Journal of Inclusion Phenomena and Macrocyclic Chemistry **43:** 239–246, 2002.

A New Functional Cyclophane Host. Synthesis, Complex Formation and Crystal Structures of Three Inclusion Compounds *

EDWIN WEBER**, CORNELIA HELBIG and WILHELM SEICHTER
Institut für Organische Chemie der Technischen Universität Bergakademie Freiberg, Leipziger Straße 29, D-09596 Freiberg/Sachsen, Germany

MÁTYÁS CZUGLER
Central Research Institute of Chemistry, Hungarian Academy of Sciences, P.O.B. 17, H-1525 Budapest, Hungary

(Received: 30 November 2001; in final form: 17 May 2002)

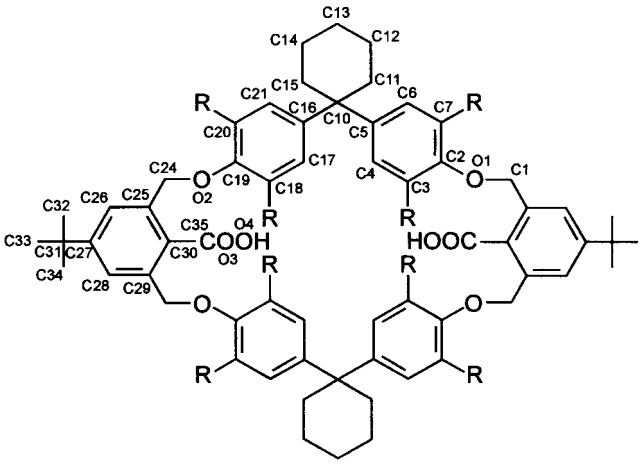
Key words: host–guest chemistry, crystalline inclusion compounds, host macrocycle, X-ray structure determination, hydrogen bonding

Abstract

A new macrocyclic host compound **2** having an octamethyl substituted cyclophane structure with two intra-annular carboxylic acid functions has been synthesized. The properties of crystalline inclusion formation are studied and X-ray crystal structures of three inclusion complexes including acetic acid, propionic acid and acetone as the guest molecules are reported. Inter-host channel formation with complexed guest molecules accommodated into the channels are typical features of the acetic acid and acetone 1 : 4 (host : guest) stoichiometric complexes being also hydrated species, while the propionic acid 1 : 2 complex is of the close packing type containing no additional water molecules. Systems of hydrogen bonds involving the host and guest functional groups are common to all structures. In the case of the acetic acid inclusion compound, a complex supramolecular hydrogen-bonded array comprising a bordering tricyclic assembly of eight molecular species exists.

Introduction

Macrocyclic host compounds [1] are of persistent interest in supramolecular chemistry [2, 3]. Apart from crown ethers and cryptands [4], cyclophane-type macrocycles [5] are exponents of this compound class. Their host frameworks are distinguished by a rather rigid cavity structure arising from the assembly of aromatic groups such as an angular diphenylmethane or an analogous building block [6, 7]. Cyclophanes are versatile host compounds represented by a great many structures in which the guest is either entrapped in the cyclophane cavity or is sandwiched between host molecules in the crystal lattice [5–8]. In this connection, the presence of a well fitting host cavity that is complementary with regard to the size, the shape and the functionalities of the guest molecule is of particular importance [9]. Such a promising case featuring a preorganized cyclophane structure with two endo carboxylic groups, host compound **1** (Scheme 1), has recently been described by us [10]. This host forms a number of inclusion compounds which among other things exhibit remarkable structures that show the carboxylic groups bound to the guest molecules in an endo mode of action (convergent binding) [10].



1 R = H
2 R = CH_3

2a = **2** · 4 (acetic acid) · 2 H_2O
2b = **2** · 2 (propionic acid)
2c = **2** · 4 (acetone) · H_2O

Scheme 1. Chemical structures including crystallographic labelling of the host atoms.

* **Supplementary Data** relevant to this publication have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications Nos. CCDC 174898–174900.

** Author for correspondence.

In order to further advance this particular design concept considering an optimized host cavity, e.g. by enlargement of the shielding spacer subunits, it was the obvious choice to introduce a number of methyl substituents. This prompted us to deal with the octamethyl substituted analogue of host compound **1**, which is macrocycle **2** (Scheme 1). We report the preparation and inclusion properties of the new macrocyclic compound **2**. We also describe the X-ray crystal structures of three inclusion complexes with acetic acid, propionic acid and acetone, as specified in Scheme 1.

Experimental

Apparatus and materials

Melting points were taken on a Kofler apparatus (Reichert, Wien). The ^{1}H-NMR spectra were recorded on a Bruker WM-300 (300 MHz) with Me_4Si as internal reference (δ values in ppm). Mass spectra were obtained with Kratos Concept 1H (FAB) and HP 59987A (EI) instruments. Microanalyses were carried out by the Microanalytical Laboratory of the Technical University Bergakademie Freiberg.

Reactions were monitored by thin-layer chromatography (TLC) carried out on Merck silica gel 60 F254 coated plates. Merck silica gel (particle size 63–100 μm) was used for column chromatography. All reagents were commercial products and were utilized without further purification. The solvents used were purified or dried by common literature procedures.

Methyl 2,6-Bis(bromomethyl)-4-tert-butylbenzoate (**3**) was prepared by NBS-bromination of methyl 4-tert-butyl-2,6-dimethylbenzoate as described [11].

Synthesis

*Preparation of 2,2-bis(4-hydroxy-3,5-dimethylphenyl)cyclohexane (**4**)*

Dimethyl sulfoxide (2 mL) was added to a cooled (15 °C) mixture of glacial acetic acid (160 g) and conc. sulfuric acid (150 g). At the same temperature and under stirring, a solution of 2,6-dimethylphenol (458.1 g, 3.75 mol) in cyclohexanone (73.6 g, 0.75 mol) was added dropwise during 30 min. Stirring was continued for 90 min. The mixture was poured onto water (2 L) and heated to 30 °C. The precipitate was collected, washed with water and suspended in water (1 L) containing sodium acetate (5 g). The suspension was heated to 90 °C, then cooled to 30 °C and filtered by suction. Recrystallization from chlorobenzene yielded 119.9 g (46%) of colourless crystals; m.p. 202–203 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.54 (m, 6 H, CH_2), 2.20 (m, 4 H, CH_2), 2.27 (s, 12 H, CH_3), 6.87 (s, 4 H Ar—H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 16.26, 22.99, 26.46, 37.39, 44.62, 122.31, 127.22, 140.60, 149.64 (9 C). *Anal. calcd.* for $C_{22}H_{28}O_2$: C 81.44; H 8.70. *Found*: 81.43; H 8.68.

*Preparation of dimethyl 5′, 28′-di-tert-butyl-12′, 16′, 20′, 22′, 35′, 39′, 43′, 45′-octamethyl-1′, 10′, 24′, 33′-tetraoxadispiro[cyclohexane-1, 17′([2](1,3)benzeno[2](1,4)benzeno [1][2] (1,3)benzeno[2](1,4)benzeno [1](1,4)benzenophane)-40′, 1″-cyclohexane]-8′, 31′-dicarboxylate (**5**)*

Under an atmosphere of argon, cesium carbonate (6.52 g, 20 mmol) and molecular sieve (5 g, 4 Å), both dried for 12 h at 200 °C, were suspended in dry acetone (1250 mL). The stirred suspension was heated to reflux, and a mixture of **3** (3.78 g, 10 mmol) and **4** (3.25 g, 10 mmol) in dry acetone (500 mL) was added dropwise during 8 h. After heating and stirring for an additional 4 h, the reaction mixture was cooled to room temperature and filtered. Evaporation of the solvent gave a yellow oily residue which was taken up in chloroform (50 mL) and thoroughly filtered through silica gel (6 cm × 10 cm^2). After removal of the solvent under reduced pressure, the oily residue was purified by column chromatography (SiO_2, eluent: dichloromethane). Recrystallization from acetone yielded 865 mg (16%) of colourless solid; m.p. >300 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 18 H, *t*-Bu), 1.49 (m, 12 H, CH_2), 2.05 (s, 24 H, CH_3), 2.17 (m, 8 H, CH_2), 2.40 (s, 6 H, OCH_3), 4.77 (s, 8 H, CH_2), 6.89 (s, 8 H, Ar—H), 7.71 (s, 4 H, Ar—H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 16.81, 22.82, 26.36, 31.11, 34.91, 36.42, 44.08, 50.58, 71.85, 126.25, 126.88, 128.56, 130.04, 135.53, 143.65, 153.49 (outset of splitting), 168.39 (18 C); EI-MS (*m/z*) 1081.6 $(M + H)^{\oplus}$. *Anal. Calcd.* for $C_{72}H_{88}O_8$: C 79.96; H 8.20. *Found*: C 79.65; H 8.09.

*Preparation of 5′, 28′-di-tert-butyl-12′, 16′, 20′, 22′, 35′, 39′, 43′, 45′-octamethyl-1′, 10′, 24′, 33′-tetraoxadispiro[cyclohexane-1, 17′([2](1,3)benzeno[2](1,4)benzeno[1](1,4)benzeno[2](1,3) benzeno[2](1,4)benzeno[1](1,4)benzenophane)-40′, 1″-cyclohexane]-8′, 31′-dicarboxylic acid (**2**)*

To a suspension of diester **5** (540.8 mg, 0.50 mmol) and a small amount (tip of a spatula) of 18-crown-6 in *n*-butanol (100 mL) was added a solution of KOH (900 mg, 16 mmol) in water (4 mL) and the mixture heated to reflux for 2 d. The solvent was evaporated, the solid residue suspended in hydrochloric acid (1 N, 50 mL) and stirred at room temperature for 1 h. The aqueous suspension was extracted three times with chloroform (25 mL). The combined organic layers were dried over Na_2SO_4 and the solvent evaporated. Recrystallization from acetone yielded 390 mg (74%) of colourless solid; m.p. >300 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 18 H, *t*-Bu), 1.45 (m, 12 H, CH_2), 1.76 (s, 24 H, CH_3 2.03), (m, 8 H, CH_2), 4.86 (s, 8 H, CH_2), 6.64 (s, 8 H, Ar—H), 7.72 (s, 4 H, Ar—H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 16.74, 23.00, 24.44, 31.07, 34.81, 36.83, 44.15, 71.70, 127.38, 129.96, 132.02, 134.05, 144.27, 151.59, 153.17, 172,57; FAB-MS (*m/z*) 1052.0 (M^+). *Anal. Cald.* For $C_{70}H_{84}O_8 \cdot 3H_2O$: C 75.92, H 8.19. *Found*: C 75.42, H 7.95.

Preparation of crystalline inclusion compounds

They were obtained by recrystallization from a saturated host solution in the respective guest solvent or by dissolving

Table 1. Crystalline inclusion compounds (host : guest stoichiometric ratios) of **2**

Guest solvent	Host : guest
Methanol	1 : 2
Ethanol	1 : 2
Acetic acid	1 : 4
Propionic acid	1 : 2
Dimethyl sulfoxide	1 : 2
Acetone	1 : 4
Benzoquinone	1 : 1
1,4-Diazabicyclo[2.2.2]octane (DABCO)	1 : 1
Chlorobenzene	1 : 1
Toluene	1 : 1
Benzene	1 : 1
Cyclohexane	1 : 1

the host in chloroform and addition of the respective guest solvent, and slow cooling. The crystals which formed were collected by suction filtration and dried. The host : guest stoichiometric ratios were determined by ^{1}H-NMR integration. Data for each compound are given in Table 1.

X-ray structure determination

Details of data collection and those of the refinement procedure are given in Table 2. The crystals used for data collection were obtained by slow evaporation of solutions of **2** in the respective guest solvent. Crystals of the inclusion compounds were enclosed in glass capillaries to prevent decomposition and cooled.

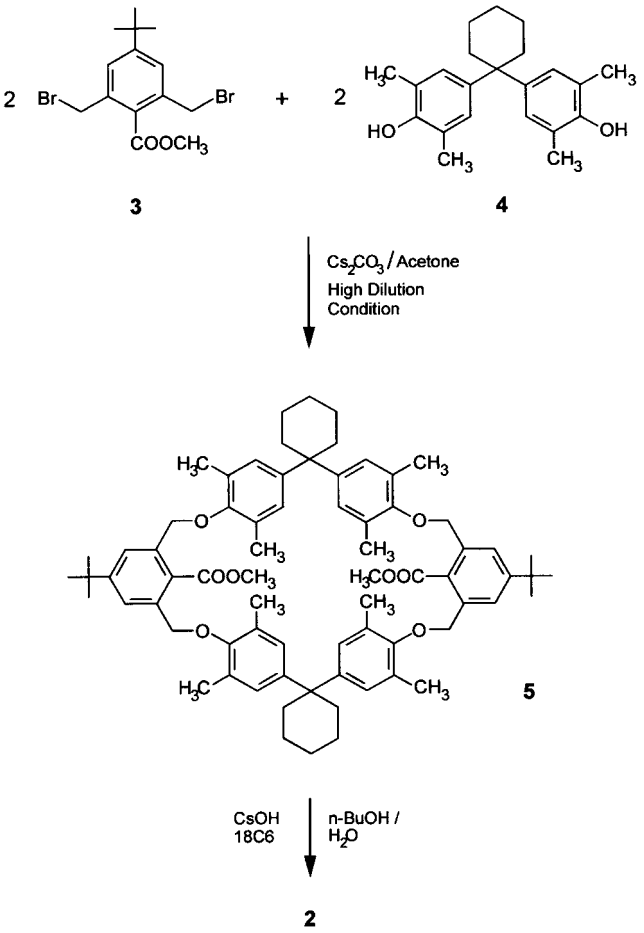
The intensity data, collected on a CAD-4 diffractometer (graphite monochromated CuK_α-radiation) were measured in the $\omega - 2\theta$ scan mode. Cell constants and orientation matrices were refined by least-squares fits of 25 reflections. Three standard reflections were measured after every hour showing no decay of the crystal during the data collection. Reflections were corrected for background Lorentz and polarization effects.

The crystal structures were solved by using direct methods [12] and difference Fourier synthesis and refined by full-matrix least squares [13]. All non-hydrogen atoms were refined anisotropically. The carboxylic and the water hydrogen atoms in **2a** were found on a differential Fourier map and refined in a "ride" mode. The positions of the water hydrogen atoms in **2c** could not be obtained from the difference Fourier map and were not considered in the model. The other hydrogen atoms were included in the models in calculated positions and were refined as constrained to bonding atoms.

Results and discussion

Host synthesis and inclusion

The synthesis of the present host compound (**2**) based on 2,6-disubstituted benzoic acid and a diphenylmethane analogous building block follows a design strategy (Scheme 2) which



Scheme 2. Synthesis of the host compound.

has previously proved to be successful in the formation of new cyclophane receptors [10]. The key step of the synthesis is the ring closure reaction of bis-benzylic dibromide **3** [11] with diphenol **4**, prepared by condensation of cyclohexanone and 2,6-dimethylphenol [14], to give the macrocyclic ester **5**. By analogy with previous findings [10], hydrolysis of the ester to yield the target molecule **2** turned out best in the solvent/base system *n*-butanol, H_2O/cesium hydroxide. Nevertheless, the addition of a small amount of 18-crown-6 also turned out to be necessary here, pointing to a steric shielding of the ester groups.

As could be expected from previous results [10], crystalline inclusion compounds of **2** are very likely to be formed, in particular with dipolar protic solvents such as alcohols. Actually this behavior of **2** is true (Table 1). In accordance with the parent compound **1**, **2** yields complexes with methanol and ethanol that have the same 1 : 2 (host : guest) stoichiometric ratio, suggesting a similar structure of both types of complexes [10]. Moreover, **2** forms inclusion compounds with a great number of other guests including dipolar aprotic, aromatic and even the apolar compound cyclohexane indicating rather high efficiency of **2** as host (Table 1).

A remarkable fact regarding the series of compounds is that the apolar and lower polar guests yield inclusion compounds with 1 : 1 (host : guest) stoichiometric ratio, while the

Table 2. Summary of crystallographic parameters of **2a**, **2b** and **2c**

Compound	**2a**	**2b**	**2c**
Formula	$C_{70}H_{84}O_8 \cdot 4C_2H_4H_4O_2 \cdot 2H_2O$	$C_{70}H_{84}O_8 \cdot 2C_3H_6O_2$	$C_{70}H_{84}O_8 \cdot 4C_3H_6O \cdot H_2O$
Molar mass	1329.61	1201.53	1303.70
Crystal system, space group	Triclinic, P-1	Triclinic, P-1	Triclinic, P-1
Unit cell dimensions			
a (Å)	10.511(3)	11.1313)	10.199(3)
b (Å)	11.902(3)	11.449(3)	12.087(3)
c (Å)	15314(3)	13.223(3)	15.598(3)
α (deg)	74.10(3)	81.05(3)	95.82(2)
β (deg)	81.50(3)	86.96(3)	98.99(2
γ (deg)	80.88	83.46(3)	100.62(2)
V (Å)	1808.2(8)	1652.7(7)	1853.5(8)
Z	1	1	1
D_{calc} (g cm^{-1})	1.221	1.207	1.168
μ (mm^{-1})	0.694	0.638	0.474
$F(000)$	716	648	706
Data collection			
Radiation (Å)	1.5418	1.5418	1.5418
Temperature (K)	293(2)	183(2	183(2)
Approximate crystal size (mm)	0.2 · 0.15 · 0.15	0.2 · 0.2 · 0.2	0.15 · 0.15 · 0.15
No. of collected reflections	7302	8259	8183
within the θ-limit (deg)	3.0–74.7	3.4–76.0	2.9–74.9
No. of unique reflections	6884	6801	7086
Refinement calculations full-matrix least-squares based on all F^2 values			
No. of refined parameters	441	399	505
$R_1 = \Sigma\|\Delta F\|/\Sigma\|F_0\|$	0.0871	0.0883	0.0745
No. of F values used [$I > 2\sigma(I)$]	2853	3495	4187
wR on F^2	0.1781	0.2218	0.1888
S (= Goodness of fit on F^2)	1.038	1.097	1.028
Min., max. residual electron density (e Å^{-3})	0.31/−0.33	0.47/−0.44	0.36/−0.47

polar and protic ones lead to 1 : 2 stoichiometric ratio, and in the case of the inclusion compounds with acetic acid and acetone the ratio is no less than 1 : 4. As outlined in the introduction, the question arises whether or not complexation takes place inside the host cavity of **2** involving the carboxy groups as binding sites. This prompted us to study crystal structures, successfully performed for the inclusion compounds with acetic acid (**2a**), propionic acid (**2b**), and acetone (**2c**). It must be added that **2a** and **2c** are hydrated species with two and one water molecules, respectively, while **2b** refers to an unhydrated compound.

Structural studies

Molecular structures and packing arrangements of the three complexes **2a–2c** are illustrated in Figures 1–5. The numbering of the host atoms is shown in Scheme 1, and the parameters of hydrogen bond interaction are given in Table 3.

Inclusion compound **2a** *(***2** *· 4 acetic acid · 2H$_2$O)*

The molecular structure of **2** in **2a** (Figure 1) shows an elongated cavity of approximate dimensions 12.3 × 7.7 Å, being restricted by four of the eight methyl groups that project inside at a distance of 3.8 Å. This means that the cavity is partly filled by the methyl groups leaving insufficient space for the carboxylic groups to allow endo orientation. As a consequence, both the carboxylic functions take a clear exo orientation with reference to the plane of the macroring, projecting out at a 68° angle (divergent binding). The filling of the macrocyclic cavity is also a consequence of the distortion of the spacer elements with the two dimethyl substituted phenyl rings being nearly perpendicular to each other, giving rise to the methyl groups turned inward. In this conformation, the present macroring **2** corresponds with a respective host compound based on a benzophenone analogous spacer element [15], while the parent host macrocycle **1**, and another one, both lacking the methyl substituents, show the usual roof-like arrangement of the spacer unit in their inclusion compounds [10].

The packing of the host molecules is characteristic of a segregated columnar mode, leading to interstitial channels of approximate cross-section 14.4 × 6.7 Å with the carboxylic groups projecting into the channel space (Figure 2). Although, due to their exposure, the host functional groups are easy to access and dimerization is the common

Table 3. Distances (Å) and angles (deg) of hydrogen bond interactions

Atoms involved	Symmetry	Distances	Angle	
D-H · · · A		D · · · A	H · · · A	D-H · · · A
2a				
O(1W)—H(1W1) · · · O(1G1)	$-x+1, -y+1, -z+1$	2.758(7)	1.787	159.0
O(4)—H(4) · · · O(1W)	$x, y+1, z$	2.668(7)	1.837	163.0
O(2G1)—H(2G1) · · · O(1W)	x, y, z	2.619(7)	1.835	162.5
O(2G2)—H(2G2) · · · O(2)	$x-1, y-1, z$	2.667(7)	1.792	145.6
C(1G3)—H(1G3) · · · O(3)	$x, 1+y, z$	3.473(7)	2.505	169.9
2b				
O(4)—H(4) · · · O(2G1)	x, y, z	2.670(6)	1.851	177.5
O(1G1)—H(1G1) · · · O(3)	x, y, z	2.634(5)	1.817	174.1
2c[a]				
O(4)—(H4) · · · O(1A)	$-x+1, -y+1, -z+1$	2.647(5)	1.825	164.0
O(1W) · · · O(3)	$x-1, y-1, z$	2.694(6)		
O(1W) · · · O(2b)	x, y, z	2.870(5)		

[a]Addition H bond contacts are likely to be present but cannot be specified because of missing H atom positions of the water molecule.

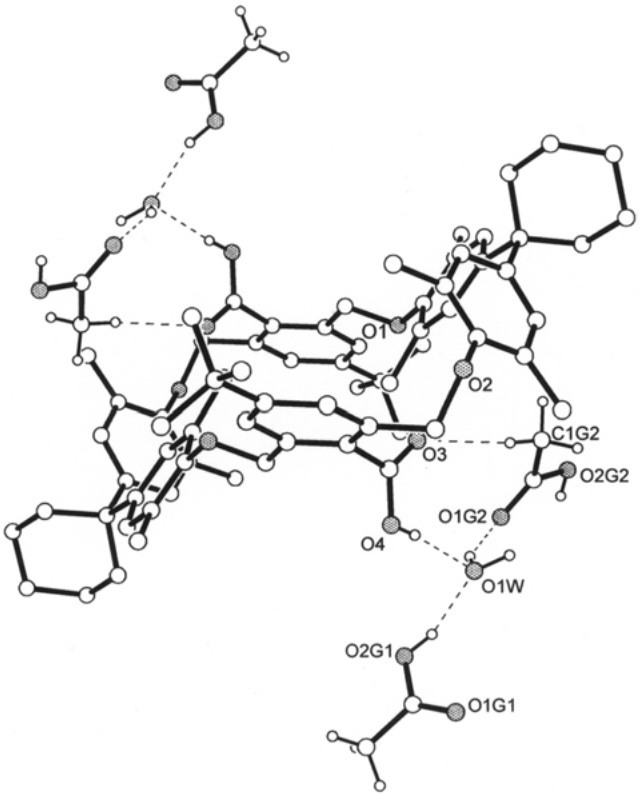


Figure 1. View of the molecular structure of **2a**. The oxygen atoms are shaded, and the hydrogen bond connections are shown by dashed lines. Non-relevant hydrogen atoms are omitted for clarity.

supramolecular interaction between carboxylic groups [16] not one such contact is seen in the packing structure. Instead of this, a 12-membered hydrogen-bonded ring composed of alternating acetic acid and water molecules (two of each) is found, being accommodated in the channel space. This mode of interaction is not an unknown property but is also realized in several inclusion complexes between bulky carboxylic hosts and alcoholic guests [17]. However, because of the double proton donorship of the water molecules compared to alcohol, there are two potential hydrogens not involved in the hydrogen-bonded ring. Each of these hydrogens is used for H-bonding of an additional molecule of acetic acid, contributing to another 10-membered hydrogen-bonded ring where the host carboxylic group is a component. In the formation of this latter ring, a C—H· · ·O contact [18] between a methyl-H of the acetic acid and the carbonyl oxygen of the host molecule is involved and the water oxygen is in a full H-donor and acceptor fashion linking the two H-bonded rings. Moreover, the carboxylic OH of the acetic acid contributing to the 10-membered ring is hydrogen-bonded to a benzylic oxygen of a second host molecule, thus acting as a bridge between hosts of different stacks. Altogether, the complex array of hydrogen bonds (Table 3) in this supramolecular structure comprises a bordering tricyclic assembly of eight molecular species, taking part with full capacity of hydrogen bonding.

Inclusion compound **2b** *(***2** · *2 propionic acid)*

Though **2b** also involves a carboxylic acid guest very comparable to **2a** (propionic instead of acetic acid), the host–guest relationships exhibited by **2a** and **2b** are completely different in that the mode of interaction between host and guest in **2a** is complex (see above), while it is the expected usual case in **2b**. Here, each of the host carboxylic groups binds to a guest carboxylic group forming a common hydrogen-bonded dimer [16] and giving the observed 1:2 host–guest stoichiometry (Figure 3) and Table 3.

The conformations of **2** in **2a** and **2b** are also different. In **2b**, the macrocycle is more flattened having cavity dimensions 2.3 × 11.9 Å. The torsional angle given by the atoms C(5)—C(10)—C(16)—C(17) and defining distortion of the two aromatic units contained in the spacer element is 45.2°. Consequently the carboxylic group functionalized aromatic rings also change conformation with reference to the mean plane of the macrocycle. The interplanar angle of 53.1° gives rise to the fact that the appended carboxylic groups neither take a distinct exo nor an endo orientation

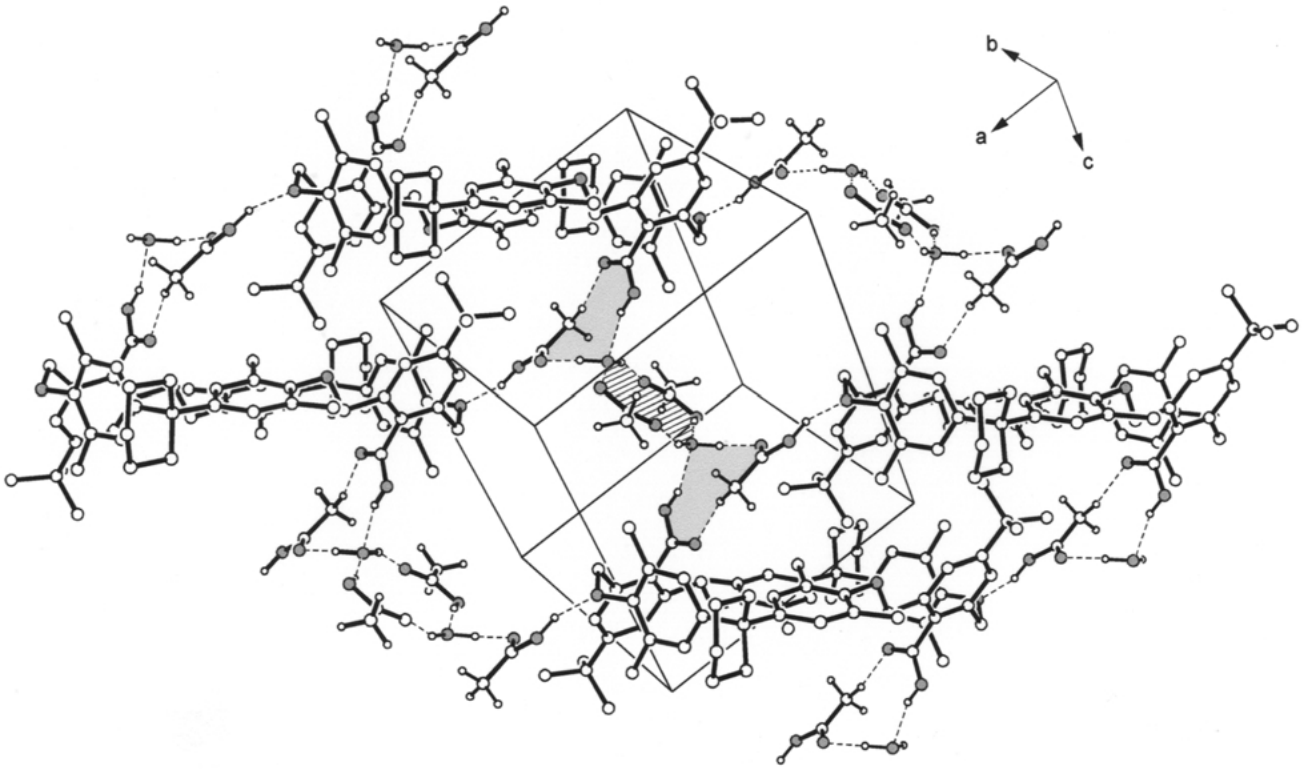


Figure 2. Packing diagram of **2a**. The oxygen atoms are shaded, and the hydrogen bond connections are shown by dashed lines. The tricyclic system of hydrogen bonds is indicated by the hatched and shaded regions. Non-relevant hydrogen atoms are omitted for clarity.

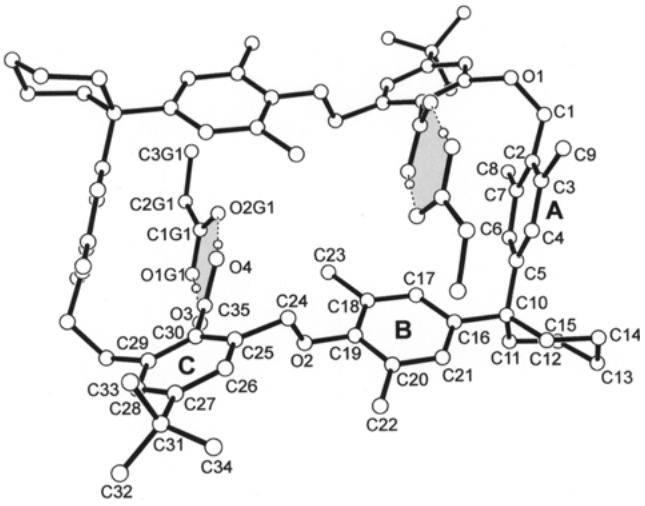


Figure 3. View of the molecular structure of **2b**. The hydrogen bond connections are shown by dashed lines, and the carboxylic group dimers are indicated by shading. Non-relevant hydrogen atoms are omitted for clarity.

(Figure 3). On the contrary, the eight-membered H-bonded rings formed from host and guest carboxylic groups are in a position nearly coplanar to aryl units A and almost orthogonal to aryl units B while being only moderately distorted against C. This arrangement affords a rather compact shape of the host–guest unit. Thus, this quasi-convergent binding enables dense package of the complex units with stacking along the b axis of the crystal lattice (Figure 4).

Inclusion compound **2c** *(***2** *· 4 acetone · H_2O)*

With reference to the conformational feature of the host macroring (cavity dimensions 12.4 × 8.1 Å), **2a** and **2c** (Figure 5) are nearly the same. This is a remarkable fact since the guest molecules involved (acetic acid in **2a** and acetone in **2c**) belong to different compound classes. While acetic acid is typical of a highly polar proton donor and acceptor, acetone is only a less polar proton acceptor but the sizes of the two molecules are about the same. Nevertheless, there are certain differences in the conformation of **2** in **2a** and **2c**, mostly relating to the orientation of the carboxylic group with reference to the aromatic unit being attached. In this particular point, compound **2c** is closer to **2b** than to **2a**. A potential reason may be seen in the different binding properties of the respective guests.

In the case of **2c**, determination of the host–guest interaction raises a problem since the acetone molecules are disordered and the hydrogen positions of the water molecule are missing. However, a potential system of hydrogen bonds involving the host carboxylic group, one of the acetone molecules and the water molecule seems likely while the other acetone species remains free of any specific productive interaction.

A columnar packing mode is also a characteristic feature of the crystal packing regarding compound **2c**. As for **2a** (Figure 2), this results in the formation of interstitial channels running along the crystallographic *b* axis. The channels show a cross-section of approximate dimensions 10.9 × 8.3 Å, thus being more circular than in **2a**. They include the guest molecules which are accommodated in a chain-like

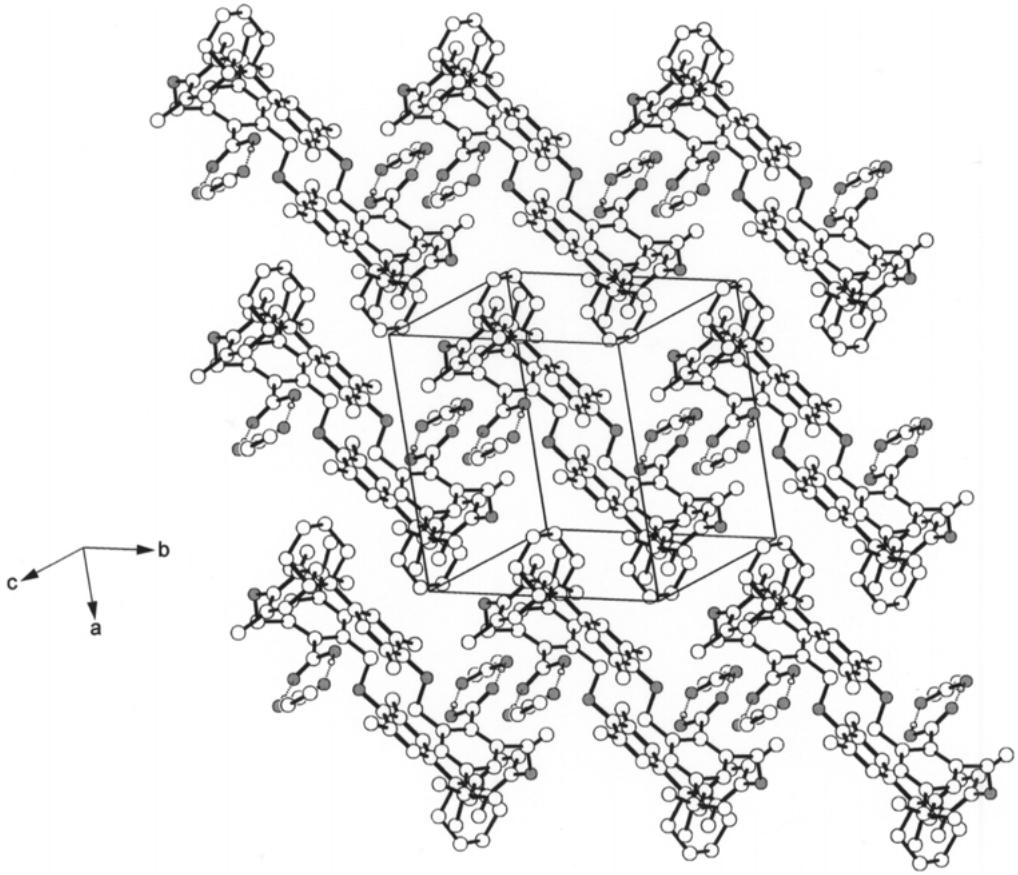


Figure 4. Packing diagram of **2b**. The oxygen atoms are shaded, and the hydrogen bond connections are shown by dashed lines. Non-relevant hydrogen atoms are omitted for clarity.

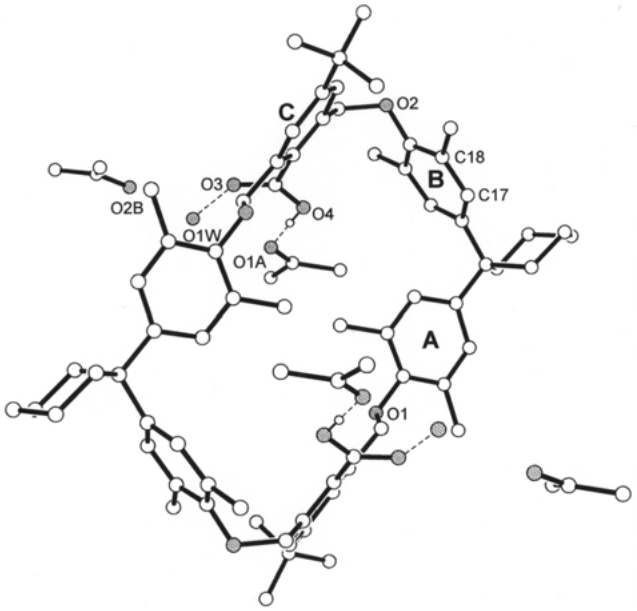


Figure 5. View of the molecular structure of **2c**. The oxygen atoms are shaded and the hydrogen bond connections are indicated by dashed lines. Non-relevant hydrogen atoms are omitted for clarity. Only one possible position of the disordered acetone molecule is shown.

fashion but the molecules forming the chain do not reveal specific interactions other than steric fit between each other. The similarity of the unit cell dimensions between **2a** and **2c** and a less dense packing of **2c** gives a rationale for the above logic.

Conclusions

A new functional cyclophane compound **2** being composed of two benzylic 4-tert-butylbenzoic acid building blocks and two tetramethyl-substituted 1,1-bis(oxyphenyl)cyclohexane bridging elements was prepared and its ability to form crystalline inclusion complexes was tested, showing that this new macrocycle acts as a rather efficient host compound for guest molecules of different compound classes such as small alcohols and carboxylic acids but also dipolar aprotic compounds or even apolar aromatic and aliphatic hydrocarbons. In this respect, host compound **2** is similar to the parent macrocycle **1** (Scheme 1) lacking the eight methyl substituents, but there are also marked differences between the two compounds [10]. The crystal structures of three different inclusion compounds of **2** show that the nature (acetic or propionic acid vs. acetone) and the size (acetic acid vs. propionic acid) of the guest molecules are of importance and have a decisive influence both on the host guest stoichiometric ratio and on the supramolecular structure of the inclusion crystals, although in no case of the studied compounds are the guests accommodated inside the macrocyclic cavity but occupy interstitial channels between the host molecules. This is certainly a consequence of the

methyl substituents partly filling the host cavity and pushing the carboxylic groups into exo orientation. Thus, unlike the parent compound **1** [10], the structurally modified analogue **2** is an exo rather than an endo receptor, demonstrating that relatively small alterations of the host structure may result in distinct changes of the host property.

In conclusion, future structural modifications based on this host design should allow for less conformational freedom of the macroring in order to stabilize a permanent host cavity having endo-convergent functional groups. Apart from this, investigation of the metal ion binding of **2**, as compared to **1** [19], using solvent extraction is also a promising challenge.

Acknowledgements

This work was financially supported by the Deutsche Forschungsgemeinschaft (WE 1016/5, FOR 335) and the Fonds der Chemischen Industrie.

References

1. B. Dietrich, P. Viout and J.-M. Lehn: *Macrocyclic Chemistry*, VCH, Weinheim (1993).
2. (a) J.W. Steed and J.L. Atwood: *Supramolecular Chemistry*, Wiley, Chichester (2000). (b) H.-J. Schneider and A. Yatsimirski: Principles and Methods in Supramolecular Chemistry, Wiley, Chichester (2000).
3. J.L. Atwood, J.E.D. Davies, D.D. MacNicol and F. Vögtle (eds.): *Comprehensive Supramolecular Chemistry*, Vols. 1–10, Elsevier, Oxford (1996).
4. (a) G.W. Gokel: *Crown Ethers and Cryptands, Monographs in Supramolecular Chemistry*, Vol. 3, The Royal Society of Chemistry, Cambridge (1991). (b) S. Patai and Z. Rappoport (eds.): *Crown Ethers and Analogs*, Wiley, Chichester (1989).
5. (a) F. Diederich: *Cyclophanes, Monographs in Supramolecular Chemistry*, Vol. 2, The Royal Society of Chemistry, Cambridge (1991). (b) F. Vögtle: *Cyclophane Chemistry*, Wiley, Chichester (1993).
6. F. Diederich: *Angew. Chem.* **100**, 372 (1988); *Angew. Chem. Int. Ed. Engl.* **27**, 362 (1988).
7. More recent examples: (a) S. Apel, S. Nitsche, K. Beketov, W. Seichter, J. Seidel and E. Weber: *J. Chem. Soc., Perkin Trans. 2*, 1212 (2001). (b) M. Nissinen, A.D. Cort, S. Amabile, L. Mandolini and K. Rissanen: *J. Incl. Phenom.* **39**, 229 (2001).
8. F. Vögtle (ed.): *Comprehensive Supramolecular Chemistry*, Vol. 2, Elsevier, Oxford (1996).
9. E. Weber, in J.J. Kroschwitz (ed.), *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th edn, suppl., Wiley, New York (1998), pp. 352.
10. E. Weber, R. Haase, R. Pollex and M. Czugler: *J. Prakt. Chem.* **341**, 274 (1999).
11. F.J. Urban, L.R. Chappel, A.E. Girard, B.L. Mylari and I.J. Pimblett: *J. Med. Chem.* **33**, 765 (1990).
12. G.M. Sheldrick: *SHELXS-86: Program for Crystal Structure Solution*, University of Göttingen, Germany (1986).
13. G.M. Sheldrick: *SHELXL-93: Program for the Refinement of Crystal Structures*, University of Göttingen, Germany (1993).
14. M.E. McGreal, V. Niederl and J.B. Niederl: *J. Am. Chem. Soc.* **61**, 345 (1939).
15. E. Weber, R. Pollex, and M. Czugler: *J. Org. Chem.* **57**, 4068 (1992).
16. G.R. Desiraju: *Angew. Chem.* **107**, 2541 (1995); *Angew. Chem. Int. Ed. Engl.* **34**, 2311 (1995).
17. (a) E. Weber: *J. Mol. Graphics* **7**, 12 (1989). (b) E. Weber: in D.D. MacNicol, F. Toda and F. Vögtle (eds.), *Comprehensive Supramolecular Chemistry*, Vol. 6, Elsevier, Oxford (1996), pp. 535.
18. G. Desiraju and T. Steiner: *The Weak Hydrogen Bond, IUCr Monographs on Crystallography*, Vol. 9, Oxford University Press, Oxford (1999).
19. K. Gloe, H. Stephan, O. Heitzsch, H. Bukowsky, E. Uhlemann, R. Pollex, and E. Weber: *J. Chem. Soc., Chem. Commun.* 1955 (1994).