

Double Molecular Encapsulation of Tetrahydrofuran by an Amphiphilic Calix-[4]-arene

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Abstract

The crystal structure of *para*-octanoylcalix-[4]-arene:2 tetrahydrofuran complex reveals double inclusion of the guest molecules, one deep in the aromatic cavity and the other held in a four-fingered molecular hand formed by the aliphatic chains, the inclusion changes the molecular packing from a bilayer system in the absence of guest, to a head-to-tail antiparallel chain packing.

Introduction

Amphiphilic host–guest systems have seen wide application for the complexation of metal ions [1–3] and as sensors for gases [4–7] and small molecules [8, 9]. However few structures of such compounds are known, and no complexes with well-determined guest molecules have been studied. Amphiphilic cyclodextrins [10, 11], calixarenes [12] and calix-resorcinarenes [13] are capable of forming highly stable monodisperse colloidal suspensions. We have clearly demonstrated that such colloidal suspensions are composed of solid lipid nanoparticles (SLNs) [14]; the incorporation of these supramolecular SLNs into gels of pharmaceutical interest has been observed [15] as their interaction with proteins such as serum albumin [16], initial studies have shown that amphiphilic calix-[4]-arene based SLNs show no haemolytic activity [17]. One interesting feature of these supramolecular SLNs is their ability to encapsulate a wide variety of organic molecules with complexation ratios considerably higher than the 1:1 complexation observed for the parent non-amphiphilic molecule. Recently the incorporation of guests at two sites and even modification of the size and number of sites in amphiphilic calix-[4]-arene based SLNs has been demonstrated by ourselves using Xe NMR [18].

In this paper we report on the novel structure of *para*-octanoylcalix-[4]-arene, *I*, in the presence of tetrahydrofuran. The molecular structure in which two guest molecules are complexed, one within the calix cavity and the other held by the four aliphatic chains and the

molecular packing are novel and totally different from those of the molecule in the absence of guest [19].

Experimental

The chemical structure of *para*-octanoylcalix-[4]-arene, *I*, is given in Figure 1, the compound was synthesized as previously described [20].

Crystals of the title compound were grown by layering a tetrahydrofuran solution of *I* onto an aqueous phase and allowing solvent diffusion into the lower layer. This process simulates the solvent displacement method [12] used in the production of the SLNs. During the course of the slow crystal growth, the total time taken was approximately 3 months, there is initially formation of thin wide plates at the interface, followed by growth of the crystals of the title compound. The crystals form at the boundary of the solvents and can be isolated for analysis.

Crystallographic data

Intensity data for *I* were collected at 200 K on a Bruker SMART-APEX diffractometer using Mo_{K α} radiation ($\lambda = 0.7107 \text{ \AA}$). The data were corrected for Lorentz and polarization effects and for absorption using the SADABS (Siemens Industrial Automation, Inc. program). Structures were solved using direct methods and refined by full-matrix least-squares on $|F|^2$. All non-hydrogen atoms were refined anisotropically and hydrogen atoms were placed in geometrically calculated positions and refined with temperature factors 1.2 times those of their bonded atoms. All crystallographic calculations were conducted with the SHELXTL 5.1 program package.

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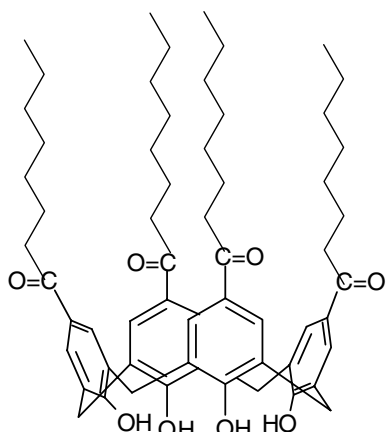


Figure 1. Molecular formula of *para*-octanoylcalix-[4]-arene

Crystal data for 1

Monoclinic, $P2(1)/n$, $a = 15.210(9)$, $b = 24.610(14)$, $c = 15.932(9)$, $\beta = 91.632(8)^\circ$, $V = 5961(6) \text{ \AA}^3$, $Z = 4$, $D_c = 1.192 \text{ g cm}^{-3}$, $\mu = 0.078 \text{ mm}^{-1}$, $F(000) = 2320$, $2\theta_{\text{max}} = 43.92^\circ$ ($-15 \leq h \leq 13$, $-24 \leq k \leq 25$, $-15 \leq l \leq 15$). Final residuals (for 707 parameters) were $R1 = 0.1279$ for 6394 reflections with $I > 2\sigma(I)$, and $R1 = 0.3361$, $wR2 = 0.3558$, $\text{GOF} = 0.986$ for all 16659 data. Residual electron density was 0.243 and $-0.227 \text{ e \AA}^{-3}$.

Results and discussion

The molecular structure of the complex is shown in Figure 2, and as can be seen two molecules of tetrahydrofuran are present. The first is deeply included in the calix-[4]-arene cavity with a vertical distance of ca. 4.0 \AA from the phenolic rim. $\text{C-H} \cdots \pi$ interactions between the guest and the aromatic rings range from 2.99 to 3.11 \AA , consistent with expected values [22] and

hydrophobic interactions between $\text{Csp}^3\text{-H}$ of the tetrahydrofuran and the acyl chain with $d(\text{C-H} \cdots \text{H-C}) = 2.20 \text{ \AA}$ sustain the inclusion. Encapsulation of a single tetrahydrofuran molecule in the *p-tert*-butyldihomooxacalix-[4]-arene has been previously reported with similar interactions [23].

The second guest molecule is held by the four hydrophobic acyl chains of 1 in the form of a 'molecular hand'. One chain acts as the thumb and projects linearly from the cavity with an angle of 95.5° formed by the alkyl chain and the axis of the corresponding aromatic ring whereas the other three chains curl around this guest molecule to hold it in place, as with a ball held in the hand. The shortest methylene-methylene distances are 2.17 \AA typical of tight van der Waals [24] packing distances between two hydrophobic hydrogen atoms [25].

Attempts have been made to enlarge the cavity of the calix-[4]-arene, either by covalent linking (the Venus flytrap molecule described by Atwood [26]) or by hydrogen bonding (4,4'-bipyridine bonded to the upper rim of a calix-resorcinarene as described by MacGillivray), in neither case was the inclusion of more than one guest observed [27].

The structure at the molecular level is further stabilised by a short oxygen-methylene contact of 3.93 \AA between the two tetrahydrofuran molecules. A search in the Cambridge Structural Database has revealed only one other calix structure in which a guest molecule is inserted between alkyl chains, that of *bis*(2,8,14,20-Tetrapentyl-4,6,16,18-tetrahydroxy-10,12,22,24-tetrakis(2-thiophenoyloxy) calix-[4]-arene where a BF_4^- anion is present [28], however, the chains are bent away from the guest reflecting either charge-hydrophobic repulsion or the typical dephasing between fluorinated systems and alkyl chains often observed in mixed monolayers [29–31]. Thus at the molecular level, the structure is totally different from the crystal system grown from acetone and recently

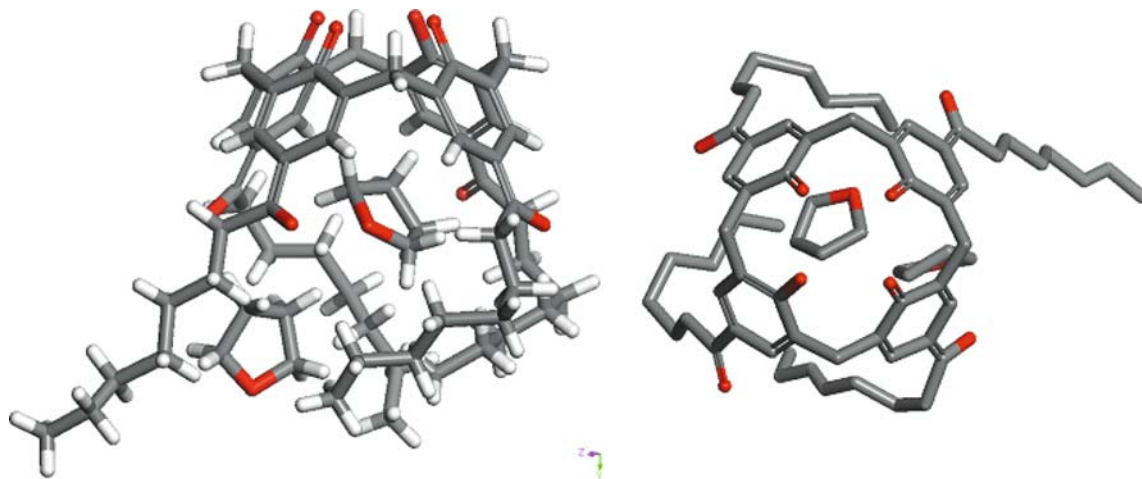


Figure 2. Crystal structure of the complex *para*-octanoylcalix-[4]-arene-2 tetrahydrofuran (left) and view down the rims of the calix-[4]-arene, H atoms are omitted for clarity (right).

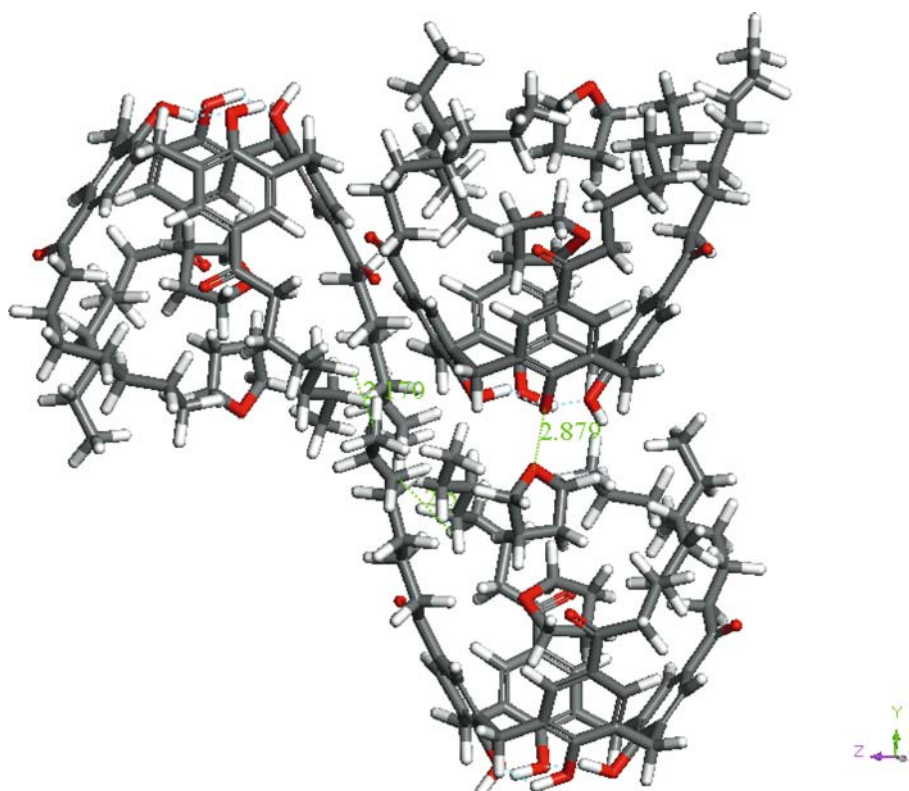


Figure 3. Intermolecular head-to-tail and hydrophobic interactions between three neighbouring complexes of *1*.

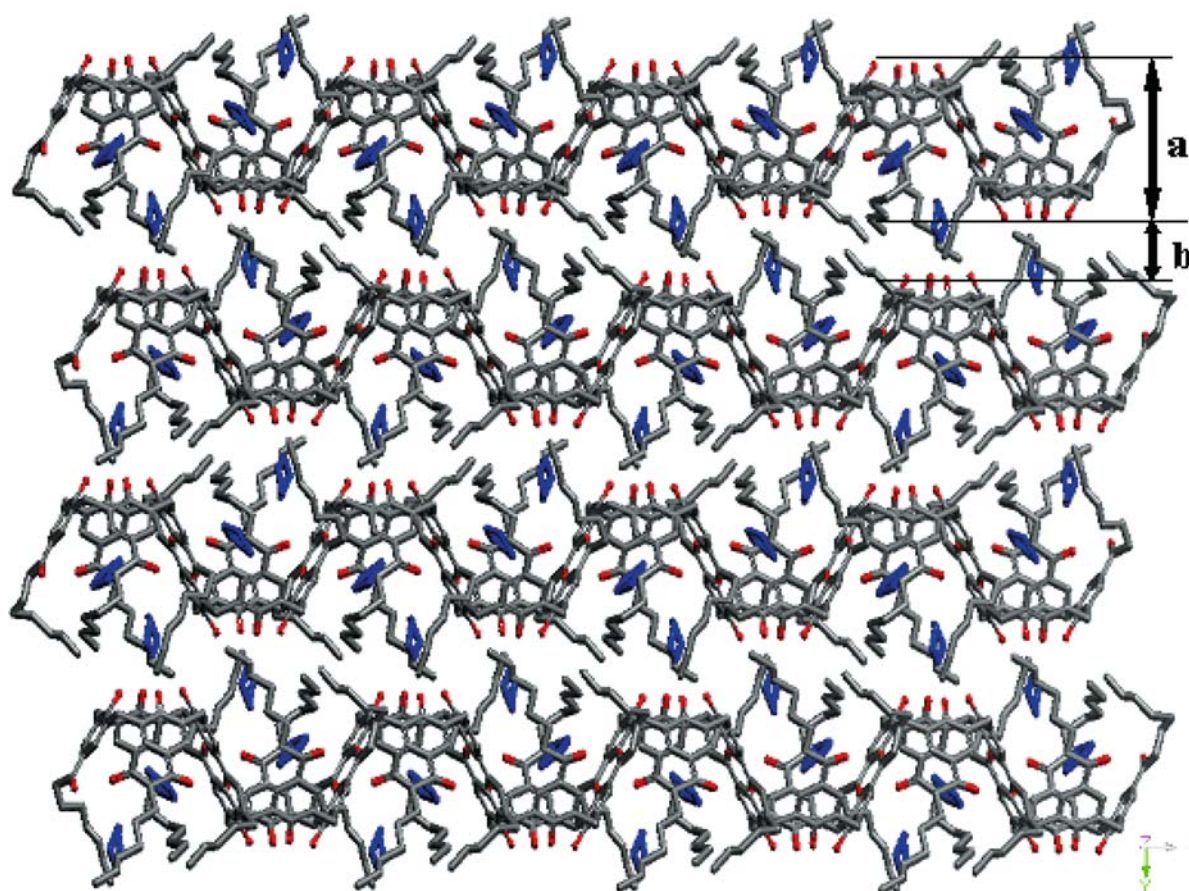


Figure 4. Crystal packing from the crystal structure of *1* down the *z*-axis, width $a = 8.61 \text{ \AA}$ and $b = 3.64 \text{ \AA}$, THF molecules are represented in blue and H atoms are omitted for clarity.

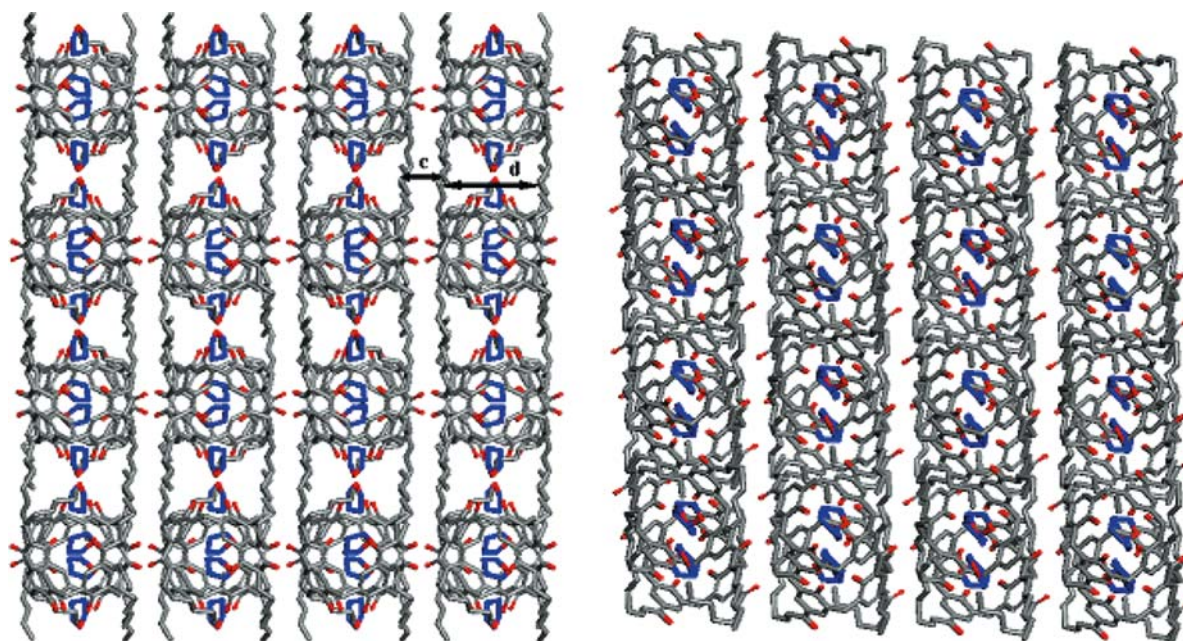


Figure 5. Crystal packing from the crystal structure of 1 down the x -axis (left) and the y -axis (right), THF molecules are represented in blue and H atoms are omitted for clarity, the distances separating the alkyl chains are $c = 4.5$ Å and $d = 7.5$ Å.

reported [19] for which no guest molecules are present in the structure. In this non-solvated structure the four acyl chains are arranged in an extended parallel manner, two extending from the cavity and two bent back across the cavity face.

Figure 3 presents the intermolecular interactions. Two molecules on top of each other are stacked in a head-to-tail fashion stabilised by a hydrogen bond ($O \cdots O = 2.87$ Å) between the outer tetrahydrofuran molecule and one of the phenolic groups on the neighbouring calix; the acyl chains that are not bent towards the cavity extend up to the level of the nearest neighbour sustained by hydrophobic interactions $H \cdots H = 2.20\text{--}2.50$ Å (van der Waals radius of $H = 1.20$ Å).

The packing parallel to the z -axis is given in Figure 4. Two distinct packing motifs can be seen. Infinite zig-zag chains formed by diametrical aromatic rings (1,3) along the x -axis form a bilayer structure slightly 'slipped' from an exact head-to-tail superposition due to the H-bonds that sustain these chains. The width of the calix-arene bilayer is 8.61 Å whereas the chains forming the fingers of the molecular hand motif form an alkyl layer of 3.64 Å. However viewed down the x - and y -axis (Figure 5, respectively perpendicular and parallel to the axis of the calixarenes) the packing shows each zig-zag chain as a ball of calixarenes with a width of ca. 7.5 Å and separated by parallel layers of alkyl chains with a distance of ca. 4.5 Å.

The packing features of the structure differ totally from the lamellar structure observed for the non-solvated system. In that structure there is a calix-arene bilayer (width 6.2 Å) separated by interdigitated acyl chains (layer width 8.5 Å).

Conclusion

In conclusion we have shown that the title compound is capable of inclusion of two small organic molecules and that such inclusion strongly influences packing and molecular structure. Current work is being undertaken both to determine the structure of the plates initially obtained at the solvent–water interface and to include other organic molecules.

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