A New Bis-cyclotribenzyl Cavitand capable of Selective Inclusion of Neutral Molecules in Solution. Crystal Structure of Its CH_2Cl_2 Cavitate

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The structure of a new bis-cyclotribenzyl cavitand, (**2**), forming an internal 1 : 1 complex ('cavitate') with dichloromethane, has been determined by single crystal *X*-ray crystallography.

Owing to the weakness of the interactions between uncharged, hydrophobic molecules, questions still arise whether entirely neutral and apolar hosts could be designed and synthesized with the ability of forming, in solution, stable internal complexes with neutral species, and, if so, how selectivity based on the size, shape or even chirality of such guests could effectively be achieved.[1]†

Recently we reported[2] the synthesis of a pair of racemic stereoisomeric cavitands (**2**) and (**3**), in which two differently substituted cyclotribenzyl sub-units are connected to one another by three $-OCH_2CH_2O-$ bridges.‡ These compounds were obtained by the intramolecular 'trimerization' of the veratryl residues of the racemic precursor (**1**), as shown in Scheme 1. The major isomer, isolated in *ca.* 25% yield, formed in solution a 1:1 internal complex with dichloromethane as revealed by ^1H n.m.r. spectroscopy.[2] The apparent stability constant of the CH_2Cl_2 complex was found to be $K_s = 1.8\,\text{M}^{-1}$ at 223 K in $CDCl_3$ solution. We have since extended these complexation experiments to other guests of the CH_2XY type, and observed the formation of similar 'cavitates' of this host with CH_2BrCl (K_s $0.9\,\text{M}^{-1}$) and CH_2Br_2 (K_s $0.15\,\text{M}^{-1}$). Thus, there is a remarkable, 12-fold difference between the stability constants of the dichloromethane and dibromomethane inclusion complexes.

Owing to the lack of chemical or spectroscopic evidence allowing us to distinguish between stereoisomers (**2**) and (**3**), we provisionally assigned structure (**2**) to the compound used in the complexation studies, by analogy with the known[5] stereochemical outcome of a similar synthesis starting from precursor (**4**) (Scheme 1); although two compounds, [D_3-, (**5**), and C_{3h}-, (**6**), structures] were expected from this reaction, only one was formed and unambiguously identified as (**5**). The structure of the major isomer obtained from precursor (**1**) has now been established to be (**2**) by a single crystal *X*-ray determination. Furthermore, this study revealed that the crystals, which were grown from dichloromethane, actually consisted of the 1 : 1 CH_2Cl_2 cavitate of (**2**). This is one of the first synthetic systems allowing a detailed investigation of the weak interactions between neutral host and guest molecules since the precise structural features of the 1 : 1 complex can be analysed in the crystal state, while the thermodynamics and kinetics of the inclusion–exclusion processes are, in principle, accessible from appropriate experiments in solution.

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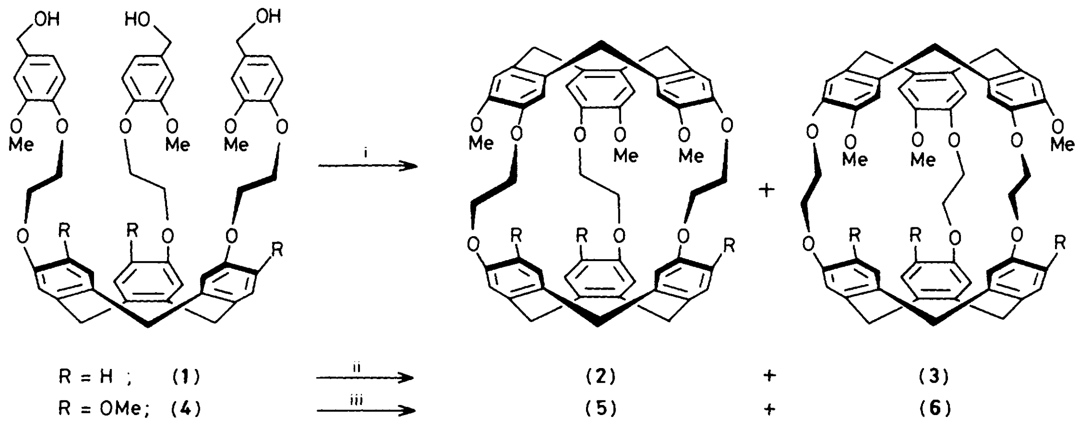
† With the exception of the cyclodextrins, which can accommodate uncharged organic molecules within their hydrophobic cavity in aqueous solvents, the formation of more or less specific associations of synthetic neutral hosts with neutral guests has only been observed in the crystal state, mainly as lattice inclusion compounds, rarely as molecular inclusion complexes. Even in the latter case, however, the binding of the partners is not strong enough to survive once the crystal has been destroyed by dissolution or melting (see ref. 1).

‡ Following Cram's and Lehn's proposals, we use the term 'cavitand' (ref. 3) for hosts containing enforced cavities, and 'speleand' (ref. 4) for those combining the elements of a rigid, lipophilic cavity with polar binding sites. Accordingly, compounds (**2**), (**3**), and (**5**) are typical cavitands, whereas examples of speleands are given in reference 4.



Scheme 1. *Reagents and products*: [only one enantiomer of (**1**)—(**5**) is shown, (**6**) is achiral]: i, HCO_2H, 90 °C, 30 min, or $HClO_4$ in AcOH, 20 °C, 5 h; ii, (**1**) yields a mixture of (**2**) (*ca.* 25%) and (**3**) (*ca.* 5%): iii, (**4**) only affords the D_3-isomer (**5**) (>80%).

Crystal data: the asymmetric unit consists of one (**2**)·CH_2Cl_2 inclusion complex with two additional dichloromethane molecules outside ($C_{51}H_{48}O_9·CH_2Cl_2·2CH_2Cl_2$), M = 1059.74, monoclinic, space group $P2_1/n$, a = 18.841(7), b = 15.943(6), c = 16.557(6) Å, β = 95.39°, Z = 4, D_c = 1.192 kg/dm³.§

The packing consists of alternate homochiral layers of the (+)- and (−)-enantiomers of host (**2**). The external dichloromethane molecules are accommodated in pairs in relatively large voids of the lattice, located at the centre of bipyramids made up of four hosts of like sign flanked on each side by one of opposite chirality.

The dichloromethane encaged in the host cavity shows no disorder, and is oriented in such a way that its Cl(1)–C–Cl(2) plane is roughly parallel to benzene rings α and β' of the cyclotribenzyl caps, with the CH_2 embedded in the niche of the upper cap [Figure 1(a)]. The distances between the chlorine atoms and the nearest phenyl rings are in the range 3.5—3.8 Å, close to the sum of the van der Waals radii. Owing to the lower symmetry of the guest, the trigonal symmetry of the host is only approximately preserved in the inclusion complex. To a first approximation, there remains a pseudo C_3-axis passing through the two caps, which are twisted from one another by *ca.* 52° as shown in Figure 1(b). The deviation from the exact C_3-symmetry is due to the $-OCH_2CH_2O-$ bridge between benzene rings α and α', which adopts a zig-zag conformation, whereas the other two (β-β' and γ-γ') exhibit the usual *gauche* conformation of ethylenedioxy chains. This relatively minor conformational change makes the α-α' bridge slightly longer (*ca.* 3.7 Å instead of 2.9 Å), enlarges the window between the bridges α-α' and β-β' to a maximum cross section of *ca.* 4.6 × 3.2 Å, and allows a better fit of the guest within the host cavity.

The three methoxy groups of the upper cap in Figure 1(a) are coplanar with the phenyl rings α, β, and γ to which they are

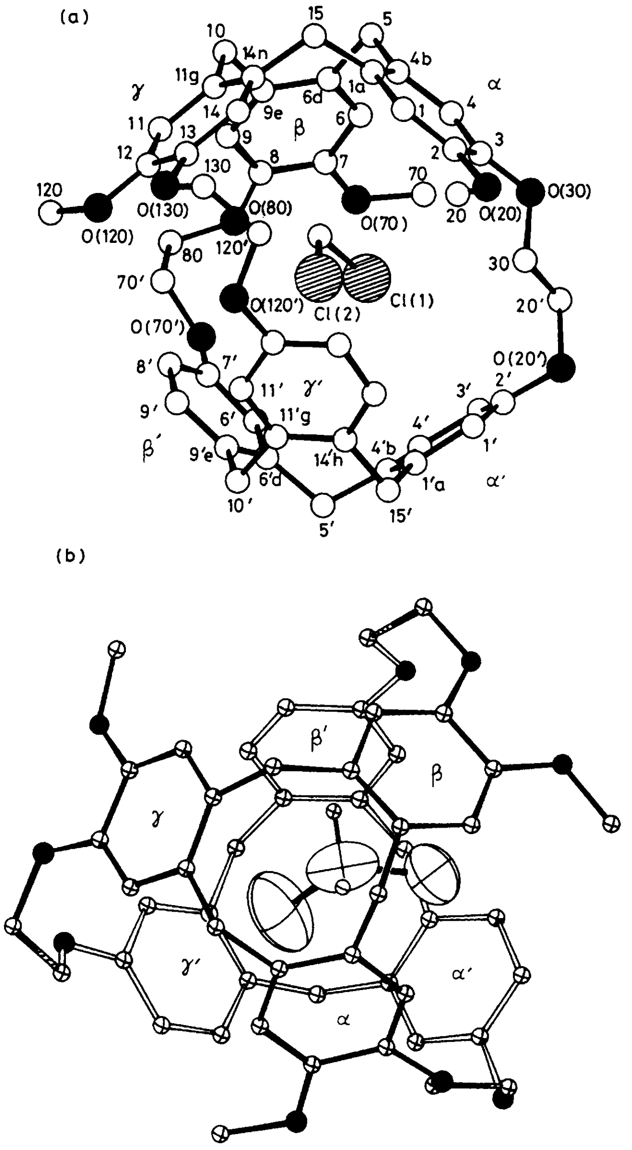


Figure 1. Structure of the (**2**)·CH_2Cl_2 cavitate; (a) view perpendicular to the pseudo C_3-axis and atom numbering; (b) view looking down the C_3-axis, with the 50% probability anisotropic thermal ellipsoids for the CH_2Cl_2 molecule (radii of the all other atoms are arbitrarily fixed).

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§ A total of 6045 independent reflections were collected on an automatic 4-circle diffractometer, of which 3592 were observed [$I > 3\sigma(I)$]. The structure was solved by direct methods (ref. 6) and the atomic co-ordinates and anisotropic thermal parameters were refined to an R value of 6.95%, using a large block least squares refinement program (ref. 7). All the hydrogen atoms have been located on a difference synthesis and included in the refinement with an arbitrarily fixed isotropic temperature factor.

The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

bound. A space-filling model based on the crystal state geometry of the complex shows that these substituents must play an important role in controlling the size of the windows and the trajectories allowing access to the cavity. These features might also explain why the related cavitand (**5**), in which the windows are narrower because of the three additional methoxy groups occupying positions 3′, 8′, and 13′, apparently does not form such cavitates with CH_2Cl_2 nor even with smaller molecules, although its cavity should be be a similar size to (**2**).

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