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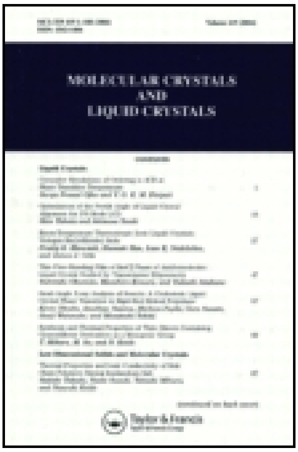

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# SMALL-RING INCLUSION HOSTS. DEVELOPMENT OF A NEW CLATHRATE FAMILY [†]

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Abstract. A new class of inclusion hosts featuring three- and four-membered ring compounds with functional groups and bulky substituents is developed. These hosts form clathrates with a variety of uncharged organic molecules ranging from polar protic to apolar compounds. Formation and selectivity depend in a systematic manner on structural parameters of the host, such as the nature, number, and position of functional groups, the substituents and ring size. Crystal structures of some relevant inclusion compounds revealing the building principles of the new clathrate family are discussed.

## INTRODUCTION

Recently we have developed a strategy for the design of new clathrate hosts that possess relationships complementary to specific guest compounds.[1] The new approach starts from particular steric requirements of the host molecule and makes extensive use of

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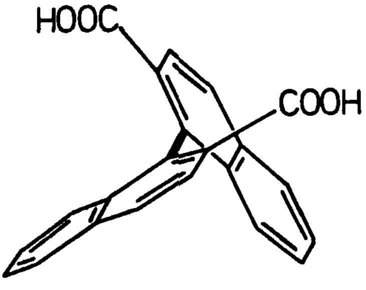
*functional group interactions* between host and guest species allowing planned inclusion properties.[2] Functional sensor groups are characterized as H bond donors and/or acceptors of different strength. The crystalline supramolecular systems formed in this way are members of the new type of "coordinatoclathrates" (coordinative group assisted clathrates) which usually are more stable than the conventional clathrates. They are highly selective and are predictable within certain limits. Also, they provide insight into the elementary interactions of functional groups on which molecular recognition is based.[3] Within this concept, the following points are important for a host molecule: (1) bulky constitution; (2) rigid conformation; (3) appropriately placed and highly affine functional groups; (4) balanced overall shape. Then, crystal cavities and the desired functional group interactions between host and guest molecules are likely.[1-3]

Typical host molecules that approach the coordinatoclathrate ideal are simple dicarboxylic acids such as **1** (1,1'-binaphthyl-2,2'-dicarboxylic acid)[1] and **2** (9,10-ethano-9,10-dihydroanthracene-*trans*-11, 12-dicarboxylic acid).[4] They are capable of clathrate formation with a large number of organic compounds including protic polar, aprotic polar, and apolar molecules of different compound classes such as alcohols, carboxylic acids, amids, nitriles, nitro compounds, DMSO, THF, dioxane, bromobenzene, and others. Also, the host molecules **1** and **2** reveal high selectivity, at inclusion formation, corresponding to their structural properties.



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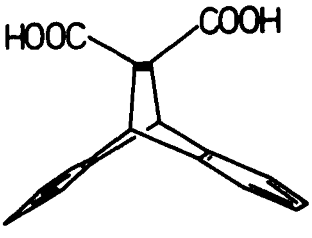

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## DISCUSSION

From a geometric point of view, host molecule 1 has a scissor-like shape and is moderately flexible. 2 is roof shaped and is more rigid in conformation.[2,3] Hence 2 was found to be less adaptable to differently sized guest molecules.[4] However, by topology, both host structures refer to structures characteristic of a central axis (bold in formulae 1 and 2 ) 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 represents limitations.

A formal extension results if the axis determining the structural element is replaced by a triangle or a quadrangle (Figure 1). Now, more than four groups (up to eight) can be accommodated in great variety and with new geometries. Adaptation to specific requirements of guest molecules is thus easier.

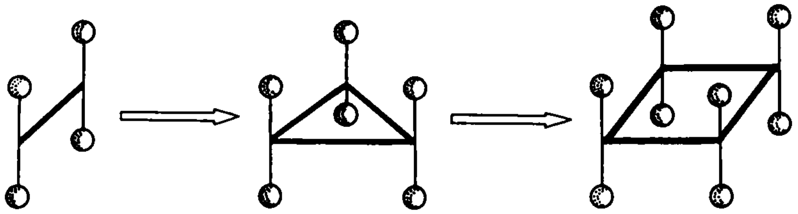

FIGURE 1. Design concept of the new hosts (schematic represen= tation; the spheres stand for replaceable groups).

It will hardly be necessary to mention that substituted cyclopropanes and cyclobutanes are molecular representatives, and the appropriate substituents could be functional groups such as in carboxylic acids, ketones or nitriles, and aromatic residues. Selected examples of molecules are specified by formulae 3 - 11.[5] There

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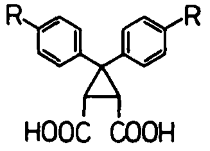

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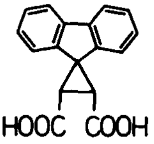

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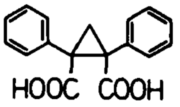

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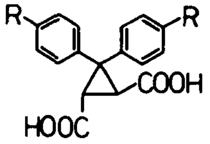

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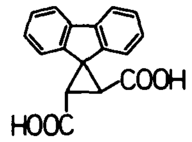

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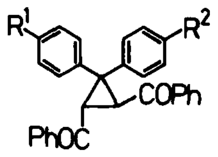
**a** R = H
**b** R = Me
**c** R = Cl



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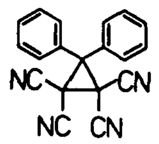
**a** $R^1 = R^2 = H$
**b** $R^1 = Me, R^2 = H$
**c** $R^1 = R^2 = Me$
**d** $R^1 = R^2 = Cl$



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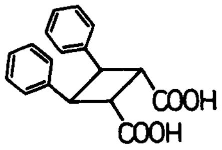

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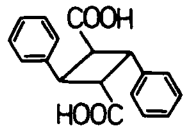

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are *cis*- and *trans*-dicarboxylic acids or ketones, with or without substituents, and bridged and unbridged molecules. Most of the cyclopropanes are obtainable by the very same synthetic method, which is cycloaddition of a diazoalkane to an olefin.[5] The diazoalkanes are readily available from the corresponding ketones and hydrazine followed by oxidation. Compounds 10 and 11 were prepared by solid-state photo-dimerization of β- and α-*trans*-cinnamic acid, respectively.[5]

As expected, all cyclopropano diacids (e.g. 3 - 7) form crystalline inclusions with alcohols, but with different species and to a different extent (Table I). The matter is as follows: *cis*-diacids (cf. 3 -

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5) are much broader in inclusion behavior compared to *trans*-diacids (cf. 6 and 7). Consequently the *trans*-diacids are more selective. Bridging the aromatic ring is an important selectivity parameter for the *cis*-diacids (cf. 3a with 4) and *p*-substitution is for the *trans*-diacids (cf. 6a with 6b). Moreover, *trans*-diacids form clathrates of 1:2 host:guest stoichiometry, as a rule (6a•2-PrOH, 1:1, is an exception), while *cis*-diacids reveal strict 1:1 host:guest stoichiometry in their clathrates. Hence, the *trans*-diacids mostly demonstrate full binding capacity towards alcohols, but the *cis*-diacids do not.[5] The latter points to strong intramolecular H bonding which is also expected for the free host 3a.

TABLE I Crystalline inclusion compounds between dicarboxylic cyclopropano hosts and alcohols (stoichiometries, host:guest).

| Host → <br> Guest ↓ | 3a | 3b | 4 | 5 | 6a | 6b | 7 |
|---|---|---|---|---|---|---|---|
| MeOH | 1:1 | 1:1 | - | 1:1 | - | 1:2 | - |
| EtOH | 1:1 | 1:1 | 1:1 | 1:1 | - | - | - |
| 1-PrOH | 1:1 | 1:1 | - | 1:1 | - | - | - |
| 2-PrOH | 1:1 | 1:1 | 1:1 | 1:1 | 1:1 | - | - |
| 1-BuOH | 1:1 | 1:1 | - | 1:1 | - | - | - |
| 2-BuOH | 1:1 | 1:1 | - | 1:1 | - | 1:2 | 1:2 |
| t-BuOH | 1:1 | 1:1 | 1:1 | 1:1 | 1:2 | 1:2 | - |

Figure 2a shows the crystal structure of unsolvated host 3a, exhibiting the intra-host H bond [O(-H)•••O(intra) = 2.513 Å, 162°] which prevents the acid from ordinary dimerization.[6] Instead of this, a linear aggregate of H-bonded molecules [O(-H)•••O(inter) = 2.590 Å, 180°] is formed which involves a simple translation motif.[6] Interestingly, the compound uses an enantiomorphous space group ($P2_1$) for crystallization.[5]

As expected, in the crystalline inclusion compound of 3a with t-BuOH (1:1) (Figure 2b), the linear strands of H-bonded host molecules ( Figure 2a) are parted. Individual molecules of the alcohol are intercalated between each of the former inter-host contacts, but the intra-host contact is not affected by the alcohol. In this way,

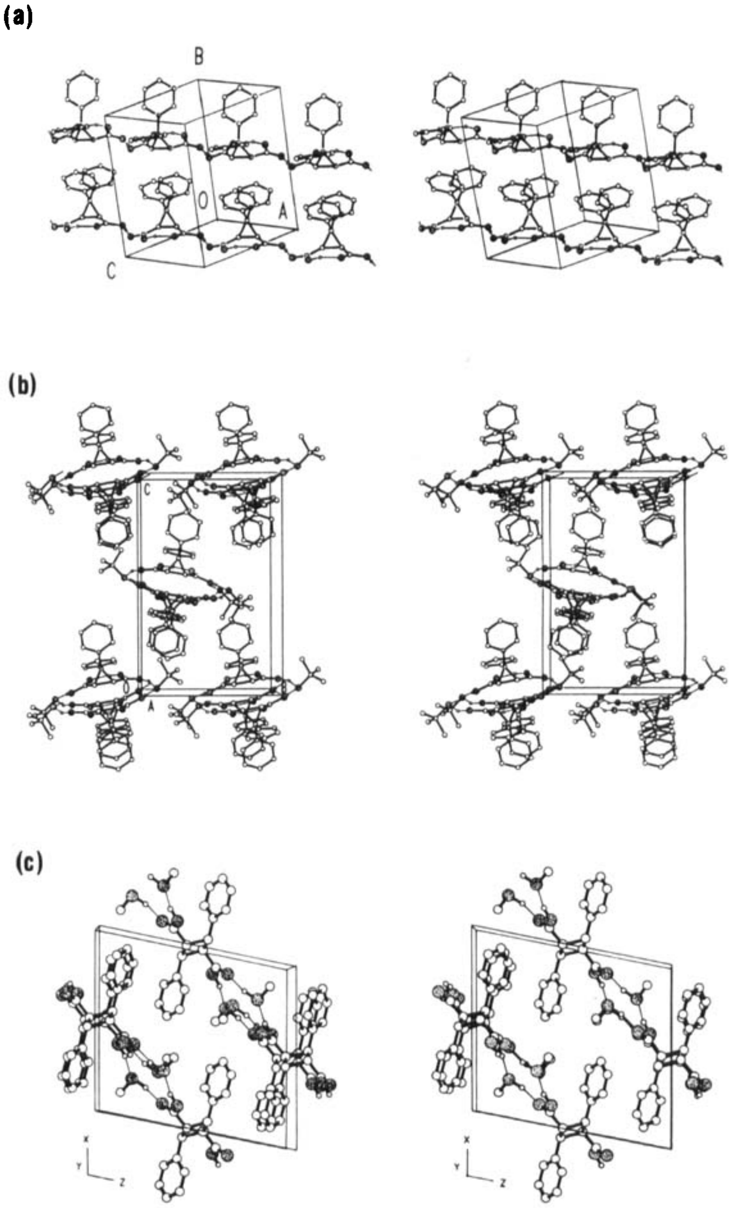

FIGURE 2. Stereoscopic packing diagrams: (a) unsolvated 3a, (b) 3a·t-BuOH (1:1) inclusion compound, (c) 11·MeOH (1:2) inclusion compound. O atoms are specified by larger spheres and dotting; H atoms are omitted, except those involved in H bonds. H bonds are indicated as thin lines.

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a helix of intra/inter H bonds is formed including alternating host and guest molecules [O(-H)•••O(intra) = 2.552 Å, 170°; O(-H)•••O(inter) = 2.566 Å, 155° and 2.861 Å, 144°]. Thus, molecular recognition between 3a and t-BuOH is reflected in a helical super-aggregate (pitch of the helix = 9.8 Å). Another remarkable point is that 3a•t-BuOH (1:1) crystallizes in an enantiomorphous space group ($P2_12_12_1$). Hence, as for unsolvated 3a, individual crystals of 3a•t-BuOH (1:1) are optically active.[5] The same mode of H bonding is found for 3b•EtOH (1:1), however, without using an enantiomorphous space group ($C2/c$) for crystallization.[7]

Relevant examples of the cyclobutano-type of host molecules having familiar groups around the ring are the diacids 10 and 11 (β-truxinic and α-truxillic acid, respectively). Compared to the cyclopropano analogues, 10 and 11 are not so broad in inclusion behavior (Table II). Apart from 11•MeOH (1:1), no other inclusions of alcohols are found. Also, the inclusions formed with dipolar aprotic compounds are relatively rare (in addition to the alcohol clathrates listed in Table I, 3 - 7 give a large number of inclusions with dipolar aprotic solvents[5]). Nevertheless, it becomes the rule that *cis*- and *trans*-dicarboxylic acids yield clathrates of 1:1 and 1:2 host:guest stoichiometry (10 and 11, respectively).

TABLE II. Crystalline inclusion compounds of dicarboxylic cyclobutano hosts (stoichiometries, host:guest).

| Host → Guest ↓ | 10 | 11 | Host → Guest ↓ | 10 | 11 |
|---|---|---|---|---|---|
| MeOH | - | 1:2 | DMF | 1:1 | 1:2 |
| EtOH | - | - | DMA | (-) | 1:2 |
| 1-PrOH | - | - | DMSO | (-) | 1:2 |
| 2-PrOH | - | - | THF | - | - |
| t-BuOH | - | - | Dioxane | 1:1 | - |

Past experience (cf. alcohol inclusions of 1)[1,2] suggests that MeOH (1:2) may form a 12-membered supramolecular ring of H bonds including two carboxyl and two hydroxyl groups. Instead of the expected cyclic mode of H bonds, a polymeric aggregate is formed (Figure 2c) which shows again a helical array of H bonds between

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alternating host and guest molecules [for both carboxylic groups; (acid)O(-H)•••O(MeOH) = 2.594 Å, 164°; (MeOH)O(-H)•••O(acid) = 2.743 Å, 167°; pitch of the helix is 5.6 Å; space group of the crystal ($P2_1/n$)].[7]

The 11•dimethylacetamide (DMA) inclusion compound (1:2) reveals single H bond contacts between each carboxylic donor and a DMA acceptor [carboxylic group of DMA; O(-H)•••O = 2.600 Å, 154°].[7] Such interactions are usual in the given field of functional groups.[2,3]

Small-ring hosts other than carboxylic acids were also designed and synthesized in large numbers.[5] A few examples are the diketones 8a - 8d as well as the tetranitrile 9. It appears that structural effects are very distinct here. For instance, the unsubstituted parent molecule 8a is an efficient host for different aprotic compounds (Table III). Addition of only one small methyl group as in 8b causes complete loss of inclusion behavior. On the other hand, extension by a second methyl group as in 8c brings back inclusion of MeCN, but solely of this guest (by way of contrast 8d is totally inefficient).[5]

TABLE III Crystalline inclusion compounds of diketo cyclopropano hosts (stoichiometries, host:guest).

| Host ⟹<br>Guest ⇩ | 8a | 8b | 8c | 8d | Host ⟹<br>Guest ⇩ | 8a | 8b | 8c | 8d |
|---|---|---|---|---|---|---|---|---|---|
| MeCN | 1:1 | - | 1:1 | - | Toluene | - | - | - | - |
| EtCN | - | - | - | - | o-Xylene | - | - | - | - |
| $MeNO_2$ | 1:1 | - | - | - | m-Xylene | - | - | - | - |
| Dioxane | 1:1 | - | - | - | p-Xylene | 1:1 | - | - | - |
| Benzene | 1:1 | - | - | - | Mesitylene | - | - | - | - |

The crystal structure of 8c•MeCN (1:1)[5] is revealing (Figure 3). It shows the guest molecules to be held in the host framework by steric barriers only. These are, however, completely efficient in forming a tight enclosure of the guest molecules. Molecules that are but slightly larger than MeCN, or slightly different in shape, would not fit into the present crystal cavity. The extremely high selectivity of 8c for MeCN also suggests that other suitable packings in the crystal rarely exist for this bulky host molecule.

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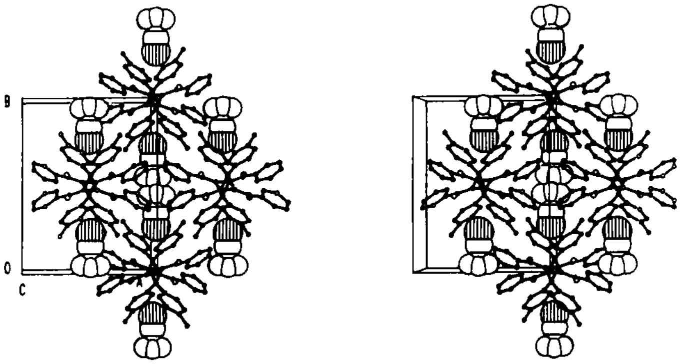

FIGURE 3. Stereoscopic packing diagram of the 8c·MeCN (1:1) clathrate. The host molecule shown as ball-and-stick (H atoms omitted), the guest molecules are in van der Waals representation; N atoms are hatched.

## CONCLUSIONS

Three- and four-membered ring compounds with functional groups and bulky substituents have proved to be highly efficients in enclathration of organic molecules. The new hosts are superior to known clathrate formers [8] in more than one respect. They are readily available by common synthetic methods. They allow structural modifications in many ways, e.g. changes in the number of bulky and/or functional groups around the ring, introduction of other substituents or variation of the substitution pattern. [5] Formation and selectivity depend in a systematic manner on these parameters (cf. Tables I-III). The crystal structures (Figures 2 and 3) illustrate that inclusions of very different character (H-bonded complexes and true lattice-type clathrates) are possible within the new host familiy. A future aspect is preparation of small-ring hosts (e.g. *trans*-diacids 6 and 7) in optically active form which would open up applications in the resolution of racemic guests via clathrate formation,and other uses. [9]

## ACKNOWLEDGEMENT

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