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Guest-induced chain folding in amphiphilic calixarene structures

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Amphiphilic calixarenes represent a promising class of derivatives, potentially useful for transporting molecules because of their ability to self-organize as Solid Lipid Nanoparticles in water. The current study shows that after derivatization of the *para*-H-calix[4]arene with hexanoyl chains, the resultant amphiphilic calixarenes retain their properties to complex small organic molecules. The solid structures of the complexes of *para*-hexanoyl-calix[4]arene with methanol, dimethylformamide–methanol, dimethyl sulfoxide–methanol and nitrobenzene are reported. As for the *p-tert*-butyl calix[4]arene, aliphatic guests are stabilized by a variety of short-range interactions including C–H$\cdots\pi$ or $\pi-\pi$ interactions. Moreover, the presence of the grafted hydrophobic chains generates an extension of the hydrophobic calixarene cavity and thus provides another site where complexation can take place. The structures show that the geometry of the hexanoyl chains is modified by the presence of the guest molecules and that the chains fold over to aid encapsulation of the guest.

Introduction

Calix[4]arenes are well known synthetic macrocyclic molecules comprising four phenolic rings linked by methylene bridges.[1] Their structure allows the complexation of a wide variety of ions, atoms and small molecules.[2] Calix[4]arene can be chemically modified[3] and such modification is of interest for numerous applications such as molecular recognition,[4] *trans*-membranes transport,[5] ions channel formation,[6] self-assembling monolayers at the air–water interface[7] and adsorption on metals.[8]

Amphiphilic calixarenes[9] can be obtained by various methods, including Friedel–Crafts acylation at the macrocyclic upper rim, and this leads to molecules exhibiting self-assembly into stable monolayers,[10] Langmuir–Blodgett layers[11] and Solid Lipid Nanoparticles (SLNs).[12] The use of SLNs as a colloidal transport system is of great interest because of their high stability and high encapsulation loads.[13] The crystal structures of host–guest inclusion compounds formed between calixarenes and guests provide a good basis for the understanding of the guest-induced structural motifs, inclusion propensities and the molecular recognition capabilities of such amphiphilic derivatives.[11]

In this paper, we report the crystal structures of the amphiphilic molecule, *para*-hexanoyl calix[4]arene, with various solvent molecules as guests. The presence of the hydrophobic chains provides a new hydrophobic environment where host–guest interactions can take place as shown by the folding of the hydrophobic chains around the guest molecules.

Experimental section

Chemicals

para-Hexanoyl calix[4]arene was synthesized according to the procedure, previously described.[9] Solvents were purchased from Anachemia. Crystals were prepared by the diffusion method, typically, the amphiphilic calixarene is dissolved in the minimum amount of dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), or nitrobenzene (NB) and methanol (MeOH) is added. Diffusion of the two miscible solvents leads to crystallization of the complex. For the nitrobenzene solution, crystallization of the amphiphilic calixarene complex took place spontaneously and the addition of co-solvent methanol was not necessary.

X-Ray diffraction. Single crystal X-ray diffraction data were collected in the ω–2θ scan mode on a Bruker Smart diffractometer equipped with a CCD detector using graphite-monochromatized MoK_α radiation at $\lambda = 0.710\ 73$ Å. The structures were solved by direct methods and refined by full-matrix least-squares on F^2 using the SHELXTL suite of programs.[14,15] Positions of disordered groups were found from the electron density maps. Then, disordered fragments were placed in appropriate positions and all distances between neighboring atoms and angles were fixed. Site occupancies were refined for the different parts with the same thermal parameters for the same atoms in the various fragments. At the end of refinement, site occupancies were fixed and hydrogen atoms were placed in calculated positions.†

Results

Structure of *para*-hexanoyl calix[4]arene.methanol (C6OH.MeOH)

The asymmetric unit and structural details of C6OH.MeOH are given in Fig. 1 and Table 1. The complex crystallizes in the centrosymmetric space group $P\bar{1}$. Hydrogen bonds of 2.68, 2.67, 2.67 and 2.71 Å, between the phenolic OH groups, stabilize the

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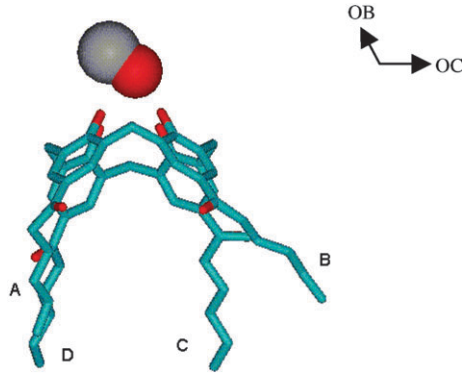

Fig. 1 Structure of C6OH.MeOH along OA axis. Hydrogen atoms are omitted for clarity.

amphiphilic calixarene in the cone conformation. The packing diagram (Fig. 2) shows that the amphiphilic calixarenes are present in an interdigitated bilayer structure with different arrangements of the four hydrophobic chains. This reduces the symmetry of the molecule as compared to the conformation of many calix[4]arenes in solution where usually fourfold symmetry is present, at least on average.[3,16] Three chains (B, C and D) point outside the cavity while the fourth (A) is directed across the face of the cavity. Chain (A) is folded by simple rotation of the acyl function (dihedral angle of A chain with respect to the aromatic ring is 67.3°). The driving force for this folding seems to be the repulsion exerted by chain (D) of the facing calixarene which is deeply included in the calixarene cavity. Furthermore, these two chains do not show disorder on account of relatively strong intermolecular interactions. Chain (D) is deeply included in the facing calixarene (the distance between the final carbon of the chain and the phenolic group of the neighboring aromatic ring (corresponding to the ring of chain (A) is 4.45 Å) although there is no evidence of strong C–H···π interactions[17] between protons of the respective methyl and the aromatic ring of A (C···π = 3.74 Å [sum of van-der-Waals radii is 3.40 Å]). Chain (B) is partially included in the environment formed by the hexanoyl chains. This chain is disordered over two positions with site occupancies of 0.66 and 0.34. There is thus one amphiphilic calixarene interacting with two other calixarenes of the facing layer (Fig. 3). The aromatic rings carrying the chains A and B are involved in π–π interactions with two neighbouring calixarenes with values of 3.71 and 3.84 Å, respectively. Finally, chain (C) is disordered over two positions (0.75 and 0.25) and lies in the vacant space formed by two calixarenes of the same layer. The two other aromatic rings corresponding to chains (C) and (D) are found at short distances from two other facing calixarenes (π···π distances of 4.66 and 4.69 Å, respectively). Methanol molecules are present, with only 50% of the sites occupied in the crystal, lying in the void space between two calixarene layers facing their lower rim, at hydrogen bond distances of 2.95, 2.72, 2.91 and 3.15 Å from the phenolic oxygens corresponding to hexanoyl chains A, B, C and D, respectively.

Structure of *para*-hexanoyl calix[4]arene.dimethylformamide.methanol (C6OH.DMF.MeOH)

The *para*-hexanoyl calix[4]arene crystallizes in an asymmetric manner in the triclinic space group $\bar{P}$ with two molecules in the unit cell (Table 1). The amphiphilic calixarene is in a cone conformation stabilized by hydrogen bonds involving the phenolic OH groups which are at distances of 2.67, 2.68, 2.68 and 2.86 Å. Structural details are given in Fig. 4. All four aliphatic chains exhibit positional disorder (A 0.7 and 0.3; B 0.35, 0.37 and 0.28; C 0.58 and 0.42; D 0.9 and 0.1). Two of them (B and C) are relatively straight (dihedral angles of the chains close to 180°) while the other two (A and D) are bent at the carbonyl atom (dihedral angle with respect to the aromatic

Table 1 Crystallographic data[1]† for *p*-hexanoyl-calix[4]arene.methanol, *p*-hexanoyl-calix[4]arene.dimethylformamide.methanol, *p*-hexanoyl-calix[4]arene.dimethylsulfoxyde.methanol and *p*-hexanoyl-calix[4]arene.nitrobenzene

Compound	C6OH.MeOH	C6OH.DMF.MeOH	C6OH.DMSO.MeOH	C6OH.NB
Formula	$C_{52.5}H_{66}O_{8.5}$	$C_{55.7}H_{73.8}NO_{9.7}$	$C_{55}H_{73}O_{10}S$	C_{58} H_{69} N O_{10}
FW	833.05	910.7	926.19	940.14
Temperature, K	173	173	173	173
Colour	Colourless	Colourless	Colourless	Colourless
Crystal size, mm	0.5 × 0.35 × 0.25	0.5 × 0.4 × 0.35	0.4 × 0.3 × 0.15	0.45 × 0.4 × 0.2
Crystal system	Triclinic	Triclinic	Triclinic	Monoclinic
Space group	$\bar{P}$	$\bar{P}$	$\bar{P}$	$P2_1/c$
a, Å	11.616(1)	10.397(1)	10.246(1)	15.264(1)
b, Å	13.100(1)	15.658(2)	15.864(2)	19.874(2)
c, Å	15.408(1)	16.657(2)	16.591(2)	22.237(1)
α, °	105.17(1)	90.95(1)	83.70(1)	90
β, °	90.20(1)	107.93(1)	107.75(1)	130.90(1)
γ, °	91.80(1)	100.73(1)	99.41(1)	90
V, Å^3	2261.8(3)	2527.0(3)	2528.6(4)	5098.7(5)
Z	2	2	2	4
ρ_{calc}, g cm^{-3}	1.223	1.197	1.218	1.225
F(000)	898	982	1000	2016
μ(MoK$_\alpha$) mm^{-1}	0.081	0.081	0.121	0.083
Scan type	ω	ω	ω	ω
$2\theta_{max}$, deg	57.44	50	57.48	57.46
Total no. of reflcns	27 086	23 077	30 252	59 868
No. of unique reflcns	11 618	8906	12 951	13 161
No. of reflcns $I > 2.5\sigma$ (I)	8455	4536	7730	8590
No. of variables	617	802	733	762
R	0.066	0.062	0.079	0.069
wR	0.190	0.164	0.227	0.182
GOF	1.049	0.93	1.040	1.034
max Δ/σ (final cycle)	0.006	0.029	0.090	0.022
Residual density, *e* Å^{-3}	−0.379–0.545	−0.233–0.238	−1.373–0.687	−0.460–0.444

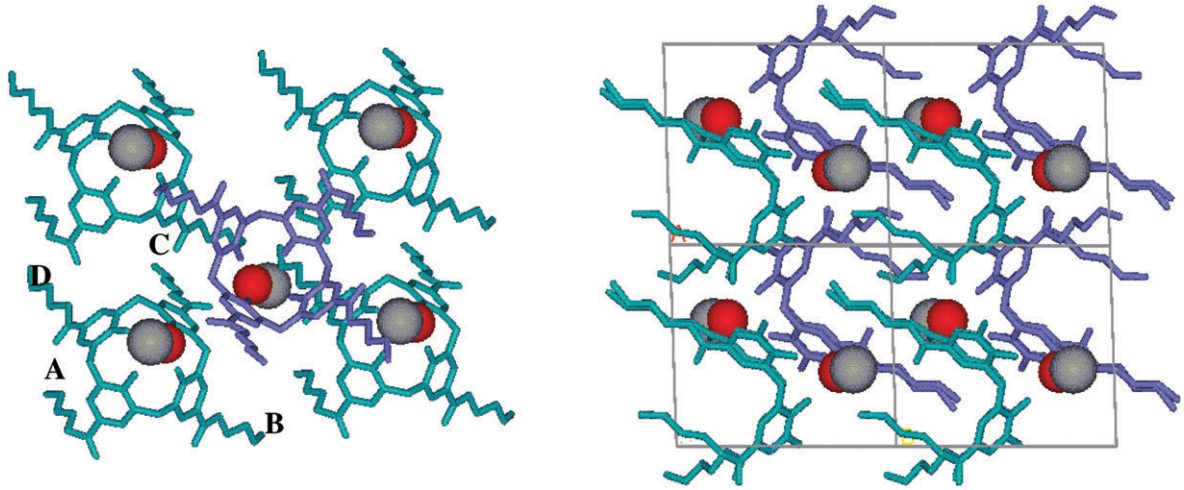

Fig. 2 Packing diagram of C6OH.MeOH. Hydrogen atoms are omitted for clarity.

ring is 76.1° in the case of chain A and chain D). While A, B and C chains point outside the calixarene cavity, the D chain is strongly bent (the dihedral angles of the chain starting from the aromatic ring are: 76.07°; 78.46° and −73.18°) and points inside the calixarene cavity and appears to enfold the *N*,*N*-dimethylformamide guest molecule. There are two types of solvent guest molecules. The *N*,*N*-dimethylformamide molecules are complexed deep inside the calixarene cavity. Methyl groups point inward into the cavity although the distances all either exceed or are close to the sum of the van der Waals'radii – ($CH_3\cdots\pi$(D) = 3.58 Å; $CH_3\cdots\pi$(C) = 3.64 Å; $CH_3\cdots\pi$(A) = 3.31 Å and $CH_3\cdots\pi$(D) = 3.30 Å). Moreover, interaction of DMF with the hexanoyl chains of the amphiphilic calixarene can take place, involving folding of chain (D) (distances of 3.36 Å and 3.68 Å; Σ van der Waals (vdW) radii = 3.4 Å). The second solvent molecule, methanol, interacts with the phenolic OH groups *via* hydrogen bonds (all phenols may be involved in H bonds, as a function of occupancy of the methanolic OH, the shortest distances measured being: 2.59 Å, 2.89 Å, 2.80 Å and 2.60 Å corresponding to rings A, B, C and D, respectively), with the straight aliphatic chains of the adjacent calixarene (a distance of 3.212 Å from chain A, and distances of 3.53, 3.57 and 3.53 Å from chain B for the disordered part; Σ vdW radii = 3.4 Å) and also with the DMF molecule belonging to the same adjacent calixarene (CH_3–CH_3 distances of: 3.33, 3.16, 3.18 Å; Σ vdW radii = 3.4 Å and OH(Me)–OH(DMF) distances of 2.69 and 2.71 Å; Σ vdW radii = 3.1 Å). The packing diagram in this system is quite different from the previous one as the amphiphilic calixarenes are arranged in a bilayer structure facing each other in a head-to-tail motif (Fig. 5). Both of the guest molecules are strongly disordered, and the methanol site is not fully occupied (site occupancy 70%). No face to face interactions are found between the neighbouring calixarenes.

Structure of *para*-hexanoyl calix[4]arene.dimethyl sulfoxide.methanol (C6OH.DMSO.MeOH)

The *para*-hexanoyl calix[4]arene crystallizes in an asymmetric manner in the triclinic space group with a unit cell equivalent to that of C6OH.DMF.MeOH (Table 1, Fig. 6). The amphiphilic calixarenes are $P\bar{1}$ in the cone conformation stabilized by hydrogen bonds involving the phenolic OH groups (2.67 Å, 2.68 Å, 2.69 Å and 2.72 Å) and are packed in a head-to-tail motif (see Fig. 7). All the hydrophobic chains are oriented in the same direction with respect to the plane perpendicular to the phenolic ring. Only two chains present disorder (chain C and D, respectively). Chains B and C point inside the cavity, which includes one molecule of DMSO and one of MeOH. Torsion angles of the aliphatic chains are: −174.7° for A, −172.2° for B, −55.7° for chain C and 179.3° for chain D. The guest methanol molecules are disordered, with 93% and 7% occupancy of the two sites in the crystal, while the dimethyl sulfoxides present a greater degree of disorder (over six positions with occupancies of 41%, 27%, 14%, 11%, 4% and 3%). CH–π(A) contacts of 3.16 Å between DMSO molecule and the aromatic ring A of the calixarene stabilize the packing. The guest methanol presents interactions between the methyl and the carbon of the aliphatic chain (3.46 Å). The OH group is oriented towards the phenols of the adjacent calixarene molecule, forming H bonds (2.43 Å, 2.70 Å, 2.76 Å and 3.02 Å for

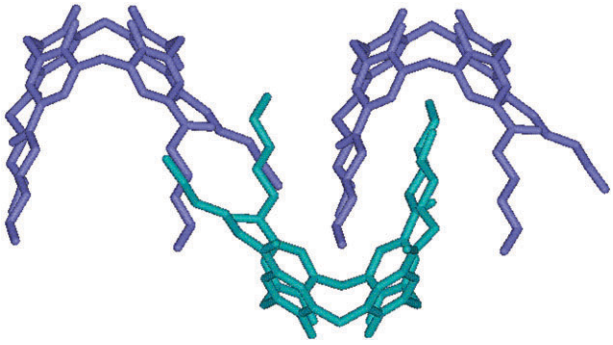

Fig. 3 Trimer of C6OH.MeOH. Hydrogen atoms are omitted for clarity.

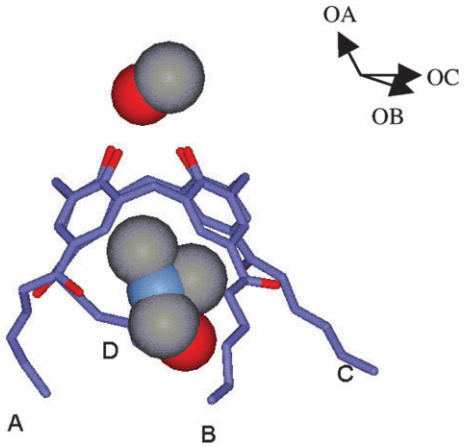

Fig. 4 Structure of C6OH.DMF.MeOH. Hydrogen atoms are omitted for clarity.

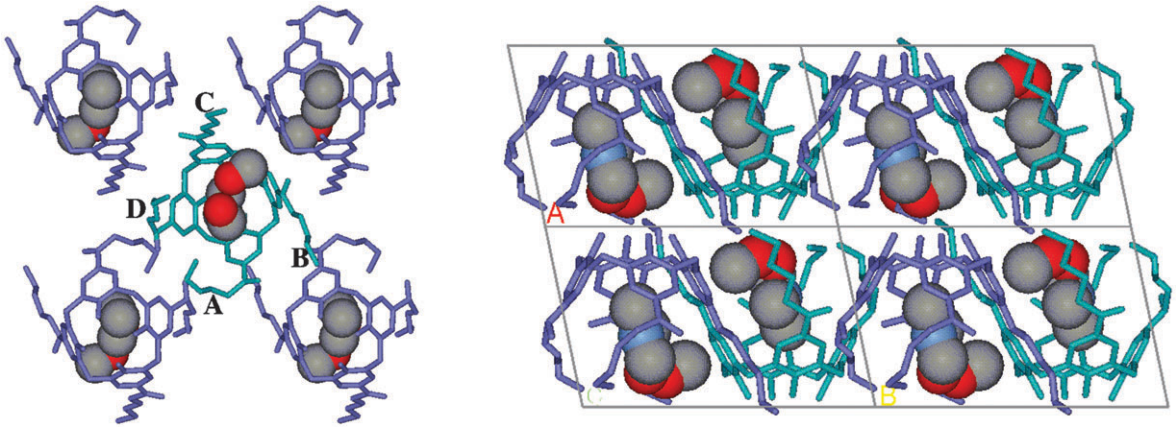

Fig. 5 Packing diagram of C6OH.DMF.MeOH along OA and OC axis, respectively. Hydrogen atoms are omitted for clarity.

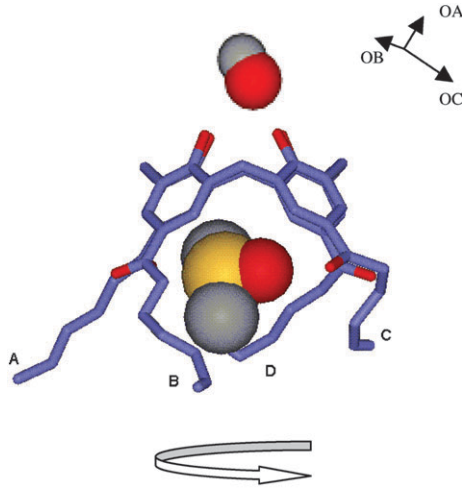

Fig. 6 Structure of C6OH.DMSO.MeOH. Hydrogen atoms are omitted for clarity. The flash indicates the direction of hydrophobic chains orientation.

the two possible positions). No π−π aromatic interactions are observed between calixarene aromatic rings.

Structure of *para*-hexanoyl calix[4]arenenitrobenzene (C6OH.NB)

The asymmetric unit and structural details for C6OHNB are given in Fig. 8 and Table 1. The *para*-hexanoyl calix[4]arene-nitrobenzene crystallizes in the monoclinic system with a $P2_1/c$ space group (pseudo tetragonal) and the amphiphilic calixarene exhibits no symmetry. The amphiphilic calixarene is in a cone conformation stabilized by hydrogen bonds involving the phenolic OH groups (2.68, 2.71, 2.68, 2.73 Å). The four phenolic groups lie in the same plane and each *para*-hexanoyl-phenol moiety (labelled A, B, C and D) makes a dihedral angle with this plane of 47.2°, 62.9°, 49.2° and 63.9°, respectively. The NO_2 group extends outward from the calixarene axis between residues A and B.

The packing diagram (Fig. 9) shows that the amphiphilic calixarenes are packed in a bilayer structure with calixarenes head-to-tail along the *y*-axis.

Three of the four hexanoyl chains of C6OH (B, C and D) exhibit disorder with site occupancies of 0.44 : 0.44 : 0.12 (B), 0.35 : 0.25 : 0.31 : 0.09 (C) and 0.89 : 0.11 (D). Furthermore, two of these chains (C and D) do not point outside the host cavity but display a folding across the molecular cavity. The torsion angles for the C and D chains are −112°, 65.8°, −78.5° and 68.2°, respectively, while those for A and B chains are close to 180°, denoting a linearity of these chains.

The C_2 axis of nitrobenzene is 64.6° off the *z*-axis (perpendicular to the plane defined by the four phenolic oxygens). The plane of the nitrobenzene ring makes an angle of 56.5° with the basal plane defined by the four hydrogen-bonded host oxygens and the nitrobenzene centre is close (0.84 Å) to the *y*-axis of the host. There is no disorder of the guest, its position within the *p*-hexanoyl-calix[4]arene being quite similar to that in *p*-*tert*-butylcalix[4]arene itself.[18] The nitrobenzene guest interacts with the host amphiphilic calixarene and also with the amphiphilic calixarene in the adjacent layer. The arene moiety A sits nearly perpendicular (78.4°) to the nitrobenzene ring, and the

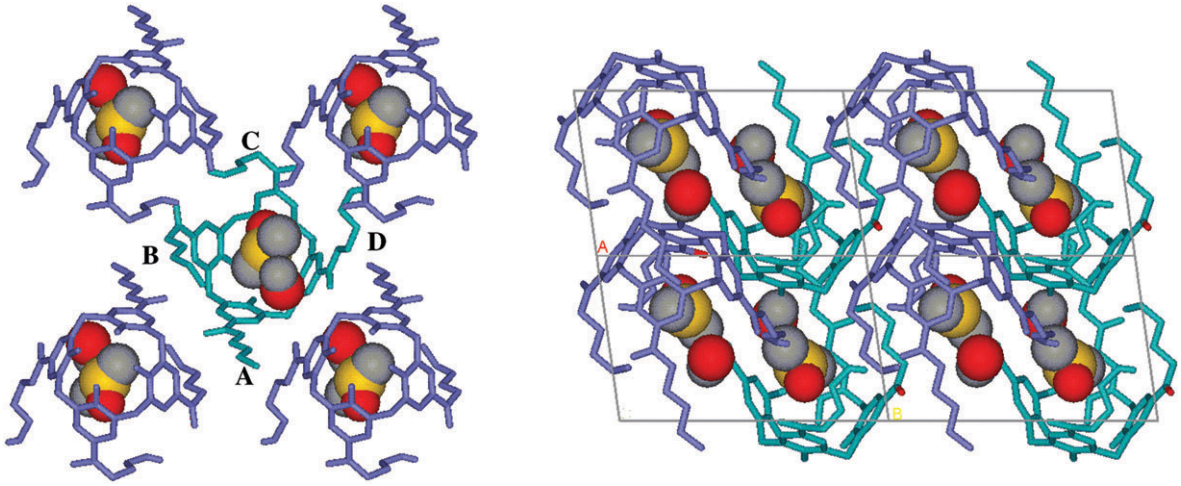

Fig. 7 Packing diagram of C6OH.DMSO.MeOH. Hydrogen atoms are omitted for clarity.

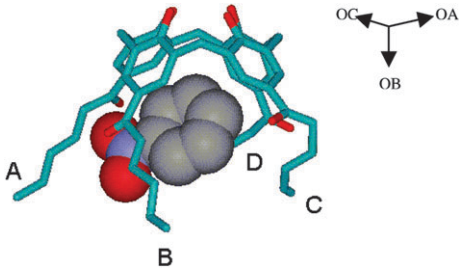

Fig. 8 Structure of C6OH.NB. Hydrogen atoms are omitted for clarity.

centroid–centroid distance is 4.98 Å. This suggests that "tilted-T" edge-to-face aromatic interactions can take place between the two aromatic rings.[19] On the other hand, the nitrobenzene ring and the B arene moiety are almost parallel (the centroid–centroid distance is 3.92 Å) and stabilizing π−π interactions can be involved. Furthermore, the guest makes significant contacts with the carbonyl of the hexanoyl chain B (3.42 Å and 3.44 Å; Σ vdW radii = 3.4 Å). The three disordered positions of chain B are equivalent with respect to the contacts established between carbonyls and the guest, and this disorder might arise from the packing of the structure.

Derivatization of calix[4]arene with hexanoyl chains has led to a new hydrophobic environment generated by these chains. There are, thus, two distinct hydrophobic sites where host–guest interactions can take place: the hydrophobic environment produced by phenolic moieties forming the deep cavity and another by the hexanoyl chains. An important difference between these two sites is that the one defined by the phenolic groups is more rigid due to cyclic organization of the ring and to hydrogen bonds involving the phenolic OH groups that maintain the calixarenes in the cone conformation, than the one formed by the hexanoyl chains. The chains can indeed occupy the space in different ways depending on the conformation-orientation that they are able to adapt because of rotation about carbon–carbon bonds.

The trimeric association of calixarenes observed here is unusual and this structure can be compared to the bilayer structure obtained with the *para*-dodecanoyl calix[4]arene,[11] where the amphiphilic calixarene retains its fourfold symmetry, and where the system shows a partially interdigitated bilayer structure with alternate self-inclusion of the acyl chains.

Conclusion

Amphiphilic calixarenes retain the property of the parent molecule *para*-H_calix[4]arene to complex small organic molecules. Moreover, the presence of a new hydrophobic environment generated by the hexanoyl chains, provides an extension of the hydrophobic calixarene cavity and thus an additional site where host–guest interactions can take place. While host–guest interactions in the calix cavity are stabilized by various short range interactions, including C–H···π or π−π, the interactions that can take place in the hydrophobic site of the hexanoyl chains are generally weaker. Small guests, such as solvent molecules which are deeply included in the calixarene cavity can moreover lead to a folding of the hydrophobic chains in order to stabilize the complex. Although this shows a greater ability of the amphiphilic calixarenes to bind small molecules, the structures do not give a clue as to why SLNs have the ability to have large encapsulation loads.

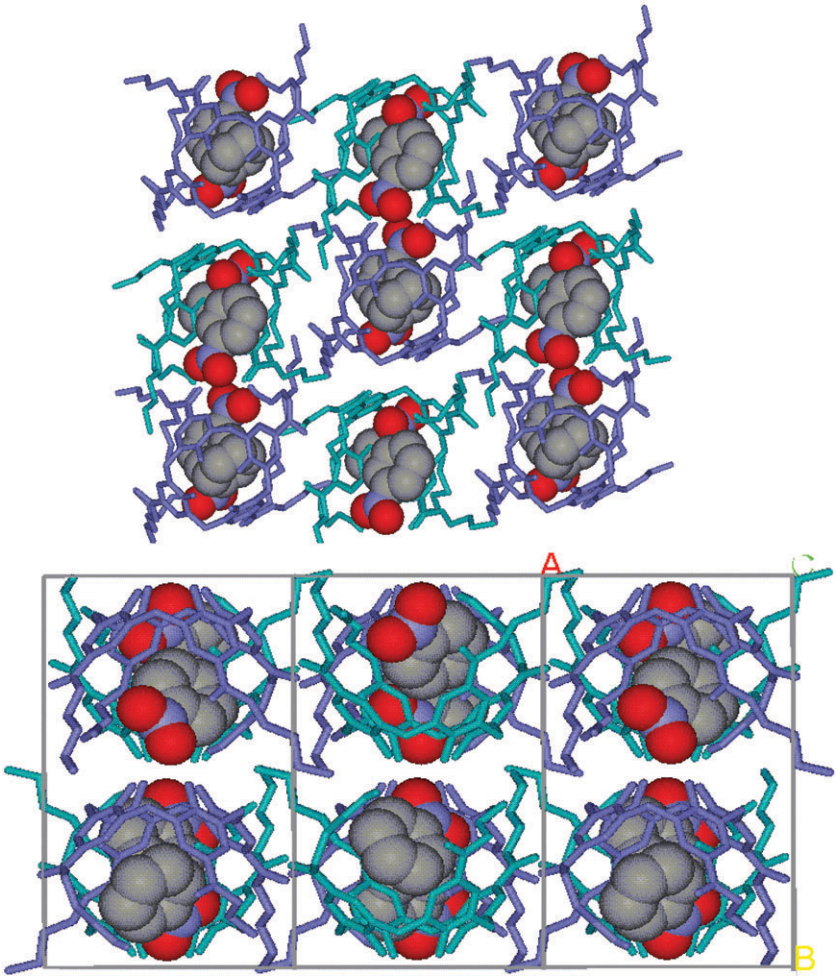

Fig. 9 Packing diagram of C6OH.NB. Hydrogen atoms are omitted for clarity.

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References

1 C. D. Gutsche, *Monographs in Supramolecular Chemistry, Calixarenes Revisited*, The Royal Society of Chemistry, Cambridge, U. K., 1998.
2 E. B. Brouwer, G. D. Enright, C. I. Ratcliffe, J. A. Ripmeester, K. A. Udachin, in *Calixarenes 2001*, eds. Z. Asfari, V. Bohmer, J. Harrowfield and J. Vicens, Kluwer, Dordrecht, 2001, **16**, 296–311.
3 (*a*) I. Thondorf, A. Shivanyuk and V. Bohmer, in *Calixarenes 2001*, eds. Z. Asfari, V. Böhmer, J. Harrowfield and J. Vicens, Kluwer, Dordrecht, 2001, 26–54; (*b*) I. Thondorf, in *Calixarenes 2001*, eds. Z. Asfari, V. Böhmer, J. Harrowfield and J. Vicens, Kluwer, Dordrecht, 2001, 280–95; (*c*) A. Arduini, A. Pochini, A. Secchi and F. Ogozolli, in *Calixarenes 2001*, eds. Z. Asfari, V. Böhmer, J. Harrowfield and J. Vicens, Kluwer, Dordrecht, 2001, 457–475.
4 (*a*) E. B. Brouwer, G. D. Enright and J. A. Ripmeester, *J. Inclusion Phenom. Mol. Recogn. Chem.*, 1996, **24**, 1–17; (*b*) E. B. Brouwer and J. A. Ripmeester, *Adv. Supramol. Chem.*, 1999, **5**, 121–155.
5 O. Tatsuya, I. Katsutoshi, F. Shintaro and G. Masahiro, *J. Membrane Sci.*, 2003, **217**, 87–97.
6 G. Droogmans, C. Maertens, J. Prenen and B. Nilius, *Br. J. Pharmacol.*, 1999, **35**, 128.
7 L. Fang, L. Guo-yuan, H. Wei-jiang, L. Min-hua and Z. Long-gen, *Thin Solid Films*, 2002, **414**, 72–77.
8 A. J. Lucke and C. J. M. Stirling, in *Calixarenes in Action*, eds. L. Mandolini and R. Ungaro, Imperial College Press, London, 2000, pp. 172–202.
9 P. Shahgaldian, A. W. Coleman and V. I. Kalchenko, *Tetrahedron Lett.*, 2001, **42**, 577–579.
10 P. Shahgaldian and A. W. Coleman, *Langmuir*, 2001, **17**, 6851–6854.
11 P. Shahgaldian, M. Cesario, P. Goreloff and A. W. Coleman, *Chem. Commun.*, 2002, 326–327.
12 P. Shahgaldian, E. Da Silva, A. W. Coleman, B. Rather and M. Zaworotko, *J. Int. J. Pharm.*, 2003, **253**, 23–38.
13 P. Shahgaldian, E. Da Silva, A. W. Coleman, B. Rather and M. Zaworotko, *Int. J. Pharm.*, 2003, **253**, 1–23.
14 G. M. Sheldrick, *Acta Crystallogr.*, 1990, **A46**, 467.
15 G. M. Sheldrick, *Acta Crystallogr.*, 1993, **A49**(Suppl.), C53.
16 J. M. Harrowfield, W. R. Richmond and A. H. Sobolev, *J. Chem. Soc., Perkin Trans. 2*, 1994, 5.
17 A. Meyer, R. K. Castellano and F. Diederich, *Angew. Chem. Int. Ed.*, 2003, **42**, 1210–1250.
18 E. B. Brouwer, G. D. Enright and J. A. Ripmeester, *J. Am. Chem. Soc.*, 1997, **119**, 5404–5412.
19 S. Paliwal, S. Geib and C. S. Wilcox, *J. Am. Chem. Soc.*, 1994, **116**, 4497–4498.