recognition. Consequently, recognition of one molecule by another may involve matching attributes as specified above.[7] In other words, we want to characterize a full complementary relationship between the two chemical species — the molecule to be recognized, and the molecule that effects recognition. Hence, we need a cavity of designed dimensions for probing the shape and size of the molecule under consideration and complementary functional groups for chemical identification (Figure 1a).

It is useful to combine both principles in a sense of what is suggestive of an enzymic active site,[1] or a functionalized cavity for endo-binding (Figure 1b). Some of the fundamental considerations[4] leading to this conclusion are illustrated in Figure 2.

Exo-binding (Figure 2a), by way of functional group interaction that does not profit from a cavity-core relationship, naturally is of inferior value in size and shape recognition compared to *endo*-binding (Figure 2b), which has this relationship. Also, as Figure 2 shows, it is difficult to use the full functional group capacity of both partners in the case of exo-binding, since all functional groups are *divergent*. Consequently, the molecule under consideration is not realized as an integral whole, but only segmentary, giving rise to mistakes in recognition. In the case of endo-binding, the functional groups are *convergent/divergent*. Hence, they can face each other with the complete set of functional groups. This shows, in principle, that endo-binding is superior to exo-binding in molecular recognition. Translation into practice of the unfolded conception, then, is a problem of forming a designed cavity.

PRINCIPLES OF CAVITY FORMATION AND DEFINITIONS

Chemists follow two basically different courses with reference to the procedure of cavity formation (Figure 3). One method is to form a *mono*molecular cavity for inclusion of the species to be recognized and bound. The other method is to form a *multi*molecular cavity. Examples are macrocyclic rings[3b] (such as crown compounds[8] or cyclophanes[9]) and crystal cavity inclu-

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Table 1. Inclusion compounds of host molecule 1

Guest compound	Host:guest mol ratio*
Methanol	1:2
Ethanol	1:2
1-Propanol (n-propanol)	2:1
2-Propanol (isopropanol)	1:2
1-Butanol (n-butanol)	1:1
2-Butanol (sec-butanol)	1:1
2-Methyl-1-propanol (isobutanol)	1:1
2-Methyl-2-propanol (t-butanol)	1:1
1-Pentanol (n-pentanol)	1:2
2-Methyl-1-butanol	2:1
2-Methyl-2-butanol	1:2
4-Methyl-1-pentanol	1:1
Benzyl alcohol	1:1
Trichloroethanol	1:1
Ethylene glycol	1:1
Propylene glycol	1:1
Acetic acid	2:3 (1:1)
Propionic acid	2:1
Lactic acid	1:1
Formamide	1:2
N-Methylformamide	1:2
N,*N*-Dimethylformamide (DMF)	1:2
Acetylacetone (2,4-pentanedione)	1:1
Acetonitrile	1:1
Nitromethane	1:1
Dimethyl sulfoxide (DMSO)	1:1
Bromobenzene	1:1

*Determined by NMR integration after a drying period of 12 h at 0.5 Torr for each compound

Table 2. Preference of guest binding by 1 (two-component solvent system)

Recrystallization solvent compd mixt (equimol ratio)	Relative guest excess, %GE*	Sizes of H-bonded rings
MeOH/2-BuOH	>95	[12]/[10]
EtOH/t-BuOH	92	[12]/[10]
EtOH/*$HOCH_2CH_2OH$*	> 95	[12]/[24]
MeOH/*EtOH*	46	[12]/[12]
EtOH/2-PrOH	79	[12]/[12]
1-PrOH/*2-PrOH*	29	[12]/[12]

*Species in italics preferentially enclathrated

Table 3. Inclusion compounds of host molecule 2 with alcohols

Guest alcohol	Host:guest mol ratio*
1-PrOH	1:1
1-BuOH	1:1
t-BuOH	1:1
1-PentOH	1:1
1-OctOH	2:1
$HOCH_2CH_2OH$	1:2

*Determined by NMR integration after a drying period of 12 h at 0.5 Torr for each compound

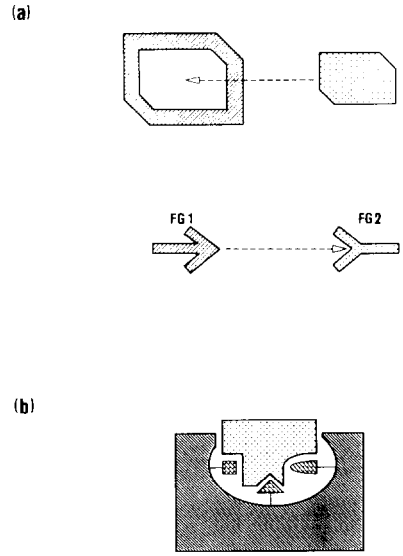


Figure 1. Principles of molecular recognition: (a) the role of steric fit and complementary functional groups (FG); (b) active site analogy

sion.[3b,3e] in another view termed *cavitate* and *clathrate* inclusions.[10]

By definition,[4a,7] the convergent binding partner of such complexes is specified as the *host*, while the divergent (and included) species is called the *guest*. Host and guest form an integral whole that is termed *supermolecule* or *supramolecular aggregate*.[4b]

DEVELOPING A NEW INCLUSION STRATEGY: COORDINATION-ASSISTED CLATHRATE FORMATION

Both methods of cavity formation specified in Figure 3 have pros and cons. The disadvantage of the cavitate approach is due to the troublesome synthesis of macrocyclic hosts, but the host cavities are well defined. Compared with this, clathrates can be formed by considerably simpler host molecules, since here the cavity is generated by aggregation of several small host molecules in the crystal lattice. On the other hand, the hosts were subject to a high degree of randomness, and only recently have some helpful design principles for clathrate hosts been developed.[11-16] Possibly the most general one in application came from our group and is called *coordination-assisted clathrate formation*.[14,17]

As suggested by the term,[10] a coordinatively assisted clathrate, or *coordinatoclathrate*, involves a hybrid between a complex and a clathrate (Figure 4a). Thus, coordinatoclathrates combine attributes of coordinative complexes and of lattice-dependent clathrates, and this is the reason that they make possible a high degree of selectivity in different directions, including chemoselectivity and constitutional selectivity, according to the origin (see Figure 4a).[14,17]

Consequently, a corresponding coordinatoclathrate host (Figure 4b) consists of two components: (1) a *bulky basic skeleton* that makes available lattice cavities typical of a clathrate and (2) *appended functional groups (sensor*

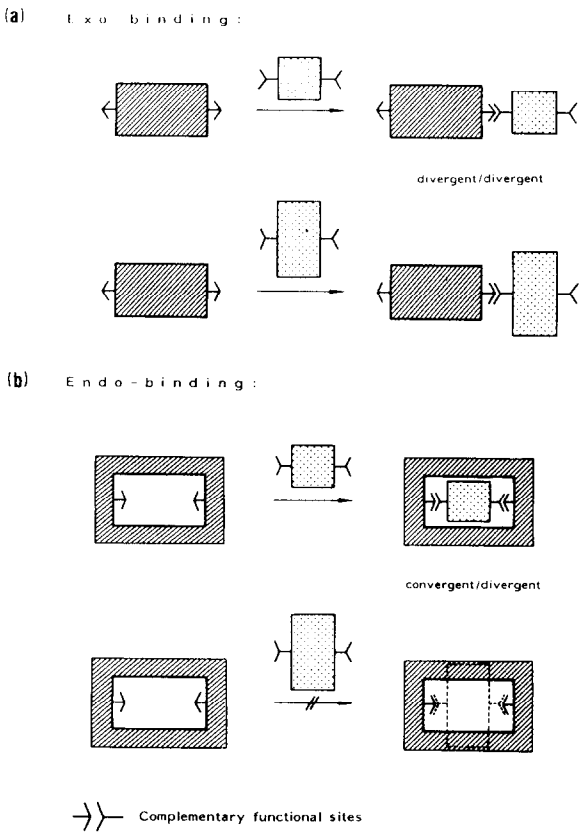


Figure 2. Exo- and endo-binding

groups) that manage the coordination to the included guest substrate.

By using a host molecule endowed with these properties, the basic idea is to create a situation in a crystal (Figure 5) in which highly affine functional groups of a host molecule are prevented from contacting for steric reasons. Yet these functions are available to complementary groups of sterically lower demanding (smaller) guest molecules that are able to bridge the gap. Normally, without steric repulsion, the pure hosts would form a dimer.

A typical host molecule based on these ideas, then, must meet these criteria:

(1) It should be *bulky* in constitution, to provide low-dense packing in the crystal.
(2) It should have a *rigid* conformation, to maintain the cavity structure and not to collapse.
(3) It should have appropriately placed and highly *affine* functional groups for reasons mentioned above.
(4) It should be aimed at a *balanced* overall shape of the molecule that will help stabilize the crystal packing in general.

A typical molecule that approaches this ideal is simple 1,1′-binaphthyl-2,2′-dicarboxylic acid (**1**) (abbreviated hereafter as BNDA; see Figure 6). The molecule has a scissor-like shape with two large lipophilic (the aromatic units) and two smaller hydrophilic terminals; (the carboxylic groups). So it is amphiphilic and possesses a well-defined geometry that favors clear orientation in the crystal.

RECOGNITION OF ALCOHOLS

Using the Scissor-type Carboxylic host BNDA

Recrystallization of compound **1** (BNDA) from different alcohols (see Table 1)[14] results in the formation of well-developed channels of approximately 6–7 Å diameter (Figure 7a) with a stoichiometric number of solvent molecules inside the channel.[17] The channels mainly have an apolar surface that is interrupted periodically by hydrophilic narrowings consisting of the carboxylic groups (Figure 7b). The cross-section of electron densities in this channel area (Figure 7c) clearly shows two facing carboxylic groups held in a noninteractive distance that follows closely the basic idea of Figure 5, namely, formation of a specific gap in the crystal lattice. Here are the sites at which the accommodated guest molecules contact the host.

This is more evident in Figure 8, which shows a detail of the crystal structure of inclusion compound **1**·MeOH (1:2).[14] Bridging the gap is via two molecules of methanol providing a set of complementary H-bonds to the carboxylic groups. Thus, a 12-membered ring system of coupled H-bonds is formed [mean (acid)O(−H)···O-(MeOH) = 2.610 Å, 172°; mean (MeOH)O(−H)···O (acid) = 2.761 Å, 156°].

Besides methanol, other alcohols (Figure 9b) are also involved in the same binding pattern of H-bridges with the BNDA host, as demonstrated by crystal structures[14] (e.g., ethanol and isopropanol, but also n-propanol, which results in the uncommon 2:1 host:guest stoichiometry; the former have 1:2 stoichiometry).[18] This means that the stoichiometric factor is not a reliable source of information on the mode of host:guest binding in this field of compounds.

Other alcohols, such as sec-butanol or tert-butanol (inclusion stoichiometry 1:1 in both cases) bind in a 10-membered ring fashion of H-bridges to the host (Figure 9a)[14,18] (e.g., the symmetric scheme of H-bonds changes to an asymmetric one that involves two carboxylic groups, but only one alcohol [mean (acid) O(−H)···O(alcohol) = 2.556 Å, 171°; mean (alcohol)O-(−H)···O(acid) = 2.685 Å, 171°; mean (acid)O-(−H)···O(acid) = 2.625 Å, 161°]). Evidently, this is a result of the more voluminous alkyl residues of these alcohols, demonstrating the influence of second rank (say steric) interactions between host and guest. In these circumstances, it is not possible to accommodate two neighboring molecules of alcohol in the host channel. Crystal structures[14,18] point to the same conclusion.

The case of the inclusion compound with bivalent ethylene glycol also merits mention. Here, a huge centrosymmetric 24-membered ring of coupled H-bonds including four carboxyl and four hydroxyl groups is formed [mean (acid)O(−H)···O(alcohol) = 2.634 Å, 169°; mean (alcohol)O(−H)···O(acid) = 2.828 Å, 167°]

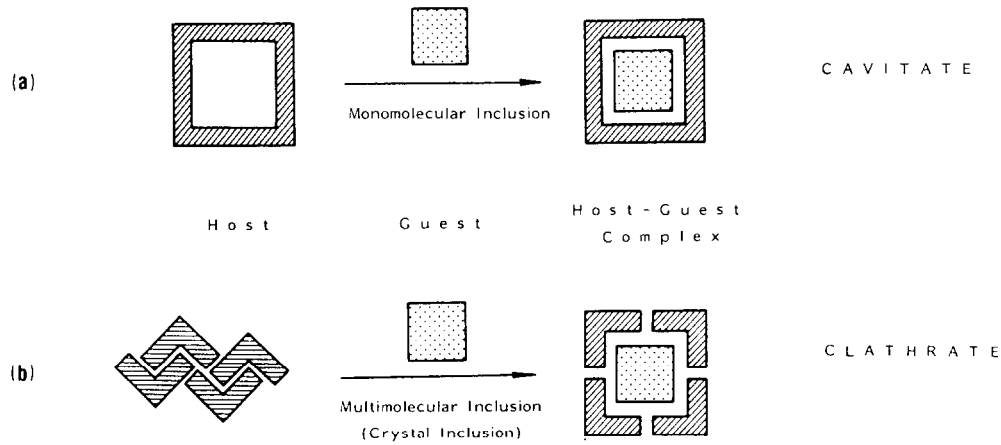


Figure 3. Strategies of inclusion formation

(Figure 9c).[14] Because of the extended pattern, the original channel structure cannot be detected any longer.

Albeit of some variance, the inclusion compounds of BNDA with alcohols show a common structural behavior, namely, the formation of *closed H-bonded loops* at the contact surface of host and guest, which may reflect a characteristic recognition pattern between carboxylic and hydroxylic groups, or carboxylic acids and alcohols.

Examination of some of the inclusion selectivities from two component mixtures of alcohols — which means preferred inclusion of one alcohol species when a second one is present — suggests in the first place that the highest discrimination occurs when differing ring sizes of the formed systems of H-bridges between host and guest are involved (Table 2).[14]

In the second place, the alcohol leading to the larger system of H-bonds is normally preferred (e.g., ethanol [a 12-membered ring] is preferred over tert-butanol [a 10-membered ring], or ethylene glycol [a 24-membered ring] is preferred over ethanol). Otherwise, the discrimination is lower. Thus, the particular contact pattern may also be connected with the stability properties of the different inclusion compounds in a systematic way.

Using the roof-shaped carboxylic host FADA

To probe the generality of this behavior, we studied the recognition properties of other carboxylic hosts with regard to alcohols. Such an example of different constitution is compound **2** (9,10-ethano-9,10-dihydroanthracene-trans-11,12-dicarboxylic acid; see Figure 10), the simple Diels-Alder adduct of fumaric acid to anthracene (abbreviated as FADA).[17,19,20]

This host molecule was developed by a geometric approach similar to **1**. While the preceding BNDA-host **1** is suggestive of a pair of scissors (Figure 6), **2** relates to a roof (Figure 10). Compared to **1**, FADA (**2**) has a more rigid structure. Hence, adaptability to differently sized alcohols is supposed to be reduced or influenced in a way, but the net tendency of alcohol binding with **2** should exist.

In fact, FADA (**2**) is not capable of forming crystal inclusions with the small alcohols methanol and ethanol, but only with the higher homologues from 1-propanol up to 1-octanol (Table 3).[19,21] A crystal inclusion of **2** with ethylene glycol is also obtained. The favorite host:guest stoichiometry here is 1:1; BNDA inclusions showed almost to the same extent 1:2 and 1:1 stoichiometries (Table 1).

Nevertheless, looking at Figure 11, which shows a detail of the X-ray crystal structure of **2**·1-BuOH,[19,20] one realizes that host and guest are linked together in a 12-membered ring of H-bonds [(acid)O(−H)···O(BuOH) = 2.599 Å, 176°; (BuOH)O(−H)···O(acid) = 2.741 Å; H atom not located] corresponding to the inclusions of BNDA with small alcohols (Figure 9b). Here (Figure 11), it is more voluminous 1-butanol that is involved in the H-bonded ring system, but the dimensions of the rings[17] are largely the same, as seen in Figure 8.

The reason for the 1:1 host : guest stoichiometry for the FADA-inclusion instead of the 1:2 stoichiometry for the BNDA inclusion is a direct host-host interaction via functional group dimerization [O(−H)···O = 2.646 Å, 173°] (Figure 11), which formally reduces the original bivalency of the host molecule to monovalency. Properly speaking, we deal with a bivalent supramolecule as host, whose components are two individual molecules of **2**. This dimer supramolecular host unit is observed in all inclusion structures involving **2**[17,21] (see below); it even exists in the crystal structure of solvent-free **2**.[19,20]

The most important point, however, is the exact correspondence of the recognition pattern between alcohols and carboxylic hosts, respective of their constitution. One may learn from this behavior that at best steric conditions by the lattice, the 12-membered ring of H-bridges formed between the given functional groups possibly represents a standard mode of interaction in the crystalline state. This statement is supported by other examples in the literature[22,23] not related to the scissor- and roof-type hosts.

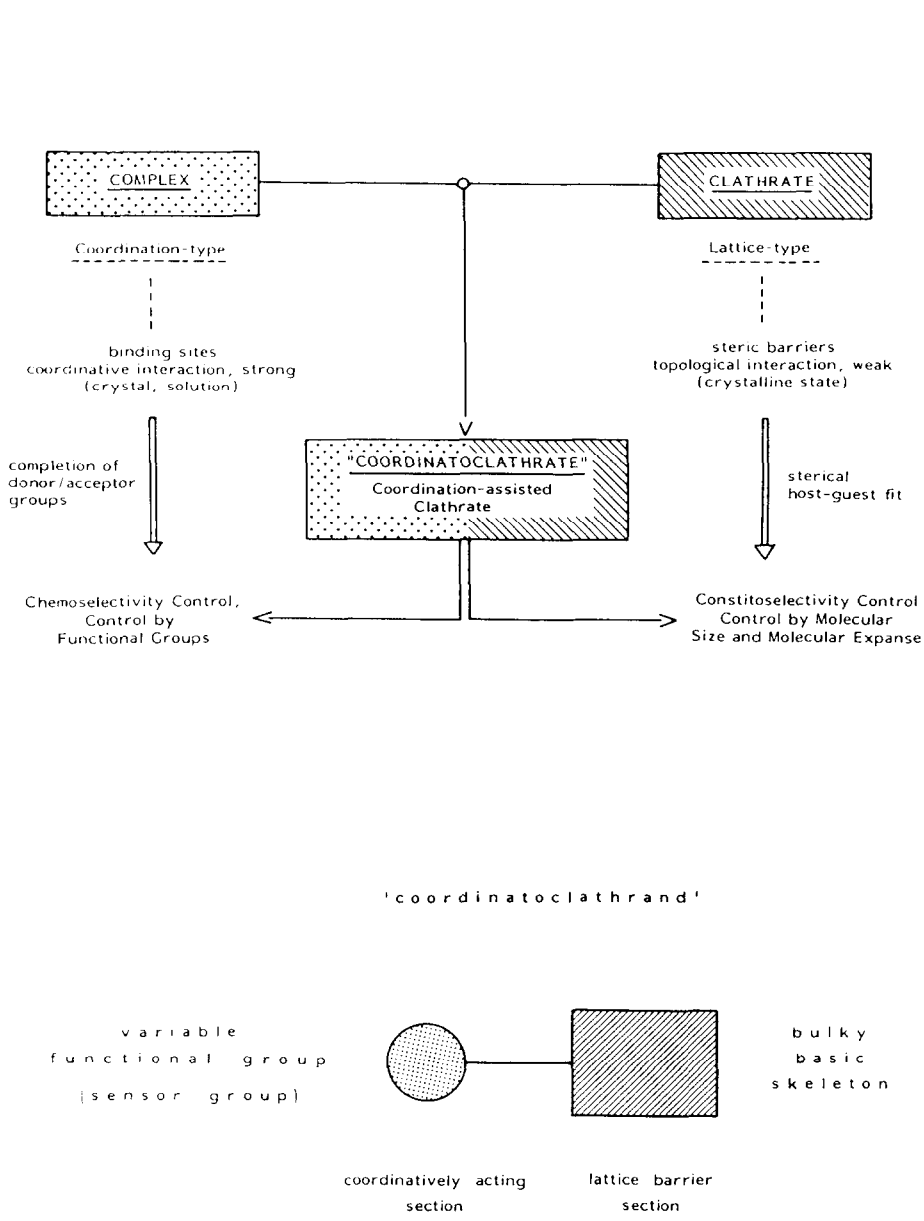


Figure 4. Coordinatoclathrate concept (a) and abstracted structure of a coordinatoclathrate host (b): definitions, relations, and functions of control

However, based on recent X-ray studies, a third new family of carboxylic hosts determined by a small-ring as a primary building element shows different behavior.[24]

Using small-ring carboxylic hosts

Introducing a rigid small-ring unit as a structural building block into host compounds requires a strategy as follows: On principle, both the scissor- and the roof-type hosts **1** and **2** refer to configurational rigid structures (Figure 12a) characteristic of a central axis with lipophilic (aromatic units) and hydrophilic groups (carboxylic functions) on each terminal. For reasons of geometry, the terminals may be occupied by four groups at the most, and their distribution is more or less fixed (one lipophilic and one hydrophilic group on each side), which presents limitations.

A formal extension results if the axis determining the structural element is replaced by a triangle or a quadrangle (Figure 12b); now more than four groups (up to eight) can be accommodated in a high variety and with new geometries. Adaptation to specific requirements of guest molecules is thus easier.

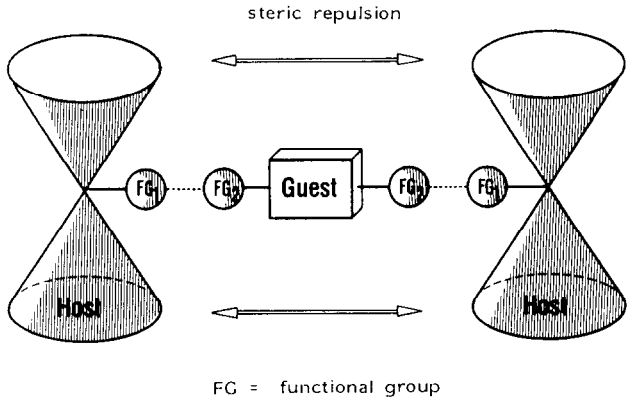
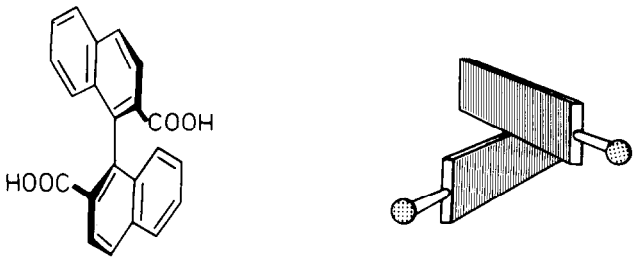


Figure 5. Coordinatoclathrate formation (diagramatic representation)



1 'BNDA'

Figure 6. Prototypical host molecule **1** *and graphic abstraction*

Because of the limited number of inclusion structures presently available,[18] we will discuss only one representative of each host family (three- and four-membered ring constitutions), namely host compounds **3** and **4** (Figure 13).

As expected, both hosts form crystalline inclusions with alcohols, but with different species and in a very different scale.[24] The cyclobutano host **4** allows only clathrate formation with methanol, while the cyclopropano host **3** does not. The latter, however, renders possible inclusions with ethanol, 1-propanol, 2-propanol, 2-butanol, and tert-butanol. Thus, **3** is typical of clathrate formation with relatively bulky alcohols and discriminates methanol, while **4** is just the opposite.

The stoichiometries are different in both cases. Inclusion compounds with **3** show 1:1 host:guest stoichiometries, while **4**·MeOH has 1:2 stoichiometry. This suggests that **3**, in virtue of the *cis*-geometry of the carboxylic groups that favor an intramolecular H-bond, externally behaves as a monovalent host; *trans*-dicarboxylic acid **4**, however, is bivalent. Obviously, sizes and shapes of crystal cavities are also determined by the different host geometries.

Referring to the alcohol inclusions of **2** (see above), stoichiometries are not suitable for assessing binding modes between host and guest. This was realized again with the X-ray crystal structures of inclusion compounds **3**·tert-BuOH (1:1), **3**·EtOH (1:1), and **4**·MeOH (1:2).

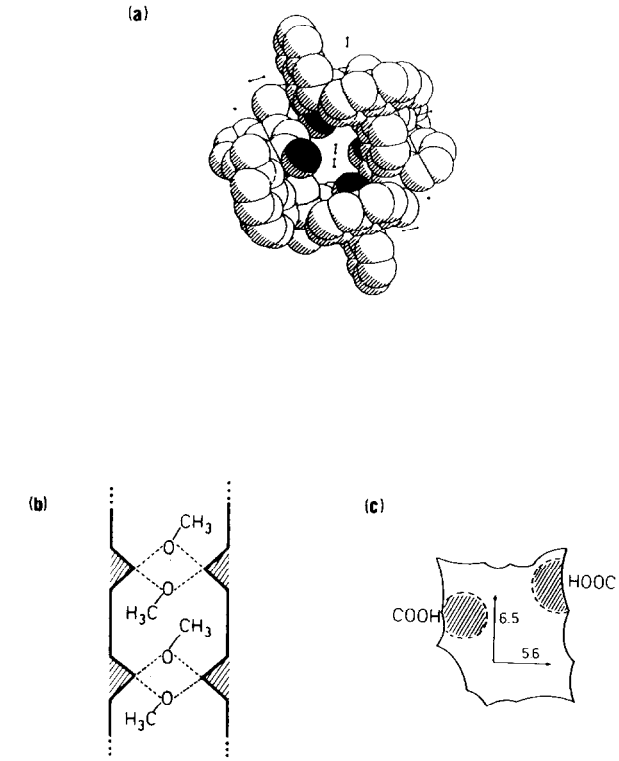


Figure 7. Inclusion channel in **1**·*MeOH (1:2). (a) Space-filling illustration (view down the channel axis, methanol molecules represented as small sticks); (b) schematic representation of the longitudinal section (hatched triangles and dotted squares represent polar areas, while the rest is of apolar property); (c) approximation of the van der Waals cross-section (dimensions are in Å; hatched regions represent O atoms of the host matrix, continuous solid lines indicate surfaces of apolar attribute)*

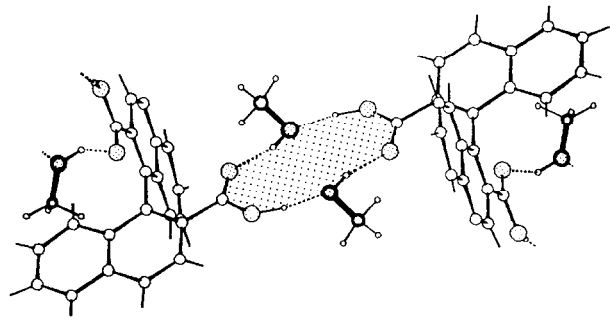


Figure 8. Packing excerpt from the crystal structure of **1**·*MeOH (1:2) showing the 12-membered supramolecular loop of H-bonds (shaded region). In all Figures H-bonds are specified as broken lines, O atoms are dotted, and N atoms are hatched*

Figure 14 shows the structure of **3**·tert-BuOH (1:1).[24] At a glance, one would think of the presence of cyclic H-bonds between host and guest (Figure 14a), but this is not true. Instead, the carboxylic groups of the achiral host and the tert-butanol molecules form a *helix* of H-

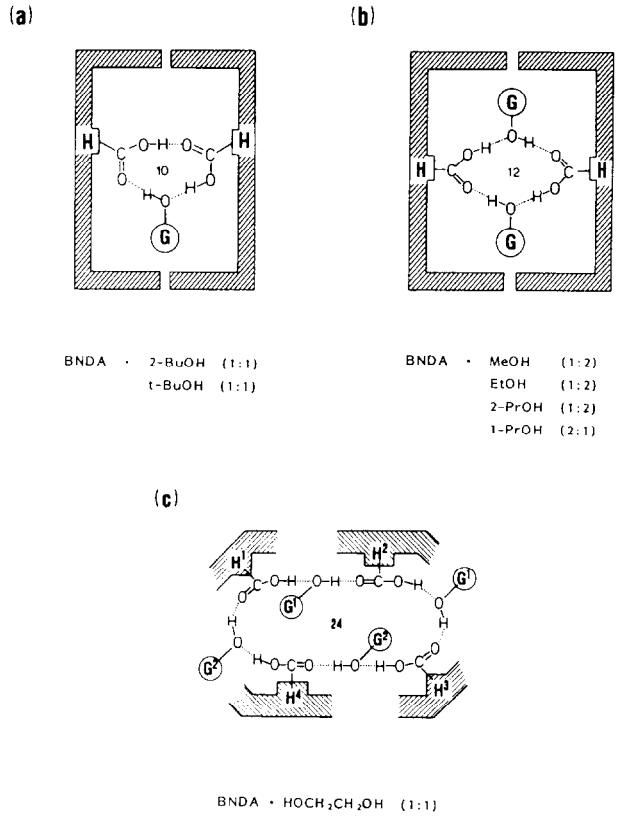


Figure 9. Diagrammatic representation of supramolecular bonding modes (H-bridge systems) found in the alcohol inclusions of **1** *(bold H and G denote host and guest, respectively)*

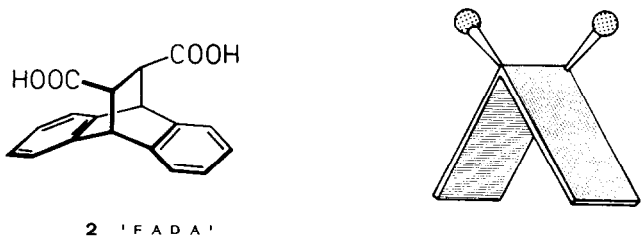


Figure 10. Perspective formula of host molecule **2** *and graphic abstraction*

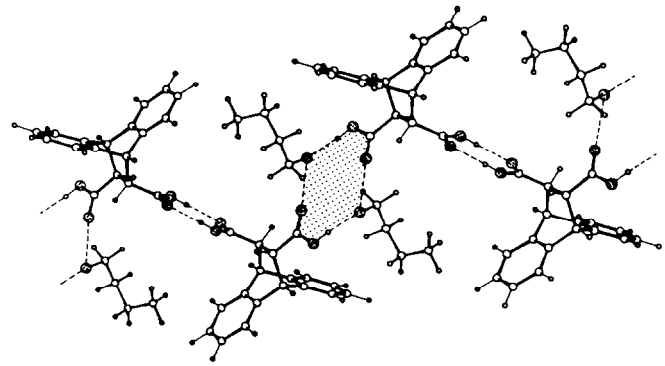


Figure 11. Packing excerpt from the crystal structure of **2**·*1-BuOH (1:1) showing the 12-membered supramolecular loop of H-bonds (shaded region); nonshaded loops of H-bonds refer to direct host-host interaction*

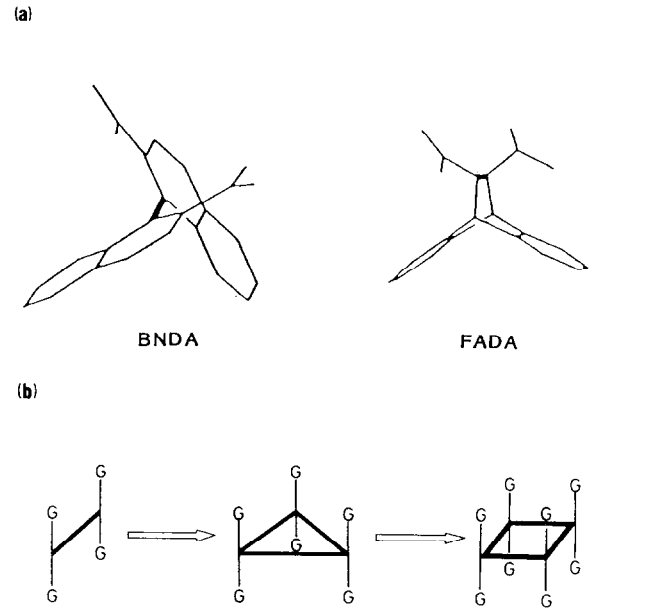
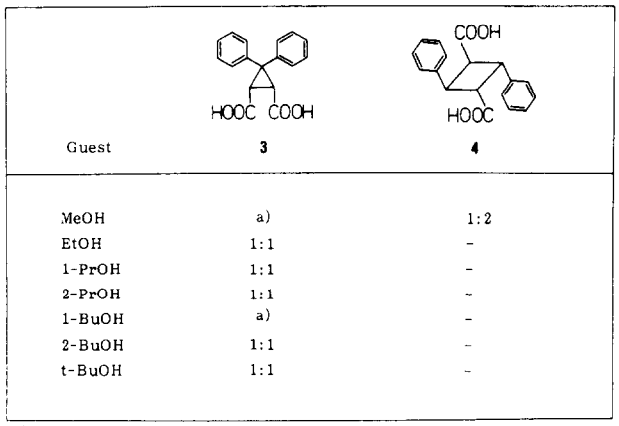


Figure 12. Dimensional approach of building elements (bold type) in host design. (a) Skeletal drawings of scissor-type and roof-shaped hosts **1** *and* **2** *showing the central molecular axis. (b) Extension to a triangular or quadrangular building block (G stands for a substituted group)*

bonds (Figure 14b) that has a topological relation only to the expected loop. In detail, one intramolecular H-bond [O(−H)···O = 2.552 Å, 170°] involving the *cis*-carboxyls and two intermolecular H-bridges [O(−H)···O = 2.566 Å, 155° and 2.861 Å, 144°] between host and guest contribute to form the helix.[25] Similar conditions exist at the **3**·EOH (1:1) inclusion.[18] Another remarkable point is that **3**·tert-BuOH (1:1) crystallizes in an enantiomorphous space group ($P2_12_12_1$); thus, individual crystals are optically active.

The free host compound **3**, which is given for comparison, also has an enantiomorphous space group ($P2_1$) that involves not a helical but a *linear* system of H-bonds [O(−H)···O(intra) = 2.513 Å, 162°; O(−H)···O(inter) = 2.590 Å, 180°] (Figure 15).[18] This means that only when **3** is in contact with a guest molecule is the helix formed. The inclination to spiral H-bonds in host-guest complexes possibly is connected with the particular geometry of **3**.

A behavior similar to the inclusions of **3** (i.e., no closed loops of H-bonds) is shown by **4**·MeOH (1:2).[24] Because of the trans-configuration of the carboxylic groups, instead of *cis* for **3**, *zigzag lines* of H-bonds between host and guest are formed [(acid)(O−H)···O(MeOH) = 2.594 Å, 164°; (MeOH)O(−H)···O(acid) = 2.743 Å, 167°] (Figure 16b). The structure can be described as



Guest	3	4
MeOH	a)	1:2
EtOH	1:1	-
1-PrOH	1:1	-
2-PrOH	1:1	-
1-BuOH	a)	-
2-BuOH	1:1	-
t-BuOH	1:1	-

a) Low tendency to crystallize.

Figure 13. Constitutions of small-ring hosts **3** *and* **4**, *and specification of their inclusion compounds with alcohols*

a framework of channels including the molecules of methanol H-bonded to the host (see Figure 16a). In a manner of speaking, the channel walls have seams made of the carboxylic groups where the guest molecules bind. The channel dimension can accommodate only small alcohols, such as methanol.

Hence, we deal with topologically different H-bonding between alcoholic guests inside a channel or channel-like matrix of carboxylic hosts as schematized in Figure 17: (a) along an infinite *zigzag*-line; (b) in a *helical* fashion; and (c) in the way of *closed loops*. Examples are **4**·MeOH (1:2) (Figure 16), the alcohol inclusions of **3** (as seen in Figure 14) and the alcohol inclusions of **1** and **2** (see Figures 8 or 9 and 11), respectively.

Despite the differences in binding topology and thus of the recognition pattern with reference to alcohols and carboxylic acids, there is still one common point in the large number of discussed inclusion structures: *cooperativity*,[26] indicated by the coupled systems of H-bonds existing between host and guest. One may connect it with the strong or relatively strong H-donor/H-acceptorship of the contributing functional groups. To learn more, we shall turn to inclusions of the given hosts (and derivatives) involving other guest functional groups and discuss a few of their structures.

RECOGNITION OF CARBOXAMIDES (DIMETHYLFORMAMIDE)

Dimethylformamide (DMF, Figure 18a) is an organic molecule of suitable size for lattice cavity inclusion.[3b,3c] It provides a polar group that is rather a proton acceptor than a donor, as obvious from its resonance formulae (Figure 18a). Would it allow cooperative binding to the carboxylic hosts and, if so, which is the particular recognition pattern with reference to this guest molecule?

Supposing similarity to the alcohol inclusions, this would require C-H···O type interactions,[27] and one may expect 11- and 14-membered rings, as specified in Figures 18c and 18d, respectively. However (based on the present results), only half of it is true, namely the formation of the large 14-membered H-bonded ring that includes two formyl and two carboxyl groups, while the smaller 11-membered ring species with one formyl and two carboxyls is not observed. Instead, a "monomeric" 7-membered H-bonded ring, as specified in Figure 18b, is found several times, unlike the alcohol case, where this ring type does not occur. Examples of each of the two ring constitutions are given by the DMF inclusions of **2** (FADA) and of **1**-analogous **5** (spiro-type host).

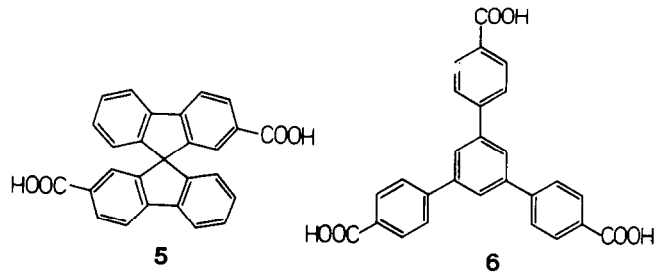


Figure 19a shows a packing excerpt of the **2**·DMF (1:1) inclusion compound studied by X-ray crystal structure.[19] The 14-membered (dimeric) ring of H-bridges including host and guest is seen in the center [O(−H)···O = 2.623 Å, 179°; C(−H)···O = 3.240 Å, 160°]. There is also a direct carboxylic group dimer per host molecule [O(−H)···O = 2.616 Å, 170°], which is typical of **2** (c.f., 1-BuOH inclusion compound of **2**; see Figure 11). Another remarkable detail of the structure is the use of *anti*-oriented hydrogens at the carboxylic groups for guest recognition. Normally, the carboxylic hydrogens are involved in *syn*-fashion, as obvious from Figure 19b, which illustrates the 7-membered (monomeric) ring formation in the crystal structure of **5**·DMF (1:2).[17,28] Here, both carboxylic groups of the host are involved in guest recognition via a direct two-point contact to the formyl part of DMF [O(−H)···O = 2.593 Å, 167°; C(−H)···O = 3.112 Å, 126°].

However, this is not always the case, since the two H-bridge contacts are classified as different in binding strength; the formyl-H bond is the weaker of the two. Hence, one can assume that under environmental constraints, the formyl-H bond is broken first. In doing so, the two-point interaction reduces to a simple one-point interaction that has a lower qualification in molecular recognition, as seen in Figure 2. This exact behavior is shown by the **1**·DMF (1:2) inclusion compound (Figure 19c).[17,29] One of the two DMF molecules of the asymmetric unit is bound in the 7-membered ring fashion to the bicarboxylic host [O(−H)···O = 2.692 Å, 152°; C(−H)···O = 3.054 Å, 129°]; the other is in *linear single* contact only [O(−H)···O = 2.613 Å, 159°; formyl-H *anti* to the host carbonyl], owing to packing conflicts.

An inclusion structure showing DMF exclusively in the linear state of H-bond interaction with carboxylic groups [O(−H)···O = 2.611 Å, 178°] is in **6**·DMF (1:3) (Figure 19d).[30] Here, probably due to crystal forces, the DMF molecule is turned around the O–H···O bond so as to incline its molecular plane through 36.2° to the plane of the carboxyl group it coordinates.

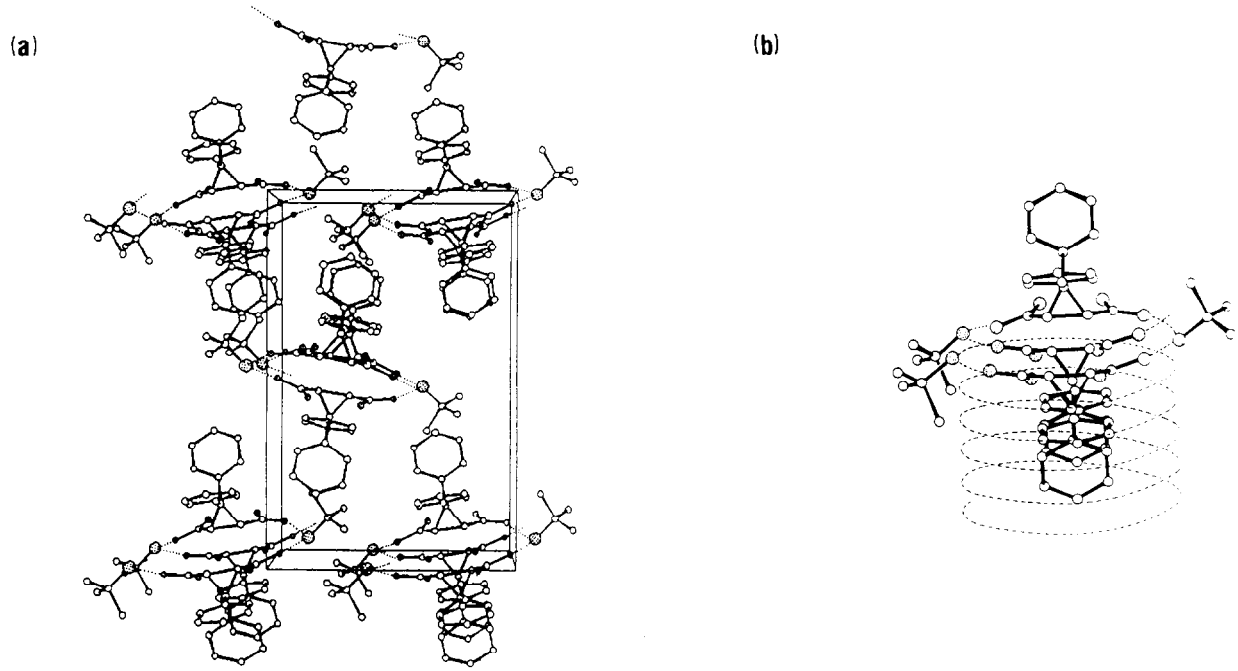


Figure 14. (a) Packing excerpt; (b) detail from the crystal structure of **3**·*t-BuOH (1:1) showing the supramolecular helix of H-bonds*

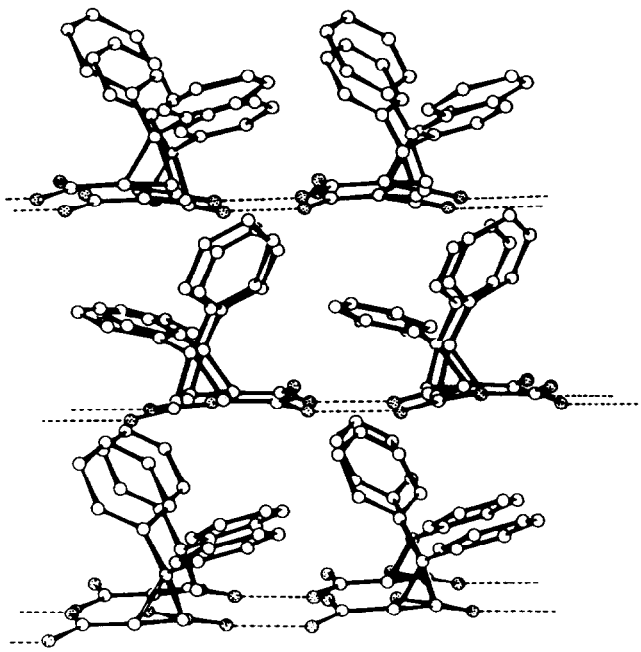


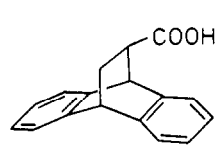
Figure 15. Packing excerpt from the crystal structure of free host compound **3** *showing the linear chains of H-bonds*

In the absence of a formyl-H, such as in homologous acetamide as a guest molecule, a two-point interaction with a host carboxyl group naturally is not possible. Hence, the host-guest binding is expected to be weak. The expectation is confirmed by the inclusion structure of **4**·acetamide (1:2) (Figure 20).[18] The loose bonding between host and guest [O(−H)···O = 2.600 Å, 154°] becomes apparent in the disorder of the acetamide molecule that is in two orientations in the crystal. The plain guest molecule is nearly perpendicular to the carboxyl plane it coordinates. Host and guest molecules form separate stacks in the crystal.

RECOGNITION OF DIMETHYL SULFOXIDE

Besides DMF, dimethyl sulfoxide (DMSO, Figure 21a) is another organic molecule that can interact with carboxylic hosts via two specific sites of different binding strength. According to the resonance formulae given in Figure 21a, it should be a relatively strong H-acceptor and weaker H-donor to a carboxylic group.

Considering the interaction of DMF with carboxylic groups (see Figures 19a and 19b), H-bonding systems most expected for the DMSO inclusions of carboxylic hosts are the 8- and the 16-membered ring constitutions specified in Figures 21b and 21c. Remarkably, the 18-membered (dimer) ring is not found here (with reference to five crystal structures,[17,29,31] but only the small 8-membered ring, inclusive of related sypramolecular structures due to packing interference. The major points of host-guest interaction and molecular recognition in this field are illustrated by Figures 22a–22c, involving hosts **1**, **2**, and **8**.



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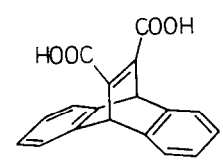

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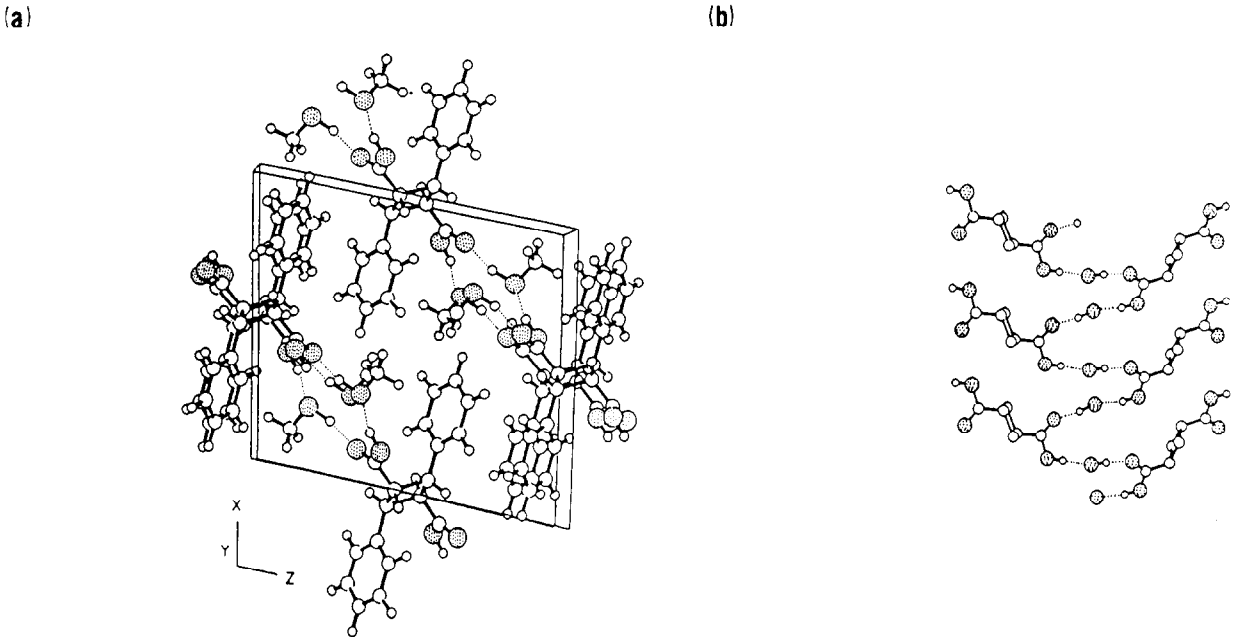


Figure 16. Packing excerpt (a) and detail (b) from the crystal structure of **4**·*MeOH (1:2) showing the supramolecular zigzag chains of H-bonds*

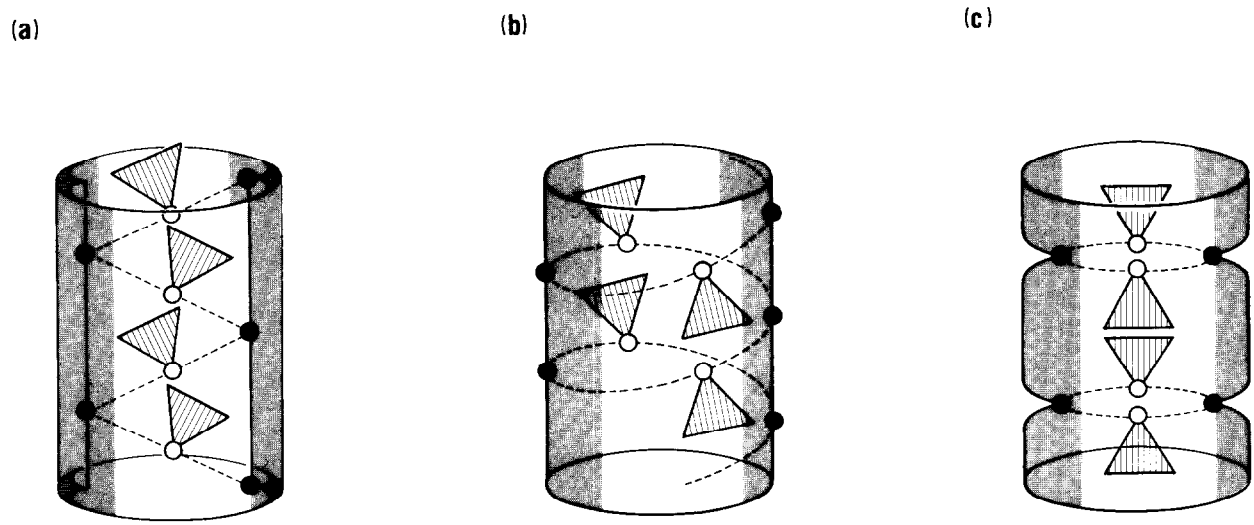


Figure 17. Diagrammatic representation of the supramolecular binding (H-bond) topology of alcohol molecules (hatched triangles) inside the carboxylic host channels (broken lines represent H-bonds; filled circles are contact sites of the host, open circles of the guest). (a) Zigzag-line; (b) helical; and (c) closed-loop mode of interaction

Figure 22a shows the asymmetric unit of the **2**·DMSO (1:1) inclusion complex.[17,21] The distances indicate a strong H-bond between hydroxy and S=O [O(−H)···O = 2.606 Å, 167°] and suggest a very weak C−H···O type interaction[27] between the carbonyl-O and a methyl-H of DMSO [C(−H)···O = 3.346 Å, 148°], thus giving rise to an 8-membered cyclic recognition pattern for the DMSO molecule. A direct host-host interaction via carboxylic group dimerization, typical of this host molecule (as seen in Figures 11 and 19a) and responsible for the 1:1 stoichiometry, is also found here.

The same cyclic recognition pattern for DMSO, including a weak C–H···O interaction between host and guest [C(−H)···O = 3.32 Å, 134°], is in the 1:1 DMSO inclusion of a corresponding mono acid **7**.[17,31]

That the C–H···O contact under discussion has to

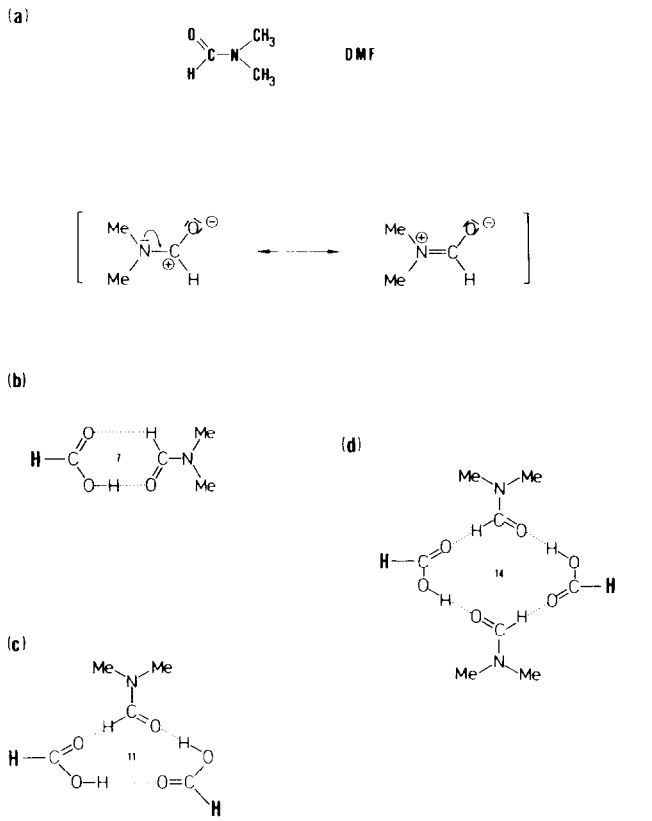


Figure 18. (a) Constitutional and resonance formulae of dimethylformamide (DMF); (b)–(d) possible modes of cyclic H-bond interactions between DMF and a carboxylic host (the bold H stands for host, H-bonds are represented by broken lines; the numbers denote ring sizes)

be classified as very weak is evident from Figure 22b, which shows the supramolecular unit of the 1:2 (host: guest) DMSO inclusion of **8** (unsaturated analogue of FADA, 2).[17,31] One molecule of DMSO (S2) of the bivalent complex is in the *cyclic* state of H-bonding [O(−H)···O = 2.562 Å, 161°; C(−H)···O = 3.38 Å, 140°], as described before. The other molecule of DMSO (S1), however, lacks the weak secondary contact to the host carboxyl it coordinates [O(−H)···O = 2.563 Å, 172°]. The methyl groups of this DMSO species are turned away from the respective carboxyl group; hence, a linear mode of binding follows. Yet, the crystal packing reveals an analogous C–H···O contact of the linearly bound DMSO molecule to the carboxyl group of a neighboring host molecule [C(−H)···O = 3.29Å, 144°]. Thus, coordination of DMSO is to the same sites for both guest molecules, on principle, but the binding topology is different, due to steric conflicts.

In the case of the 1:1 DMSO-inclusion of BNDA (**1**) (Figure 22c)[17,29] we find another interesting variant of interaction between DMSO and carboxylic hosts (see Figure 22b). As before, a cyclic and a linear recognition pattern also coexist here, this time involving the DMSO sulfoxide oxygen as a double acceptor site of H-bonds [O(−H)···O = 2.652 Å, 146°; O(−H)···O = 2.635 Å,155°; C(−H)···O = 3.308 Å, 161°]. This results in the formation of infinite H-bonded chains composed of alternating host and guest molecules running through the crystal. Consequently, molecular recognition of DMSO is effected by two host molecules via three contacts.

Possibly, there is no suitable packing for the BNDA molecule in the crystal to act as a bivalent host for two DMSO molecules, as intended. To some extent, an analogous behavior is also indicated in the corresponding DMF inclusion (Figure 19c), where one of the two DMF molecules of the supramolecular complex is in a two-point contact to BNDA, while the other binds only linearly.

RECOGNITION OF CARBOXYLIC ACIDS

Upon consideration, the ideal complement for a carboxylic function could be the carboxylic group itself. Indeed, it is a trivial property of carboxylic acids to form H-bonded dimers[32] (Figure 23.) This way of acting is frequently seen in monomolecular (non-host–guest) crystals[33] ($R^1 = R^2$ in Figure 23) and may be interpreted as a mode of self-recognition. Would it also work in host-guest fashion ($R^1 \neq R^2$ in Figure 23? The answer is not clear at the moment.

In most of the all-carboxylic acid inclusions we have studied [**1**·acetic acid (2:3), **2**·formic acid (1:2), **2**·acetic acid (1:1), and **2**·propionic acid (1:1)],[21,34] host and guest form separate dimers (R^1 goes together with R^1 and R^2 with R^2, c.f. Figure 23), or the host recognizes the host and the guest recognizes the guest, with no specific contact between the two species.

This is illustrated in Figure 24a, which shows a packing excerpt of the **2**· propionic acid (1:1) inclusion compound.[20,34] The host molecules linked together via carboxylic group dimerization [O(−H)···O = 2.661 Å, 163°; O(−H)···O = 2.651 Å, 165°] form infinite zigzag chains. These chains are arranged so that tunnels are created parallel to the *c*-axis of the crystal. The propionic acid molecules form H-bonded dimers [O(−H)···O = 2.647 Å, 167°], which reside in these tunnels (i.e., the guest dimers behave as a certain hydrophobic species with no specific interaction to the host). They are retained only by steric barriers of the host matrix. Accordingly, they are organized as in classical clathrates[11] whose recognition properties depend mainly on steric fit.

While the acetic acid and propionic acid inclusions of **2**[21,34] are isomorphous, the inclusion of **2** with small formic acid (Figure 24b) has a different structure,[20,34] suggested already by the different stoichiometries (1:1 in the case of propionic and acetic acid, but 1:2 for formic acid). The great difference between the two structures (see Figures 24a and 24b) is that in **2**·formic acid (1:2), in addition to host-host and guest-guest, host-guest carboxylic group dimers are also found, which is the direction of molecular recognition we intend.

The building principle of this inclusion structure (Figure 24b)[34] is as follows. There are supramolecular host-

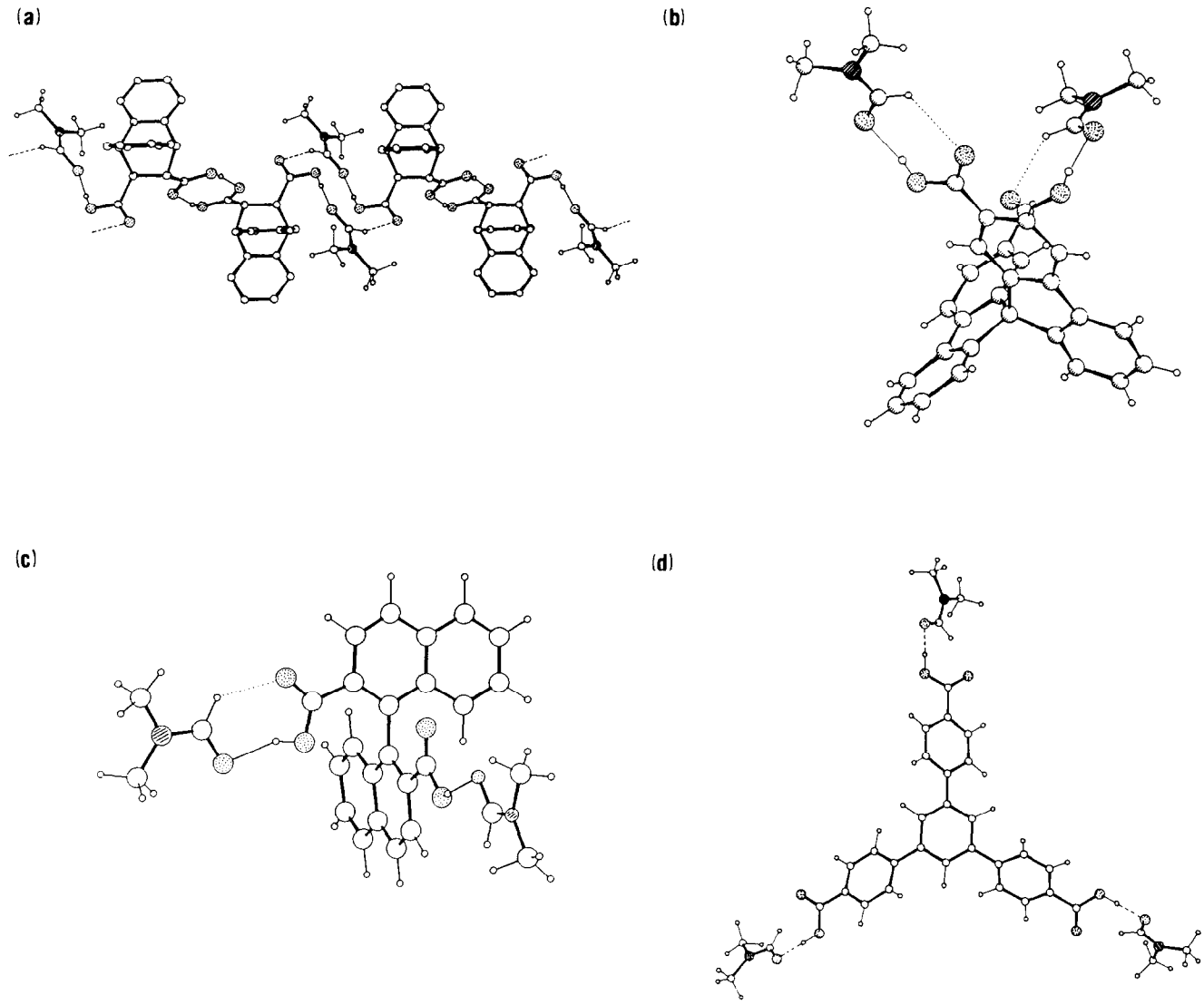


Figure 19. Recognition characteristics of dimethylformamide emanating from crystal structures of inclusion compounds between carboxylic hosts and DMF. (a) **2**·*DMF (1:1); (b)* **5**·*DMF (1:2); (c)* **1**·*DMF (1:2); (d)* **6**·*DMF (1:3); (a) packing excerpt; (b)–(d) molecular structures. Strong and weak H-bonds are represented by thin and broken lines, respectively*

guest associations with 2:2 stoichiometry [O(−H)···O = 2.647 Å, 175°; O(−H)···O(F) = 2.690 Å, 174°; (F)O(−H)···O = 2.676 Å, 172°]. These aggregates are linked together by van der Waals type forces to form the crystal lattice that provides cavities where H-bonded dimers of the guest acid residue [O(−H)···O = 2.640 Å, 146°]. These dimers have no specific interaction to the host molecules. Thus, molecular recognition by means of functional group interaction with the host is not fully exhausted here, but only in part.

Roughly, the host matrix in the propionic acid and acetic acid inclusions of **2** may be related to the structure of free host **2**,[17,19] while the formic acid inclusion of **2**, in a certain way, bears features of the corresponding DMSO inclusion (see Figure 22a). The modes of interaction in **1**·acetic acid (2:3)[17,34] are similar to **2**·formic acid (1:2) (i.e., host-host, host-guest, and guest-guest carboxylic group dimers all exist in the crystal).

We are not aware of any example where host-guest dimers of carboxylic groups are exclusively formed. The finding raises the question of whether the pK_a -values of host and guest acid play a role for the formation of a particular aggregate structure and whether this behavior is confined to carboxylic acids only or applies also to molecules with other functional groups of high H-bond capability, such as amides. Studies along these lines[35] are promising, since designed aggregate structures of H-bonded acids and amides in the crystalline state[36] are suspected as useful tools for different problems in organic solid state chemistry[37] and materials science.[38]

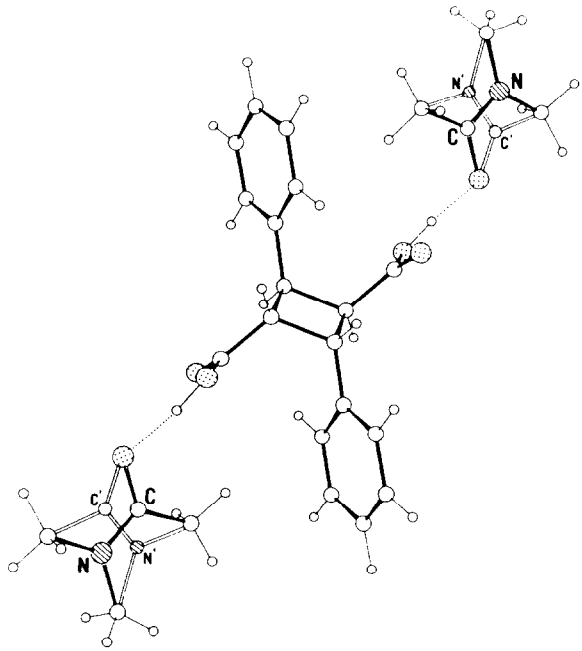


Figure 20. Molecular structure of **4**·*acetamide (1:2); the guest molecules show twofold disorder for the C and N atoms*

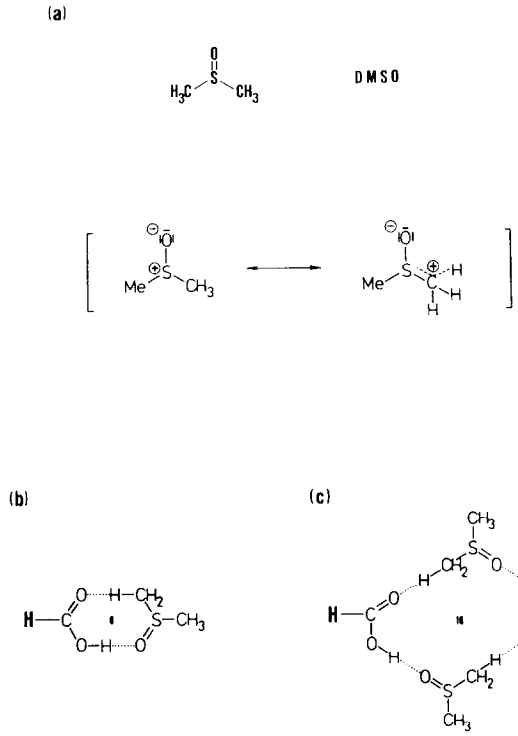


Figure 21. (a) Constitutional and resonance formulae of dimethyl sulfoxide (DMSO); (b) and (c) possible modes of cyclic H-bond interactions between DMSO and a carboxylic host (the bold H stands for host; H-bonds are represented by broken lines; the numbers denote ring sizes)

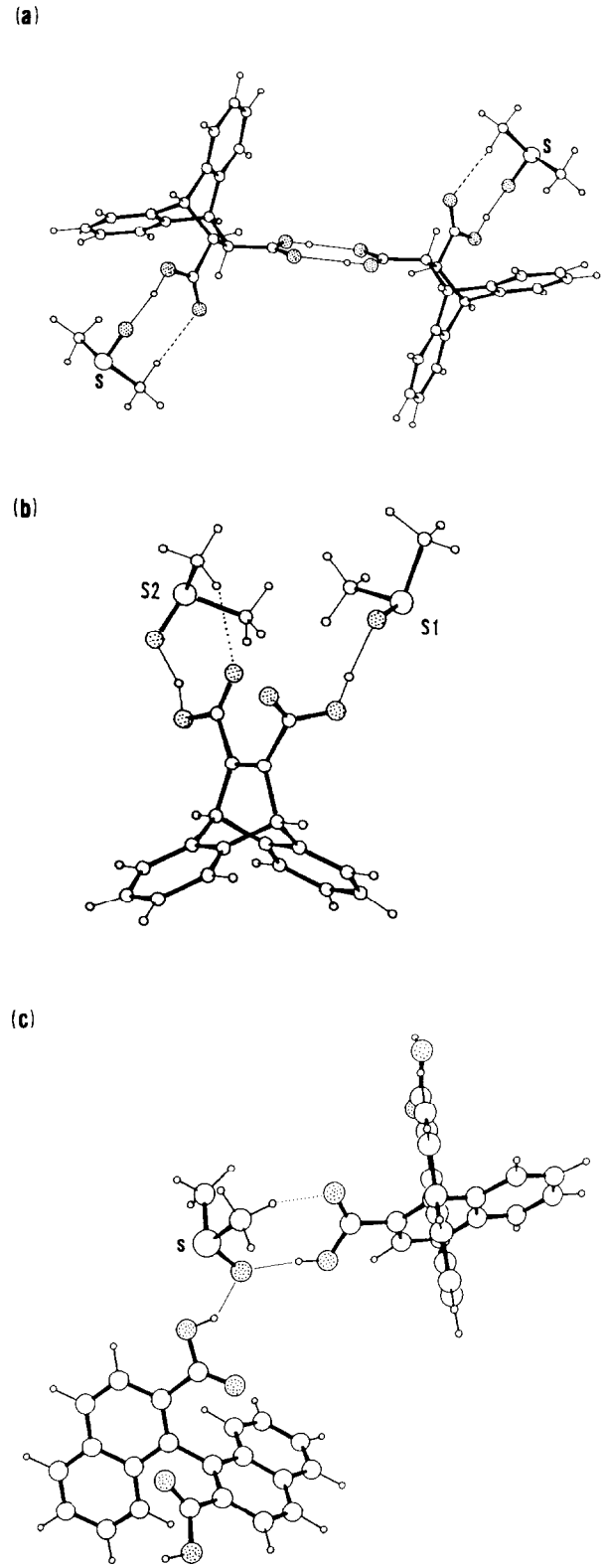


Figure 22. Recognition characteristics of dimethyl sulfoxide (DMSO) emanating from crystal structures of inclusion compounds between carboxylic hosts and DMSO (molecular structures; strong and weak H-bonds are represented by thin and broken lines, respectively). (a) **2**·*DMSO (1:1); (b)* **8**·*DMSO (1:2); (c)* **1**·*DMSO (1:1)*

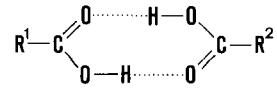
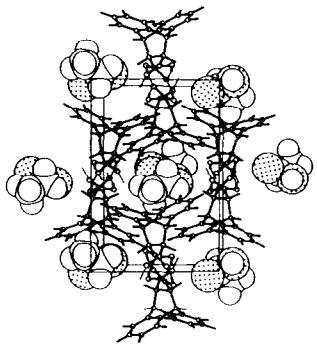


Figure 23. Conventional carboxylic dimer

(a)



(b)

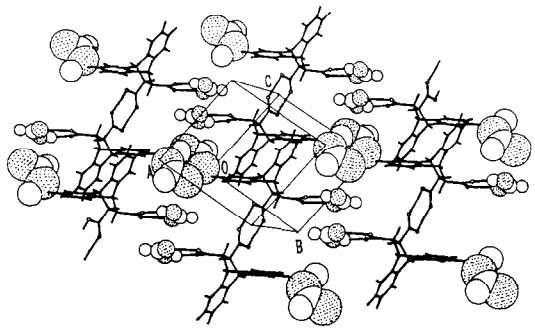


Figure 24. Packing relations of (a) **2***·propionic acid (1:1) and (b)* **2***·formic acid (1:2); complementary stick-style and space-filling representations of host and guest molecules, respectively. In (b), the small spheres refer to the host-bound guests; O atoms dotted*

CONCLUDING REMARKS

Carboxylic groups appropriately placed at a rigid molecular backbone are capable of molecular recognition in a crystalline host matrix using a specific H-donor/H-acceptor relationship to complementary functionalized guests, as schematized in Figure 25. Details have been discussed for guests with hydroxy, methylsulfinyl, and formyl counterpart groups that are suggested as H donors of decreasing order.[39] In principle, acids by themselves are also suitable guest partners for a carboxylic host, as shown in the previous section.

Nevertheless, a great variety of other guest molecules with potential H-donor/H-acceptor behavior, such as nitromethane, acetonitrile, malonodinitrile, acetylenes and ketones, remain to be studied in a similar way. We have formed ideas of how their recognition by carboxylic hosts might take place, and we look forward keenly to seeing whether our expectations are met or not.

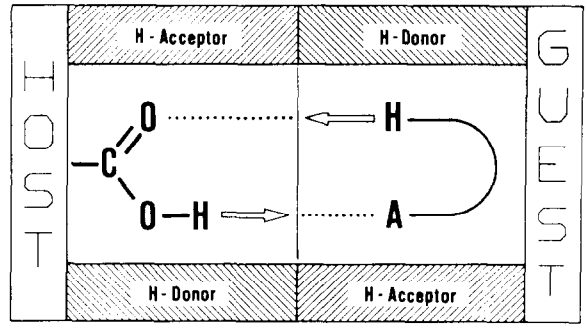


Figure 25. Fundamental H-donor/H-acceptor relationship in molecular recognition, demonstrated by carboxylic hosts

Considering the generality of the "coordinative assistance principle" in clathrate formation[17] that makes feasible a defined and predictable recognition in heteromolecular crystalline assemblies, the carboxylic acids discussed here are only a small sector in a sea of potential host molecules. I am sure that such hosts that have amide or hydroxy functions[40] are found just as effective in molecular recognition as carboxylic acids, but on different territories. Preliminary results[35,41] point to this fact.

ACKNOWLEDGEMENTS

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REFERENCES

1 (a) *Chemical Recognition in Biology*, Chapeville, F. and Haenni, A.L. (Eds.). Springer-Verlag, Berlin, Heidelberg, 1980. (b) Stryer, L. *Biochemie*, 2d ed., Vieweg, Wiesbaden, 1983. (c) *Enzyme Mechanisms*, Page, M.I. and Williams, A. (Eds.). Royal Society of Chemistry, London, 1987

2 (a) *Applications of Biochemical Systems in Organic Chemistry, Part II (Techniques of Chemistry, Vol. X)*, Jones, J.B., Sih, C.J., and Perlman, D. (Eds.). Wiley-Interscience, New York, 1976. (b) Dugas, H. and Penney, C. *Bioorganic Chemistry*, Springer, New York, 1981. (c) *Chemical Approaches to Understanding Enzyme Catalysis*, Green, B.S., Ashani, Y. and Chipman, D. (Eds.). Elsevier, Amsterdam, New York, 1982. (d) *Host Guest Complex Chemistry – Macrocycles*, Vögtle, F. and Weber, E. (Eds.). Springer-Verlag, Berlin, Heidelberg, 1985. (e) *Design and Synthesis of Organic Molecules Based on Molecu-*

lar Recognition, Van Binst, G. (Ed.). Springer-Verlag, New York, 1986

3 (a) *Progress in Macrocyclic Chemistry, Vols. 1–3*, Izatt, R.M., and Christensen, J.J. (Eds.). Wiley-Interscience, New York, 1979, 1981, 1987. (b) *Inclusion Compounds, Vols. I–III*, Atwood, J.L., Davies, J.E.D. and MacNicol, D.D. (Eds.). Academic Press, New York, 1984. (c) *Host Guest Complex Chemistry I–III (Topics in Current Chemistry, Vols. 98, 101, 121)*, Vögtle, F. and Weber, E. (Eds.). Springer-Verlag, Berlin, Heidelberg, 1981, 1982, 1984. (d) *Biomimetic and Bioorganic Chemistry, I–III (Topics in Current Chemistry, Vols. 128, 132, 136)* Vögtle, F. and Weber E. (Eds.). Springer-Verlag, Berlin, Heidelberg, 1985, 1986, 1986. (e) *Molecular Inclusion and Molecular Recognition – Clathrates I and II (Topics in Current Chemistry, Vols. 140 and 149)*, Weber, E. (Ed.). Springer-Verlag, Berlin, Heidelberg, 1987 and 1988.

4 (a) Cram, D.J. Von molekularen Wirten und Gästen sowie ihren Komplexen (Nobel-Vortrag). *Angew. Chem.* 1988, **100**, 1041–1052; *Angew. Chem., Int. Ed. Engl.* 1988, **27**, 1009. (b) Lehn, J.–M. Supramolekulare Chemie – Moleküle, Übermoleküle und molekulare Funktionseinheiten (Nobel-Vortrag). *Angew. Chem.* 1988, **100**, 91–116; *Angew. Chem., Int. Ed. Engl.* 1988, **27**, 90

5 (a) Weber, E. Crown ethers. *Ullmann's Encyclopedia of Industrial Chemistry, Vol. A8*. VCH Verlagsgesellschaft, Weinheim, 1987, 91–97. (b) Weber, E. Crown compounds – Properties and Practice. *Phase Transfer Catalysts – Properties and Applications*. Merck-Schuchardt, Darmstadt, 1987, 33–76

6 Meyer, A.Y. The size of molecules. *Chem. Soc. Rev.* 1986, **15**, 449–474

7 Cram, D.J. Präorganisation — von Solventien zu Sphäranden. *Angew. Chem.* 1986, **98**, 1041–1060; *Angew. Chem., Int. Ed. Engl.* 1986, **25**, 1039

8 Weber, E. Crystalline uncharged molecule inclusion compounds of unintended and designed macrocyclic hosts. Ref. 3a, 1987, **3**, 337–419

9 Vögtle, F. and Müller, W.M. Complexation of neutral guests within cavities of synthetic neutral host molecules. *J. Incl. Phenom.* 1984, **1**, 369–386

10 Weber, E. and Josel, H.–P. A proposal for the classification and nomenclature of host-guest-type compounds. *J. Incl. Phenom.* 1983, **1**, 79–85

11 Weber, E. Clathrate chemistry today — Some problems and reflections. Ref. 3e, 1987, **140**, 1–20

12 MacNicol, D.D. and Wilson, D.R. New strategy for the design of inclusion compounds: Discovery of the 'hexa-hosts'. *J. Chem. Soc., Chem. Commun.* 1976, 494–495

13 Vögtle, F., Löhr, H.G., Puff, H. and Schuh, W. Ein neuartiger Typ ionischer Clathranden für zahlreiche Einschlußverbindungen. *Angew. Chem.* 1983, **95**, 425–426; *Angew. Chem., Int. Ed. Engl.* 1983, **22**, 409

14 Weber, E., Csöregh, I., Stensland, B., and Czugler, M. A novel clathrate design: selective inclusion of uncharged molecules via the binaphthyl hinge and appended co-ordinating groups, X-ray crystal structures and binding modes of 1,1′-binaphthyl-2,2′-dicarboxylic acid host/hydroxylic guest inclusions. *J. Am. Chem. Soc.* 1984, **106**, 3297–3306

15 Hart, H., Lin, L.T.W. and Ward, D.L. Molecular design for hosts in crystalline host-guest complexes. *J.Am. Chem. Soc.* 1984, **106**, 4043–4045

16 Toda, F., Tanaka, K., Hyoda, T. and Mak, T.C.W. Design of a new host compound, 2,2-di(p-hydroxyphenyl)propane, and crystal structure of its 1:1 complex with methylhydrazine. *Chem. Lett.* 1988, 107–110

17 Weber, E. and Czugler, M. Functional group assisted clathrate formation — scissor-like and roof-shaped host molecules. Ref. 3e 1988, **149**, 45–135

18 Csöregh, I., Czugler, M., and Weber, E. (unpublished results)

19 Weber, E., Csöregh, I., Ahrendt, J., Finge, S. and Czugler, M. Design of roof-shaped clathrate hosts. Inclusion properties and X-ray crystal structures of a free host and of inclusion compounds with 1-BuOH and DMF. *J. Org. Chem.* 1988, **53**, 5831–5839

20 Csöregh, I., Czugler, M. and Weber, E. Structural studies of the inclusion properties of a novel coordinatoclathrate host. *Molecular Structure: Chemical Reactivity and Biological Activity*, Stezowski, J.J., Huang, J.L., Shao, M.–C (Eds.). International Union of Crystallography, Oxford University Press, 1988, 390–395

21 Czugler, M., Weber, E. and Ahrendt, J. Selective clathrate formation with the new host system cis- and trans-9,10-dihydro-9,10-ethanoanthracene-11, 12-dicarboxylic acid: Inclusion properties and X-ray structure of an encapsulated acetic acid dimer. *J. Chem. Soc. Chem. Commun.* 1984, 1632–1634

22 (a) Rebek, Jr. J. Model studies in molecular recognition. *Science* 1987, **235**, 1478–1484. (b) Rebek, Jr. J. Recent progress in molecular recognition. Ref. 3e 1988, **149**, 189–210

23 Gartland, G.L., Freeman, G.R. and Bugg, C.E. Crystal structures of tryptamine picrate and D, L-tryptophan picrate-methanol, two indole donor-acceptor complexes. *Acta Crystallogr.* 1974, **B30**, 1841–1849

24 Weber, E., Hecker, M., Csöregh, I. and Czugler, M. New host family based on small-ring compounds. (submitted for publication)

25 Cf. Kamiya, K., Takamoto, M., Wada, Y. and Asai, M. Structure of sulfazecin-methanol (1/1). *Acta Crystallogr.* 1981, **B37**, 1626–1628

26 Huggins, M.L. 50 Jahre Theorie der Wasserstoffbrückenbindung. *Angew. Chem.* 1971, **83**, 163–168; *Angew. Chem., Int. Ed. Engl.* 1971, **10**, 147

27 Taylor, R. and Kennard, O. Crystallographic evidence for the existence of C–H···O, C–H···N, and C–H···Cl hydrogen bonds. *J. Am. Chem. Soc.* 1982, **104**, 5063–5070

28 Czugler, M., Stezowski, J.J. and Weber, E. Co-ordination-assisted inclusion of neutral molecules by the racemic 9,9′-spirobifluorene-2,2′-dicarboxylic acid host lattice. X-ray crystal structure of the dimethylformamide clathrate at 170K. *J. Chem. Soc., Chem. Commun.* 1983, 154–155

29 Csöregh, I., Sjögren, A., Czugler, M., Cserzö, M.

and Weber, E. Versatility of the 1,1′-binaphthyl-2,2′-dicarboxylic acid host in solid-state inclusion: Crystal and molecular structure of the dimethylformamide (1:2), dimethyl sulfoxide (1:1), and bromobenzene (1:1) clathrates. *J. Chem. Soc., Perkin Trans. 2*, 1986, 507–513

30 Weber, E., Hecker, M., Koepp, E., Orlia, W., Czugler, M., and Csöregh, I. New trigonal lattice hosts: Stoicheiometric crystal inclusions of laterally trisubstituted benzenes—X-ray crystal structure of 1,3,5,-*tris*-(4-carboxyphenyl)benzene·dimethylformamide. *J. Chem. Soc., Perkin Trans. 2*, 1988, 1251–1257

31 Csöregh, I., Czugler, M., Ertan, A., Weber, E. and Ahrendt, J. Solid-state binding of dimethyl sulphoxide involving carboxylic host molecules. X-ray crystal structures of four inclusion species *J. Incl. Phenom.* 1989, **7**, (in press)

32 Allen, G. and Caldin, E.F. The association of carboxylic acids. *Quart. Rev.* 1953, **7**, 255–278

33 Leiserowitz, L. Molecular packing modes. Carboxylic acids. *Acta Crystallogr.* 1976, **B32**, 775–802

34 Csöregh, I., Czugler, M., Weber, E., and Ahrendt, J. Formation of isolated guest dimers vs. host-guest coordination. X-ray crystal structures of four carboxylic acid inclusion compounds by roof-shaped and scissor-like host molecules *J. Incl. Phenom,*1989, **7** (in press)

35 Weber, E., Finge, S. and Csöregh, I. (unpublished results)

36 Etter, M.C. Aggregate structures of carboxylic acids and amides. *Isr. J. Chem.* 1985, **25**, 312–319

37 (a) *Organic Solid State Chemistry (Studies in Organic Chemistry, Vol. 32)*, Desiraju, G.R. (Ed.). Elsevier, Amsterdam, New York, 1987. (b) *Organic Chemistry in Anisotropic Media (Symposia-in-Print, Number 29)*, Scheffer, J. (Ed.) *Tetrahedron,* 1987, **43**, 1197–1745

38 (a) Williams, D.J. Organische polymere und nichtpolymere Materialien mit guten nichtlinearen optischen Eigenschaften. *Angew. Chem.* 1984, **96**, 637–651; *Angew. Chem., Int. Ed. Engl.* 1984, **23**, 690. (b) *Nonlinear Optical Properties of Organic Molecules and Crystals, Vols. 1 and 2*, Chemla, D., Zyss, J. (Eds.). Academic Press, New York, 1987

39 Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed. VCH Verlagsgesellschaft, Weinheim, 1988, 51

40 Toda, F. Isolation and optical resolution of materials utilizing inclusion crystallization. Ref. 3e 1987, **140**, 43–69

41 Weber, E., Dörpinghaus, N. and Goldberg, I. Selective clathrate inclusion of primary and secondary amines in a new host series. Crystallographic reasoning of the inclusion behaviour. *J. Chem. Soc., Chem. Commun.* 1988, 1566-1568