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Complexation of Neutral Guests Within Cavities of Synthetic Neutral Host Molecules

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Contents

1. Introduction

Molecular cavities are of topical research interest because of their ability to enclose and bind suitable guest molecules. They may serve as models to study binding sites of receptors, drugs, odourant/taste substances, antigenes etc. Cyclodextrins, as prime examples of uncharged water soluble host cavities, have found many useful applications. This is due to the fact that guest molecules are held within the cavity and their properties, such as solubility, volatility and reactivity, are changed.

This report presents a survey of the progress achieved within the last few years, in the field of complexation – especially molecular inclusion – of *uncharged* guest molecules by *uncharged* host molecules [1]. In particular, attention will be directed to several new molecular host/guest complexes, in which the guest is either partially (a,b) or completely (c) enclosed by the large host molecule. This is shown schematically in Figure 1.

Many suitable neutral guest molecules have been enclosed in the cone-shaped molecular host cavities of the 6, 7, and 8 glucose units of the α-, β- and γ-cyclodextrins [2] with cavity diameters of 4.7 to 8.3 Å. Among these guests are iodine, water, and krypton in α-cyclodextrin [2b], substituted benzenes, naphthalene and adamantane in β-cyclodextrin [2b,c] and anthracene [2], crown ethers and cryptands in γ-cyclodextrin [3].

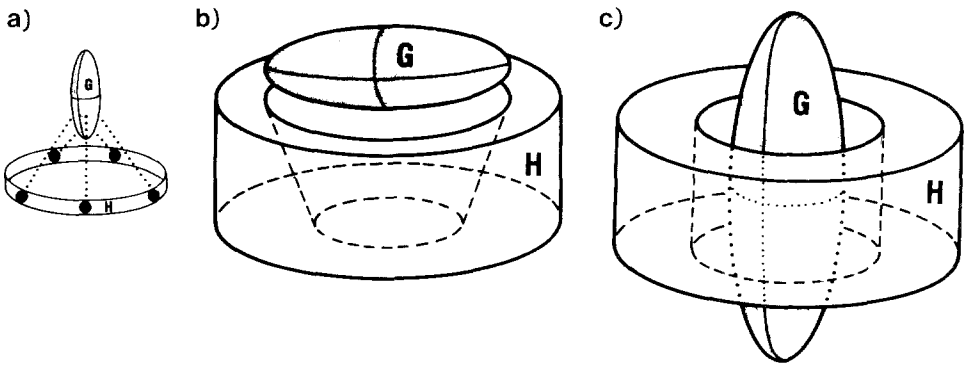


Fig. 1. Complexation of uncharged convex guest molecule *G* upon (a,b) and within (c) the cavity of uncharged concave host molecules *H* (schematically): (a) small host cavity, interaction through hydrogen bonds (dotted lines); (b) large host cavity, a guest deposited in a niche; (c) large host cavity, guest encapsulated.

For a long period, in spite of the knowledge gained of the varied inclusion ability of cyclodextrins, it was not possible to synthesize satisfactory analogous uncharged cavities. This would be all the more important because cyclodextrins have disadvantages – for example, some have moderate water solubility and possible toxicity.

Such a binding between *uncharged* host cavities and *uncharged* guests is especially interesting, because there are no strong binding forces such as full positive or negative charges involved. Host/guest binding must be due to several (multiple) weak attractive interactions of the hydrogen bond, dipole-dipole or hydrophobic type, in addition to the guest's steric fit into the cavity.

When the guest or the host bears *charges*, permitting stronger host/guest bonds, the conditions are much simpler. Not only have complexes of simple crown ethers with cationic organic guests (ammonium salts, amino acids) [4] been prepared in the past few years, but also numerous ones with sophisticated hosts [5] and cations [6]. A typical example, con-

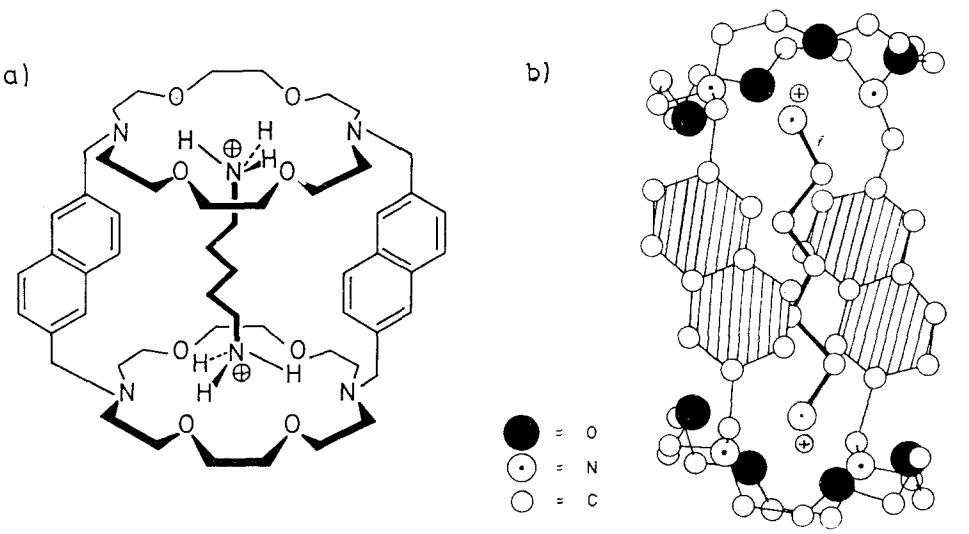


Fig. 2. The inclusion of a pentamethylene-diammonium compound as guest *cation* in an uncharged cryptand [7]: (a) formula, (b) crystal structure arrangement.

firmed by X-ray analysis, is the inclusion of a guest-dication in the cavity of a [3]cryptand shown in Figure 2 [7].

Conversely, the inclusion of neutral guest molecules within charged host molecules has more often been successfully achieved and exactly proved: as an example, Figure 3 shows the results of the X-ray analysis of durene encapsulation in the host cavity of a multimembered tetra(ammonium) cation.

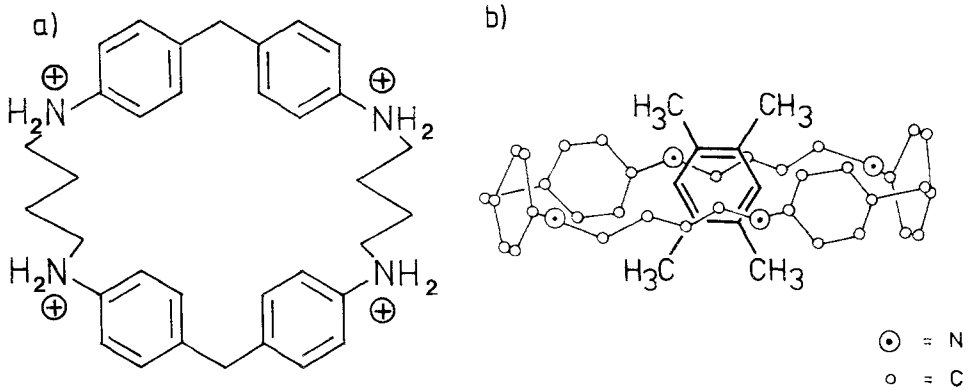


Fig. 3. Durene as a neutral guest in the cavity of a 30-membered host *cation* [8]: (a) host cation, (b) structure of the complex.

Even though complexes between charged or uncharged host molecules and charged guest molecules are systematically accessible, the complexation, especially the encapsulation of uncharged guests by uncharged host molecules can neither, as yet, be easily nor systematically obtained.

Figure 4 shows the macrocycle **1**, synthesized by Stetter [9]. It forms an adduct with benzene, when recrystallized from the latter [9]. For decades, it was believed to be a molecular inclusion compound, but X-ray analysis revealed that benzene is not encapsulated within the molecular cavity, instead it is found in between the crystal lattice [10]. Similar adducts have been reported by Pallas *et al.* [11], which probably have to be interpreted as crystal inclusion compounds.

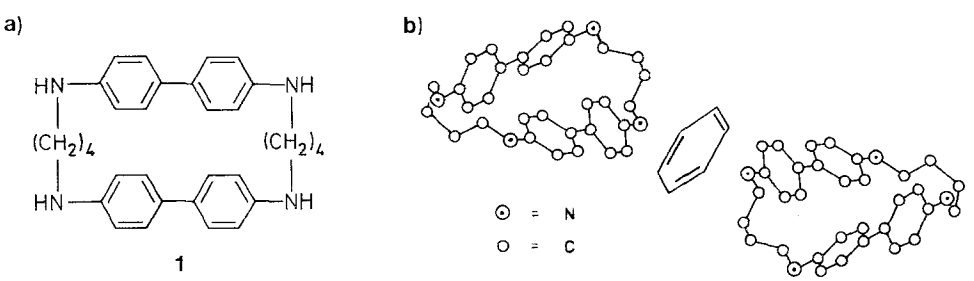


Fig. 4. Stetter's benzene adduct of **1** according to the X-ray analysis [10].

It was not until Koga *et al.* [8] used similar host structures, with the nitrogen as a quaternary ammonium salt, that water soluble host salts could be obtained [12–14]. It was proved, in solution as well as in the crystal state, that neutral organic guest molecules, such as durene, were actually within the charged host cavity (cf. Figure 3).

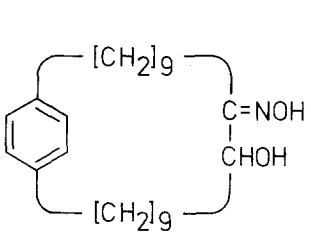
We will mainly limit the examples to those uncharged guests interacting within the cavity of uncharged host molecules, whose structures have been confirmed by X-ray analyses. They will demonstrate the model-kind identification of two more-or-less exactly complementary formed neutral molecules. Host structures which, in spite of having suitable cavities, do not encapsulate the corresponding neutral guest molecules within the cavity, but place them in the crystal lattices, forming clathrates, will not be quoted here.

2. Encapsulation of Neutral Guests by Large Host Cavities

2.1. CONFIRMED LIQUID STATE COMPLEXATION

2.1.1. *Paracyclophane-oximes as Enzyme Models*

It has been found that enzyme model reactions [17–20] can be carried out with simple macrocyclic hydrocarbon rings of the paracyclophane type, which can be considered to be similar to substituted cyclodextrins bearing functionalized side arms [15,16].



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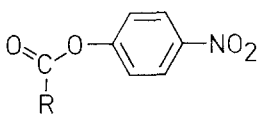
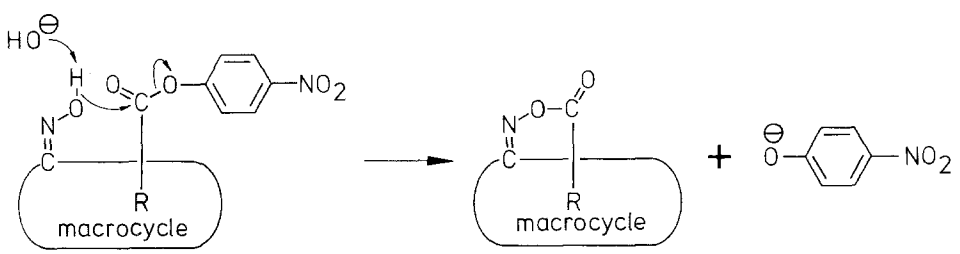


3a : R = $CH_3(CH_2)_{10}$
3b : R = $CH_3(CH_2)_8$
3c : R = CH_3
3d : R = $CH_3(CH_2)_4$

The mechanism of acyl transfer from the carboxylic acid esters **3** of 4-nitrophenol onto the paracyclophane oximate host molecule (**2**) in alkaline aqueous acetone has been interpreted as shown in Figure 5. The selectivity of binding the guest molecules **3a-3d**, though the transition state was formulated for the water-soluble host *anion*, instead of a neutral host molecule, should also be characteristic for the free (uncharged) host. The multimembered

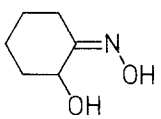


a : R = $CH_3(CH_2)_{10}$
b : R = $CH_3(CH_2)_8$
c : R = CH_3
d : R = $CH_3(CH_2)_4$

Fig. 5. Mechanism proposed for the catalyzed acyl transfer onto the oxime-functionalized host cavity molecule **2** [17].

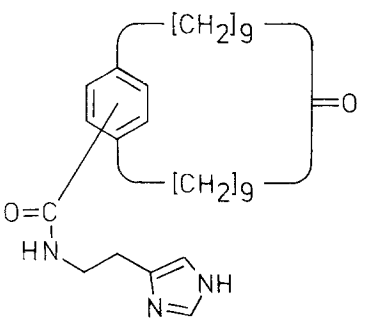
paracyclophane oxime **2** indeed demonstrates enzyme model features: Under certain conditions it can be acylated by long chained esters of 4-*nitrophenyl laurate* (**3a**) and -*decanoate* (**3b**), but not by the shorter and less lipophilic guests, 4-*nitrophenyl acetate* (**3c**) and -*hexanoate* (**3d**). This is probably due to the stronger complexation between the host **2** and the more lipophilic longer chained guest molecule. The latter also leads to a higher hydrophobic effect in aqueous acetone solution. The cavity of the cyclophane oxime host (**2**) is approx. 6.5 Å in length and has a depth of approx. 4.5 Å.

When using analogous conditions and a more simple host molecule such as 2-hydroxycyclohexanone oxime **4**, or just acetone oxime, as a potential acyl acceptor, no complexation seems to take place. The results confirm the assumption that the acyl transfer reaction of cyclophane oxime **2** takes place by encapsulating the lipophilic substrate in the host cavity. Multimembered host compounds of type **2**, thus show substrate selectivity. The guest ester, as a folded chain, seems to be enclosed in the host's cavity, comparable to natural receptor and enzyme systems. The host oxime **2**, therefore, can be considered as a simple esterase model. With regards to enzyme analogies, it is also noteworthy that copper(II) ions reduce the reaction velocity of 4-nitrophenyl laurate **3a** with the host cyclophane oxime **2** so that it reacts slower than without the addition of catalyst [17].



4

The main reaction step of the 23-membered [19]paracyclophane oxime is initiated from the anion of the oxime, the host not remaining neutral, whereas, conversely, the *imidazole derivative* **5** of [19]paracyclophane is catalytically active in its uncharged form. Its aggregation behaviour in a mixed aqueous organic solution and its kinetic consequences for the deacylation of different 4-nitrophenyl carboxylic acid esters have been described in detail [18]. This revealed that a significant hydrophobic interaction between the host and the hydrophobic ester substrates occurs.



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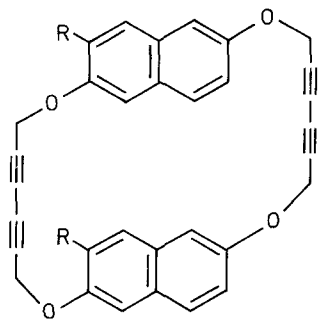
Owing to the accumulation of acyl derivatives of **5** in the course of the reaction, host **5** reacts smoothly with hydrophobic esters. When comparing the acylation velocity with that of its regeneration 'turn over', under these experimental conditions it was extremely small. Relatively,

hydrophobic esters are acylated faster by the *monomeric* host than corresponding reactions only catalyzed with imidazole. Reactions of the host imidazole group **5** with long chained carboxylic acid esters in the *micellar phase*, have the highest velocity rates found hitherto for reactions of synthetic 4-substituted imidazoles with 4-nitrophenyl esters. The strong catalytic activity of the host is primarily ascribed to its high binding ability to the substrates.

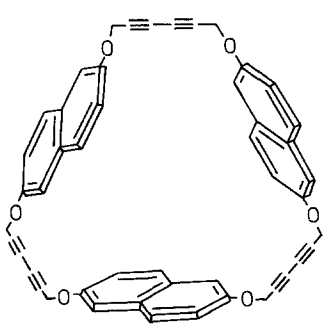
2.1.2. *Large Rings Enforced by Triple Bonds*

Naphthalenophanes of the type **6**, separated by acetylene units, were designed as hosts for aromatic guest molecules. The 'dimeric' **6** and the trimeric cyclization products **7** have been called donut-shaped cyclophanes [21]. Due to the shift of NMR signals, induced by aromatic solvents, it may be assumed that the functionalized host cavity **6** can enclose solvent molecules.



6

a : R = COOH
b : R = H



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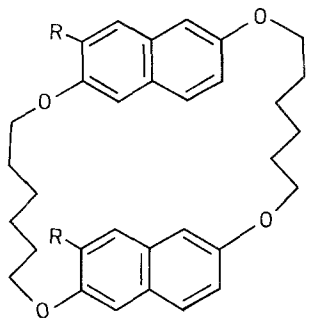


8

a : R = COOH
b : R = H

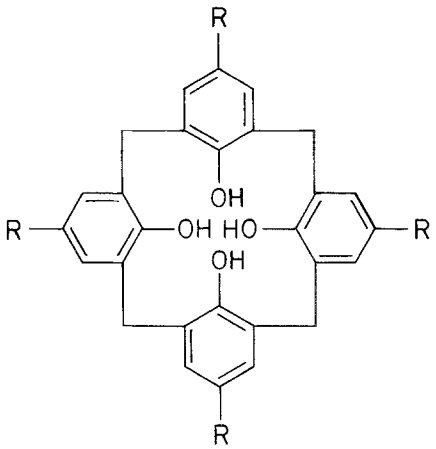
In rings, not enforced by diacetylene spacer units, the cavity is partly intramolecularly occupied by naphthalene rings of the host itself, turned inward [21]. Owing to the behaviour of the dicarboxylic acid **6a** in aqueous solution it may be assumed that when enclosing the guest in the host molecule, hydrophobic interactions may play a role.

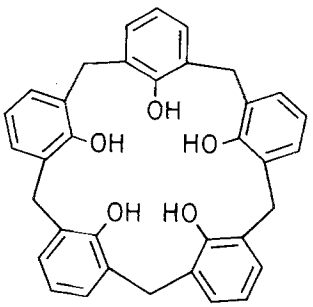
Contrary to the naphthalenophane **6**, enforced by triple bonds, the corresponding derivatives with saturated bonds **8** have collapsed conformations and seem unable to enclose aromatic guests [22]. So far, in no case have crystalline host/guest complexes been obtained.

The hydrocarbon phane **6** has a layered arrangement, without a guest inclusion. Fluorescence studies and NMR spectroscopy of aqueous soluble phanes of this type have revealed that complexes with 2-*anilino*-1,8-*naphthalenosulfonic acid* are formed in solution with an association constant of 590 M^{-1}. The exact location of complexation, i.e., whether the guest is within the cavity or attached outside the host, cannot as yet be definitely decided. For examples of charged macrocyclic hosts as catalysts we refer to the literature [12–14,19,20].

2.2. TOLUENE, ACETONE AND DICHLOROMETHANE AS GUESTS IN CALIXARENES

Similar to cyclodextrins, calixarenes (**9,10**) [13] form molecular inclusions as well as clathrates. In connection with this, the inclusion of toluene in the calixarene **9a**, synthesized from 4-*tert*-butylphenol [24] is interesting. As revealed by X-ray analysis, this [1.1.1.1](1,3)-





10

9a: R = $-C(CH_3)_3$

9b: R = $-C(CH_3)_2-CH_2-C(CH_3)_3$

cyclophane encapsulates *toluene* in such a way that its 1,4-axis coincides with the symmetry axis of the host. In addition to this, the methyl group of toluene projects deep into the interior of the cavity (cf. Figure 6). Contrary to this, a calix[4]arene **9b**, derived from *p*-(1,1,3,3-tetramethylbutyl)phenol, mainly forms channel-like *clathrates* when using the same guest molecule, *toluene*. *Toluene* is found in between the crystal lattice, as shown by X-ray analysis [26].

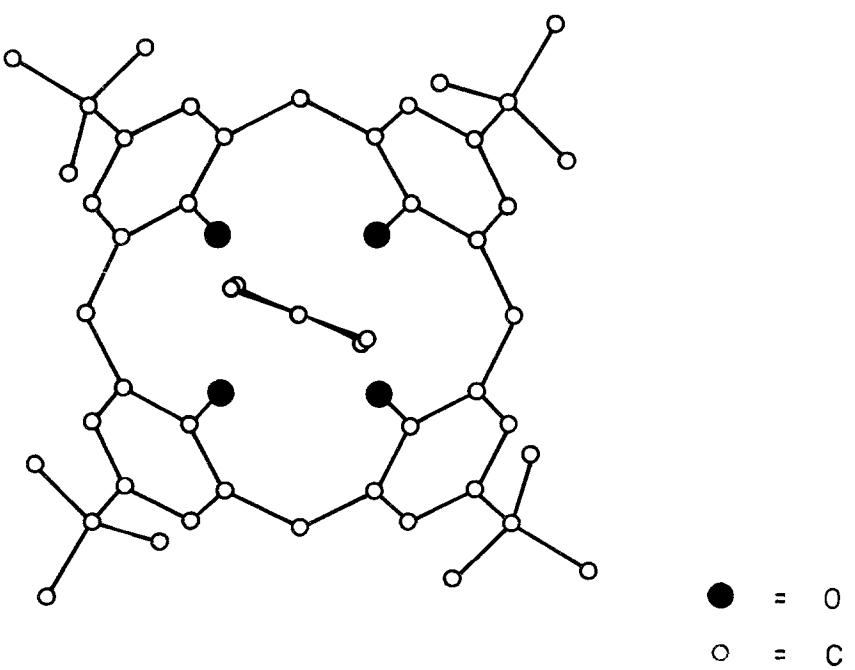


Fig. 6. The inclusion of *toluene* in the molecular cavity of the [4]calixarene **9a** [25].

Pentahydroxycalix[5]arene (**10**), a phenol-formaldehyde pentamer, forms a 1 : 2 adduct with *acetone*, in which one of the acetone molecules interacts from the outside with an interior OH group of the calixarene. There is also an interaction between the acetone molecules and the host cavity itself, by contacts between the guest CH_3- and the host phenylene groups. All in all, it resembles a crystal lattice inclusion, a clathrate [27].

2.3. DICHLOROMETHANE AS GUEST IN BRIDGED CALIXARENE DERIVATIVES

Dichloromethane is embedded in the crystal lattice of the additionally bridged calixarene **11** [28]. In Figure 7c, dichloromethane is viewed perpendicular to the plane of the calixarene ring. Figure 7b shows a section of the crystal lattice with the dichloromethane molecules situated over the molecular cavities.

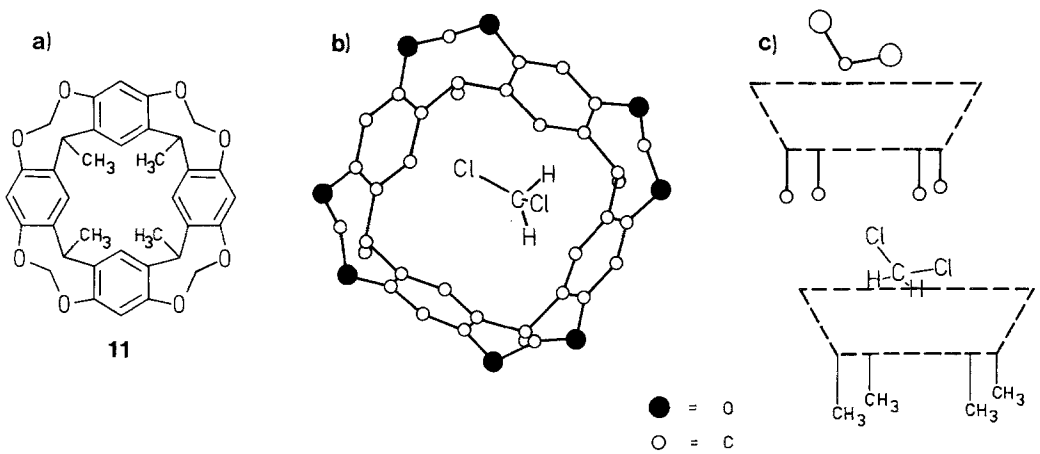


Fig. 7. (a) Formula of the host **11**, (b) a section showing *dichloromethane* encapsulated in the crystal, (c) dichloromethane as guest in the host **11**, as viewed perpendicular to the plane of the calixarene [29].

2.4. DIOXANE AND CHLOROFORM AS GUESTS IN TETRAAZA[3.3.3.3]CYCLOPHANES

Dioxane complex of 12: The 28-membered tetraazacyclophane **12** forms solvates with *benzene* and 1,4-*dioxane* [30]. An X-ray analysis was obtained from the latter [31] revealing that the dioxane is embedded in the saucer-shaped cavity of the host as seen in Figure 8.

The host molecules are layered in a saucer-like fashion (Figure 8). All the aromatic host rings are turned approximately 28° toward the crystallographic twofold axis, which goes through the center of the macrocycle. The molecular package consists of a 'continuous' channel which has maximum and minimum diameters of 7.4 and 4.4 Å, respectively (compare the van der Waals surfaces in Figure 8). The cavities, in which the dioxane is squeezed between two host molecules, are larger than needed in order to hold a guest molecule. In each cavity, therefore, the guest possesses a slightly different orientation.

Chloroform complex of 12: It seems as if host **12** can also selectively enclose chloroform and dichloromethane. Apparently, van der Waals interactions play a role. No inclusion can be observed for less well fitting molecules, for example, 2-methylbutanol. In this case, the host compound crystallized free of solvent molecules.

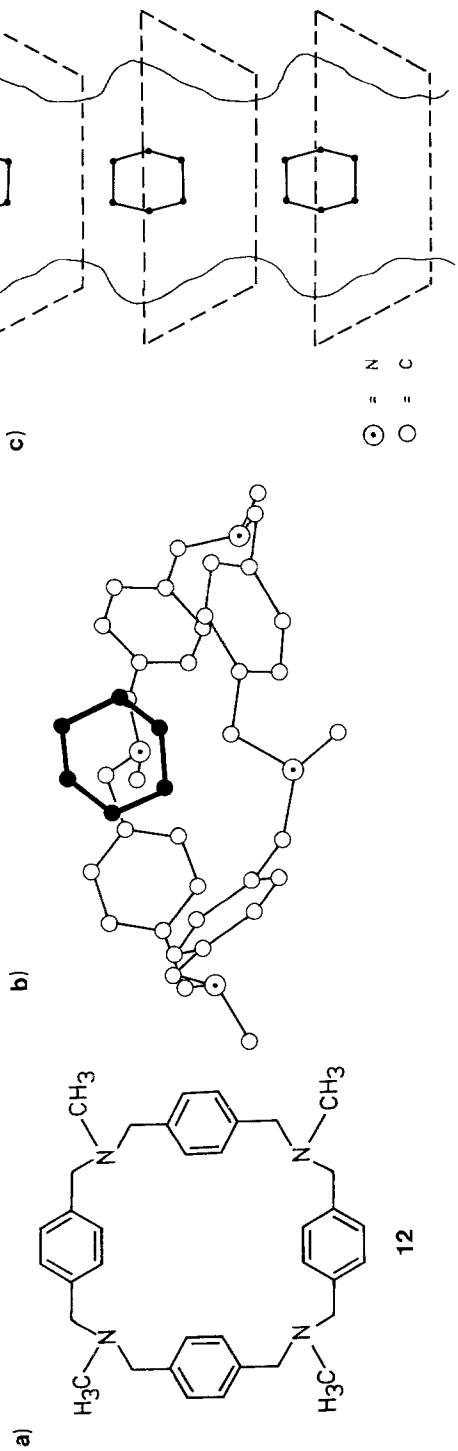


Fig. 8. (a) Host structure **12**, (b) host dioxane-guest arrangement (dioxane atoms disordered), (c) the channel structure of the layered host molecule **12** with embedded *dioxane* guest molecules [31].

The host molecules form a square cavity, flanked by four benzene ring 'walls', in the 'all-face' conformation, perpendicular to the large ring plane. The benzene rings are not distorted but planar as electronic spectra show. According to NMR spectra, they appear to rotate freely. However, in the crystal packing interactions between **12**-molecules also seem to be important (see Figure 9).

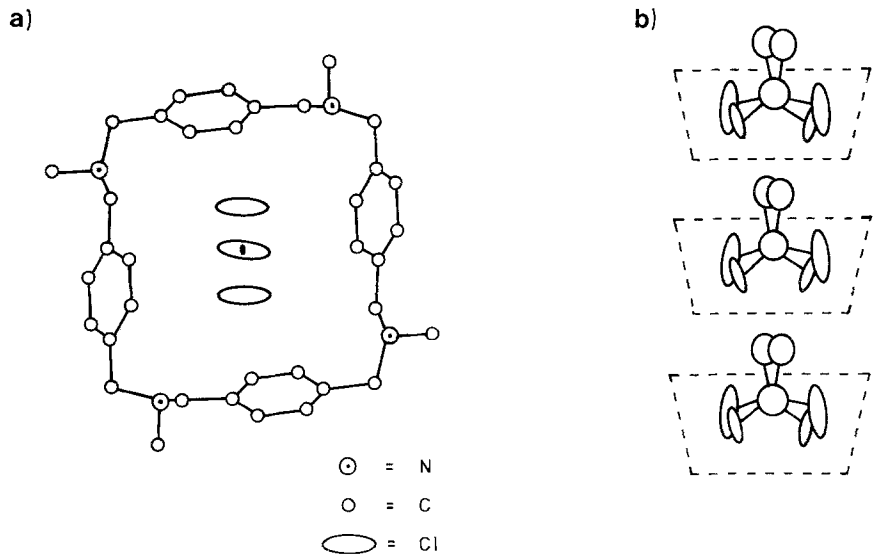
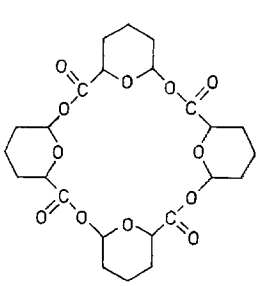


Fig. 9. X-ray structure of the $CHCl_3$ complex of **12**. (a) With molecularly encapsulated guest, and (b) the order of the guest-'filled' host molecules in the crystal lattice [20].

2.5. ACETONITRILE AND ACETONE AS GUESTS IN OLIGOLACTONES

Acetonitrile complex of tetralactone **13**: The optically active 20-membered tetralactone **13** of 6,8-dioxabicyclo[3.2]octane-7-one, and the 25-membered pentalactone **14**, form molecular inclusions with various guest molecules. The guest molecule lies closer to the center of the host cavity than in the above mentioned dioxane adduct. The tetramer binds *acetonitrile* as shown in Figure 10, derived from X-ray analysis. The 20-membered ring of tetralactone **13**



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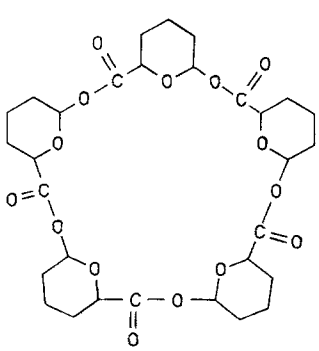

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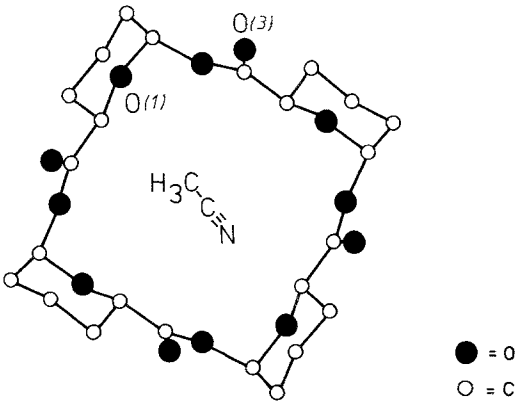


Fig. 10. X-ray structure of the *acetonitrile* complex of the cyclic tetraester **13** [32].

is approximately square, with an inner diameter of approximately 5.9 Å. The four carbonyl bonds lie almost parallel to the fourfold axis perpendicular to the ring plane. The host molecule is therefore strongly polar in the direction of this axis. Evidently, this polarity is compensated by dipole-dipole interactions of the CN-triple bond of the enclosed solvent molecule. The acetonitrile is tucked so deeply into the host cavity that the nitrile carbon atom is found approximately 0.16 Å below the mean plane of the four carbonyl atoms. The average distance between the carbonyl carbon and nitrile nitrogen atoms is approximately 3.3(39) Å, whereas between the carbonyl oxygen and nitrile carbon atoms the distance is approximately 3.5(64) Å.

Acetone complex of the pentalactone **14**: The cyclic pentaester **14** was prepared from the optically active and from the racemic 6,8-dioxabicyclo[3.2.1]octane-7-one. The crystal structure of the 1 : 1 complex with *acetonitrile*, and with *acetone* was elucidated by X-ray analysis [33]. In the cavity, the solvent molecules are arranged in such a way that the dipole moments lie opposite to the ones of the pentalactone molecule, although, this antiparallel order of dipole is not as perfect as in the above mentioned acetonitrile complex of tetralactone **13**. Figures 11a and 11b show the acetonitrile and the acetone complex of the pentalactone, as seen along the fivefold axis.

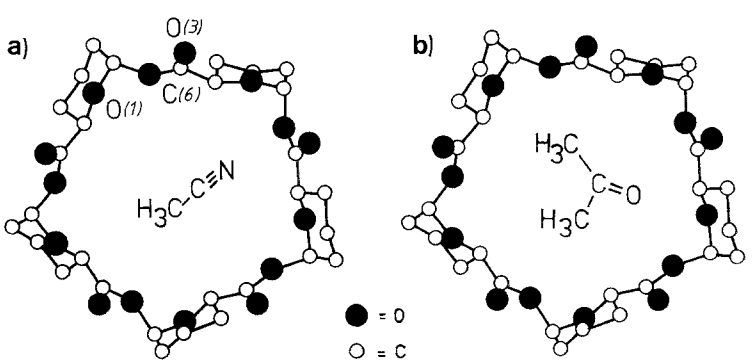


Fig. 11. X-ray structure (a) of the *acetonitrile*, and (b) of the *acetone* inclusion in the cyclic pentaester **14**.

The cyclic pentaester **14** has a C_5 symmetry with both the 20-membered and the 25-membered ring being rather rigid. The radius of the molecular cavity is approximately 4.13 Å. When considering the van der Waals radii of the methylene groups, the actual radius of the pentamer cavity is 2.13 Å. The corresponding radius of the tetralactone is only 0.96 Å.

Instead of being located in the center of the molecular cavity, the figures show the encapsulated solvent molecules turned outward from the fivefold axis. The nitrile bond of the acetonitrile is tilted 41° towards this axis, and the carbonyl bonds of the acetone are twisted outward at 29.5° from the fivefold axis to the outside of the ring.

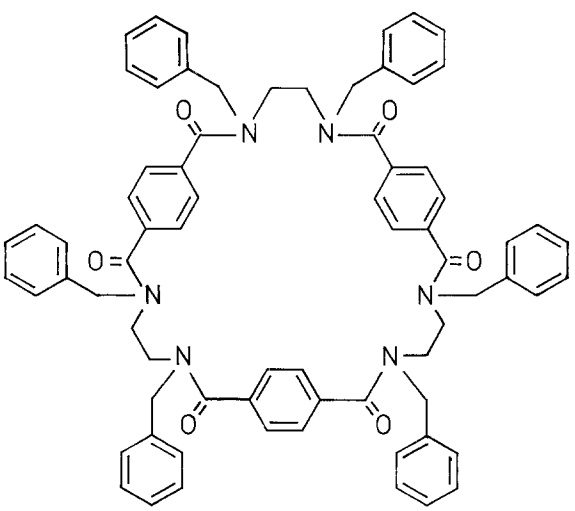
In the case of the tetramer **13** the angle is only 82°. The spatial shifting of the guest within the host is probably mainly caused by van der Waals interactions with adjacent molecules. The nitrile nitrogen in the acetonitrile pentalactone complex lies 0.3 Å above the mean plane of the O(1) oxygens, and the nitrile carbon atom is found 0.03 Å below the mean plane of the O(3) oxygen atoms.

X-ray analyses show that even though the tetra- and pentalactone have different sized cavities, they clasp the same solvent molecules, without altering their conformation. This seems to be caused by the rigidness of the host rings. Apparently, the polarity of the host molecule is also of importance.

2.6. CHLOROFORM AND BROMOFORM AS GUESTS IN A [6.6.6]CYCLOPHANE-HEXALACTAM

A selective encapsulation, also orientating the *chloroform* guest molecule in the molecular cavity, was achieved by the 30-membered hexalactam host **15**. The host molecule **15** can easily be prepared in gram amounts from terephthaloyl chloride and substituted ethylenediamines [34]. When chromatographing with chloroform, the latter remains complexed within the host, even when a recrystallization from ethyl acetate follows and it is dried *in vacuo*.

The solvent-free host **15** can be obtained by avoiding chloroform as a solvent or as an eluent, and using dichloromethane or benzene instead, for they are not encapsulated by the host. The encapsulation is selective. Until now, other than chloroform and *deuteriochloroform*,



15

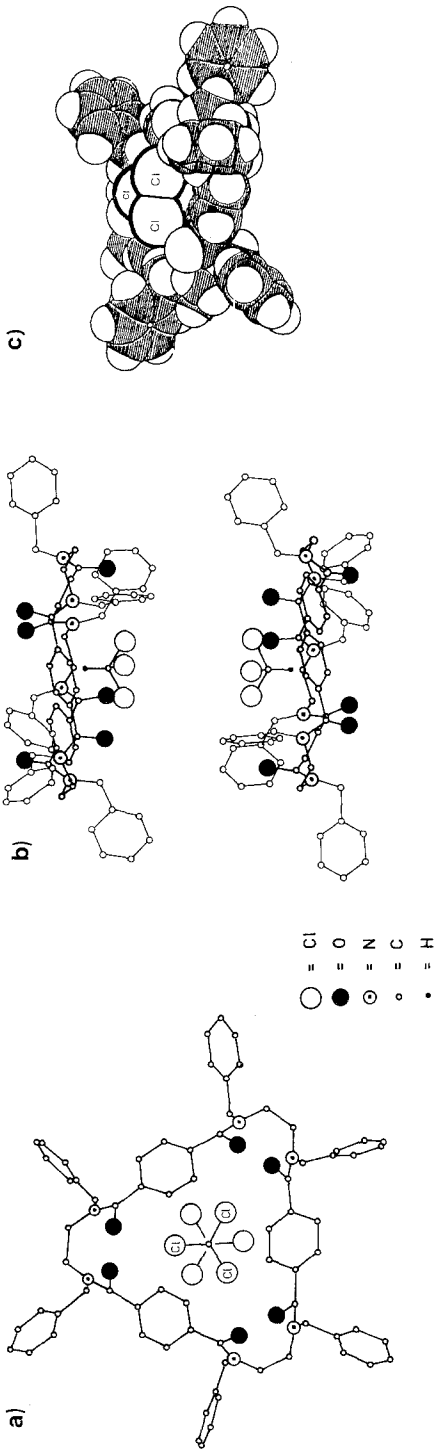


Fig. 12. Embedding of chloroform in the cavity of host **15**: (a) as viewed along the threefold axis, (b) side view of the arrangement of two host and two guest molecules in the lattice, (c) perspective view of a space-filling model [35].

only a few guest molecules such as *bromoform*, *chloral tetrachloromethane*, *halothane*, *acetone* and *trichloroacetonitrile* have been found to form adducts. The structures of the latter have not been reported as yet.

The chloroform is fixed in the molecular cavity, in such a way that the shortest distance between the chloroform hydrogen and the mean plane of the 30-membered ring is only 0.83 Å, as seen in Figure 12. The chloroform guest fits in a niche of the host, the CH group projecting into the center of the cavity, exactly coaxial to the threefold axis of the host structure. The two chloroform guest molecules, situated in between two host molecules, are found in an intermolecularly staggered order. The 1,4-phenylene units of the host molecules are turned at an angle of 17° towards a plane perpendicular to the threefold axis. A key and lock type of spatial complementary order can be assumed from the space-filling model. This host therefore can be regarded as a simple synthetic receptor model.

A structure analogous to the chloroform complex was found for the less stable bromoform encapsulation (Figure 13), although, in this complex the $HCBr_3$ seems to be more strongly disoriented.

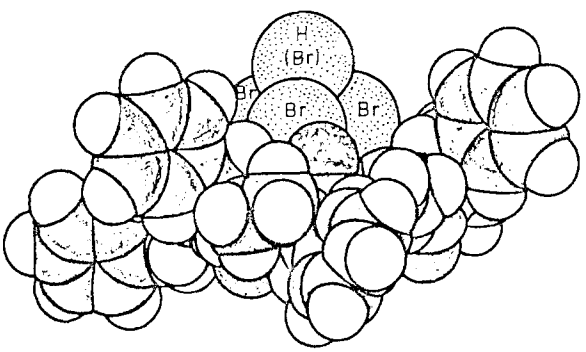


Fig. 13. *Bromoform* complex of the host **15** [36].

2.7. METHANOL AS GUEST IN A PYRIDINO CROWN CAVITY

A unique host/guest order is found for the *methanol* complex of tribenzopyridino crown **16**, prepared by recrystallization from methanol [37]. In this case, methanol is connected to the pyridino nitrogen atoms by almost linear OH · · · N hydrogen bonds (cf. Figure 14). Another feature of this complex is that the methyl group is turned into the tube-shaped niche of the host cavity. This is probably the first example of neutral guest complexation, oriented and fixed in a molecular cavity niche by hydrogen bonds.

The high selectivity of this host for short linear alcohols (methanol, ethanol) can be explained by the host/guest arrangement: branched alcohols would protrude out of the cavity niche and would interfere spatially. The same applies for longer chain alcohols, which cannot be complexed. In contrast to the inclusion of non-hydrogen bonded guest molecules, this type of complexation is also observed in solution. When complexing alcohols the conformation of the crown host structure seems to change significantly. Figure 15 shows the structure of the uncomplexed host molecule **16** in the crystal [38]: Pyridino crowns, similar to **17** and **18**, also form selective complexes with several alcohols [39]. Structural investigations are continuing. It may be assumed that they have a similar hydrogen bond fixed arrangement as shown by the methanol complex of **16**. This host thus displays two different neutral host/neutral guest

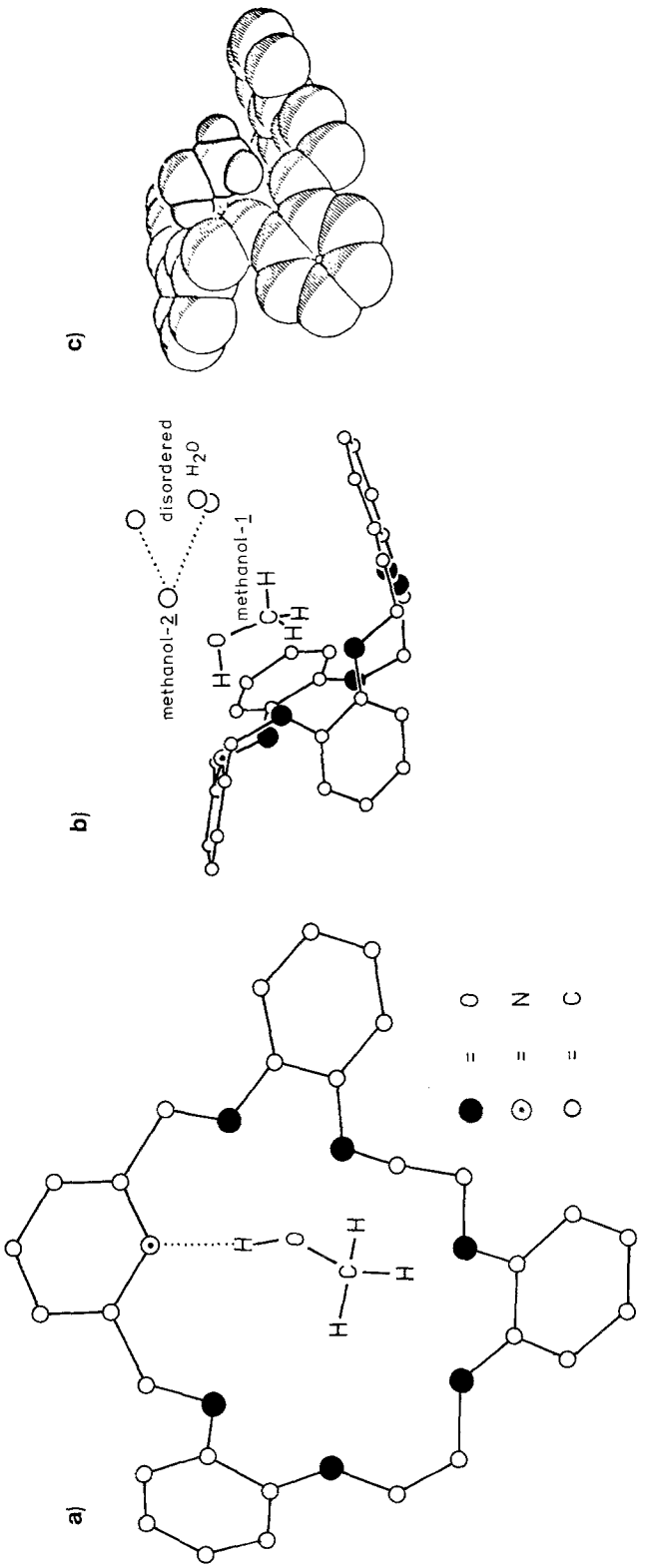
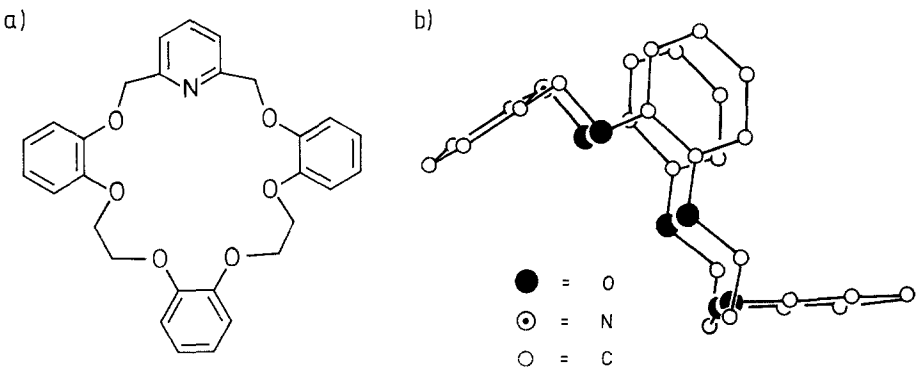


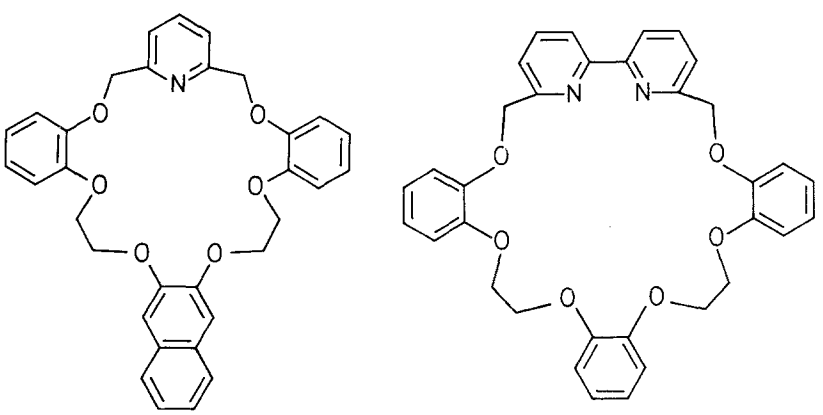
Fig. 14. Structure of the methanol complex of **16** [38]: (a) View approx. perpendicular to the crown ring, (b) side view, (c) space filling model.



16

Fig. 15. Structure of the guest-free host **16** [38].

complexation mechanisms symmetrically and spatially complementary oriented, with the chloroform inclusion, and the hydrogen bonded, fixed methanol encapsulation. In the future, these construction principles should be combined. For other low molecular weight neutral guests, both the key and lock type and also the directed highly selective hydrogen bonded host/guest interactions could be designed accordingly.



17 18

3. Conclusions and Outlook

In addition to cyclodextrin inclusions more examples are now known in which neutral guest molecules are encapsulated by synthetic neutral host molecules, the structures of which have been confirmed by X-ray analyses.

Hints may be derived from these studies as to how neutral guest/neutral host inclusions might be designed in the future: It seems necessary to construct sufficiently rigid cavities, shaped as funnels as in cyclodextrins, or better still, having cup or even tube or basket forms. The cavities should not collapse in solution, but must be held open by spacer units. The cavity

diameter should allow common neutral molecules to be enclosed. This means that a macro ring of about 20–40 ring members is favourable. The cavity should be surrounded by a 'wall', guarding the guest molecule sterically. It would also be practical for the host substances to be water-soluble or water/alcohol- or water/acetone-soluble [40]. Therefore, the host has to contain crown ether or oligo amide (or ionic) structural units or several polar functional groups. No doubt, in the near future a number of neutral molecular ligands (molecular wrappers) will be synthesized, opening a large non-classical field in the framework of bioorganic and biomimetic chemistry. Some day, when the tailoring of host/guest complexes of the receptor model type will be more efficient then the fixing of functionalized side arms and the use of chiral receptor- and enzyme models can be utilized. These should then be applicable as organic catalysts for chemical reactions, including asymmetric syntheses.

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