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The first example of a substrate spanning the calix[4]arene bilayer: the solid state complex of *p*-sulfonatocalix[4]arene with L-lysine†

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The complex of *p*-sulfonatocalix[4]arene with L-lysine shows a new type of intercalation behaviour with regard to the achiral hydrophobic bilayer assembly of the calixarenes, and represents the first structural example of a cationic organic substrate spanning such a bilayer.

It has recently been shown that the *p*-sulfonatocalix[*n*]arenes can act as heparin mimics,[1] and their interactions with the positively charged amino acids, lysine and arginine, has been investigated.[2] In the case of *p*-sulfonatocalix[4]arene, 1:1 complexes with lysine and arginine are observed, with binding constants derived from ^{1}H NMR spectroscopy at pH 5 of 600 and 1700. Undoubtedly such electrostatic interactions are also important in the activity of the sulfonatocalixarenes as chloride ion blockers.[3] In recent years, *p*-sulfonatocalix[4]arene salts have been extensively studied; these complexes crystallize with a large variety of cations in bilayer-type structures.[4] The basic molecular motif is achiral and formed by two calixarenes related by crystallographic symmetry. They are arranged in the up-down fashion with the sulfonate groups covering the surfaces of the bilayers which are separated by a hydrophilic layer containing the majority of the water molecules and cationic counterions. The structures of complexes of *p*-sulfonatocalix[4]arene with transition metal compounds[5] have demonstrated that an aromatic organic substrate can be intercalated into the bilayer. However, no example of substrates traversing the bilayer have been observed. We report here on a new type of intercalation within the calixarene bilayer system showing that a chiral cationic organic molecule possessing a flexible aliphatic side chain, in this case L-lysine, can span the bilayer. The crystalline title compound also exhibits a chiral hydrophilic layer, containing three other L-lysine molecules, which separates the bilayers.

The crystal structure belongs to the triclinic *P*1 space group,‡ and consists of two [calix[4]arenesulfonate]$^{4-}$ anions (**A** and **B**), four L-lysine counterions and 17.5 water molecules distributed over 20 sites. The calix[4]arene pattern is strongly pseudo-centrosymmetrical and similar to those already described in other complexes.[4,5] The four L-lysine molecules and the sulfonate groups interact largely with water molecules. No water sites have been detected within the calixarene cavities.

For all the L-lysine molecules, the α- and ε-amino groups show contacts indicative of N–H···O hydrogen bonds with oxygen atoms on the sulphonate groups of the calixarenes, but they display different types of interactions. One L-lysine molecule (**L1**) is seen to traverse the hydrophobic bilayer with the main chain directed towards the sulfonate groups of the 'up', (**A**), calixarenes. As its side chain is in the fully extended conformation [χ_1 = −68(1)°, χ_2, χ_3, χ_4 values close to 180°], the ε-amino group points towards the opposite edge of the bilayer, nearly at the level of the S atoms of the 'down' (**B**), calixarenes (Fig. 1). While the α-amino group is in short contact with one sulfonate group of an **A** calixarene [N···O separation of 2.75(1) Å], the ε-amino group is connected to three **B** calixarenes, related by crystallographic translations along the *a*- and *b*-axes [N···O separations ranging from 2.853(6) to 3.013(6) Å]. This L-lysine molecule is thus the first example of a ligand which truly spans the hydrophobic calixarene bilayer.

Of further interest in the structure is the chiral hydrophilic layer separating the bilayers which contains the other three L-lysine molecules. One L-lysine molecule (**L2**) is placed in the core of this layer§ and aligned parallel to the *a*-axis. As with **L1**, the side chain adopts the fully extended conformation [χ_1 = −66(1)°, χ_2, χ_3, χ_4 values close to 180°], which is that most usually observed.[6] The other two L-lysine molecules (**L3** and **L4**) lie just above the calixarene macrocycles (**A** and **B** for **L3** and **L4**, respectively). Their arrangement is illustrated in Fig. 2. For both, the α-amino and α-carboxylate groups are directed into the chiral layer and the side chain is nearly at the level of the S atoms of their respective calixarene, with the ε-amino group pointed towards the exterior of the cavity. A common structural characteristic of **L3** and **L4** is that their side chains exhibit a folded conformation (χ_1 = 65.7(6) and 54.2(7)°, χ_4 = −46.2(7) and −63.5(7)°, χ_2, χ_3 values close to 180°]. This unusual conformation[6] allows N–H···O contacts between one sulfonate group of the parent calixarene and the two amino groups of the same L-lysine molecule (Table 1). This conformation has been previously observed in the structure of the L-lysine

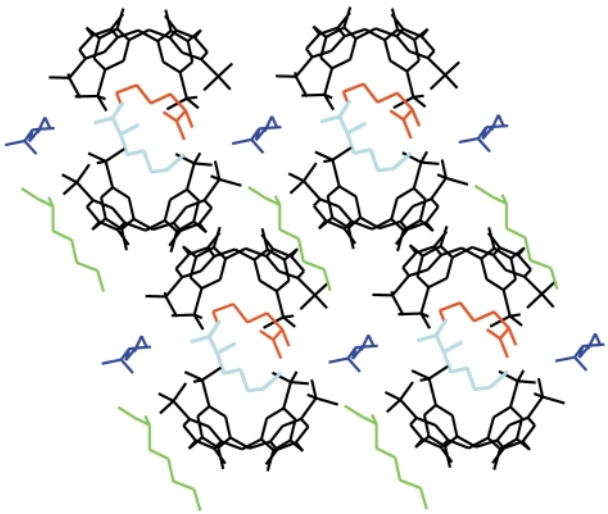

Fig. 1 Packing view along the *a*-axis of the structure demonstrating the spanning of one L-lysine molecule (**L1**, green) within the bilayer formed with the **A** (up) and **B** (down) *p*-sulfonatocalix[4]arenes. The other three L-lysine molecules are shown within the chiral layer which separates the bilayers (**L2**, dark blue; **L3**, light blue; **L4**, red).

† A figure showing the arrangement of the three L-lysine molecules within the chiral layer is available from the RSC web site, see http://www.rsc.org/suppdata/cc/a9/a906546f/

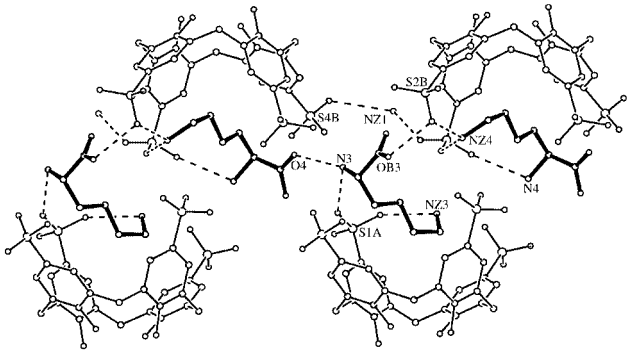

Fig. 2 A view of a section of the structure illustrating the arrangement of **L3** and **L4** within the chiral layer and representing the N(amino)··O(sulfonate) contacts (dashed lines) referred to in the text. The position of the ε-amino group of **L1** (NZ1) is also shown, the contacts between NZ1 and the sulfonate groups of two **B** calixarenes are indicated in dashed lines.

Table 1 Selected contacts (Å) between sulphonate oxygen atoms and the L-lysine molecules **L3** and **L4**

L3		**L4**	
N3···O41A	2.988(8)	N4···O43B	2.939(6)
NZ3···O21A	2.864(8)	NZ4···O33B	3.071(8)
OB3···O42B[a]	2.672(6)	NZ4···O42B	2.899(8)
N3···O31B	2.890(7)	OB4···O41A	2.635(7)
NZ3···O33B[a]	2.961(6)	NZ4···O23A[b]	2.806(10)

Symmetry codes: [a] $x + 1, y, z$. [b] $x - 1, y, z$. The minor components of the ε-amino groups are not considered.

sulfate,[7] with similar specific interactions between the L-lysine molecule and the sulfate anion. **L3** and **L4** are connected by an N–H··O contact between the α-amino group of **L3** and the carbonyl oxygen of **L4** [N··O separation 2.928(7) Å]. These dimers are only interconnected indirectly through one sulfonate oxygen atom (O42B) of the **B** calixarene, which is simultaneously in contact with the ε-amino group of **L4** and the hydroxy group of **L3**. The dimers are stacked along the *a*-axis. Thus, the L-lysine network within the chiral layer is composed of alternating rows of dimers and monomers. The bilayers are cross-linked through the chiral layer as **L3** and **L4** are also in contact with sulfonate groups of two calixarenes (**B** and **A**) lying in an adjacent bilayer (Table 1).

Thus, in contrast to the situation in solution, where a 1:1 complexation is observed, in the solid state a lysine–calixarene complex of 2:1 stoichiometry may be obtained. Actually, the system may be considered as two similar 1:1 complexes, each involving a folded L-lysine molecule (**L3** and **L4**), which would correspond to the situation observed in solution.[2] The other two L-lysine molecules, both with the side chain in the fully extended conformation, would be implicated in the solid state structure. Of the four independent L-lysine molecules, three are found within the hydrophobic layer separating the typical sulfonatocalix[4]arene bilayer, while the remaining molecule (**L1**) spans this bilayer in a manner resembling biomolecules traversing a lipid bilayer.¶ Further studies are underway to investigate the structural behaviour of the sulfonatocalix[*n*]arenes with peptides containing lysine and arginine.

Notes and references

‡ *Crystal data* for $2(C_{28}H_{20}O_{16}S_4)\cdot4(C_6H_{16}O_2N_2)\cdot17.5H_2O$: M_r = 2389.5; suitable crystals for X-ray diffraction were grown in sealed tubes from two to one lysine–calix[4]arene aqueous solution, at room temperature during six months; triclinic *P*1, a = 13.599(4), b = 14.369(2), c = 15.169(3) Å, α = 111.02(1), β = 100.02(2), γ = 99.02(2)°, V = 2646(1) Å^3, Z = 1, ρ_{calc} = 1.50 g cm^{-3}, $2\theta_{max}$ = 46°, μ(Mo-Kα) = 0.28 mm^{-1}, T = 293 K; 7673 independent reflections, 6530 with $I > 2\sigma(I)$; R_1 = 0.0863, wR_2 = 0.2553. The structure was solved by direct methods (SHELXS-86) and refined using the program SHELX-97. 17.5 water molecules were located, distributed over 20 sites. For three sulfonate groups, two O atoms are positionally disordered (two partially occupied sites for each). The ε-amino groups of **L3** and **L4** are disordered over two sites (0.75 and 0.25 occupancy factors). The parameters of the **A** and **B** calixarenes were refined in separate blocks. CCDC 182/1505. See http://www.rsc.org/suppdata/cc/a9/a906546f/ for crystallographic data in .cif format.

§ The **L2** molecule is situated in a large intermolecular space and all the atoms show high isotropic displacement parameters. Nevertheless, the amino groups of **L2** show contacts having relatively large separation distances with sulfonate oxygen atoms of two **B** calixarenes related by the *a*-translation [N··O separations of 3.02(1) and 3.07(1) Å]. A contact with a somewhat long N··O separation distance [3.09(1) Å] is also seen between the ε-amino group of **L3** and the carbonyl oxygen of **L2**.

¶ It is of interest to note that there was debate concerning whether the original sulfonatocalix[4]arene structures resembled those of bilipid membranes or clay minerals.

1 E. Aubert-Foucher, A. W. Coleman and D. J. S. Hulmes, French Patent, pending; K. M. Hwang, Y. M. Qi, S.-Y. Liu, T. C. Lee, W. Choy and J. Chen 1995, U.S. Patent No 5,409,959.

2 N. Douteau-Guével, A. W. Coleman, J.-P. Morel and N. Morel-Desrosiers, *J. Phys. Org. Chem.*, 1998, **11**, 693; N. Douteau-Guével, A. W. Coleman, J.-P. Morel and N. Morel-Desrosiers, *J. Chem. Soc., Perkin Trans. 2*, 1999, 629.

3 A. K. Singh, R. K. Juneja, J. L. Atwood and R. J. Bridges, *Biophys. J.*, 1993, **64**, 17; A. K. Singh, R. K. Juneja, R. Wang, J. L. Atwood and R. J. Bridges, *Ped. Pulm.*, 1993, **9**, 227; J. L. Atwood, R. J. Bridges, R. K. Juneja and A. K. Singh, 1996, U.S. Patent No 5,489,612.

4 J. L. Atwood, F. Hamada, K. D. Robinson, G. W. Orr and R. L. Vincent, *Nature*, 1991, **349**, 683; A. W. Coleman, S. G. Bott, S. D. Morley, C. M. Means, K. D. Robinson, H. Zhang and J. L. Atwood, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1361; S. G. Bott, A. W. Coleman and J. L. Atwood, *J. Am. Chem. Soc.*, 1988, **110**, 610; J. L. Atwood, A. W. Coleman, H. Zhang and S. G. Bott, *J. Inclusion Phenom.*, 1989, **7**, 203; S. Sinkai, K. Araki, T. Matsuda, N. Nishiyama, H. Ikeda, I. Takasu and M. Iwamoto, *J. Am. Chem. Soc.*, 1990, **112**, 9053; J.-M. Lehn, R. Meric, J.-P. Vigneron, M. Cesario, J. Guilhem, C. Pascard, Z. Asfari and J. Vicens, *Supramol. Chem.*, 1995, **5**, 97; J. L. Atwood, L. J. Barbour, E. S. Dawson, P. C. Junk and J. Kienzle, *Supramol. Chem.*, 1996, **7**, 271.

5 J. L. Atwood, G. W. Orr, F. Hamada, R. L. Vincent, S. G. Bott and K. D. Robinson, *J. Am. Chem. Soc.*, 1991, **113**, 2760; J. L. Atwood, G.W. Orr, F. Hamada, S. G. Bott and K. D. Robinson, *Supramol. Chem.*, 1992, **1**, 15; J. L. Atwood, G. W. Orr, K. D. Robinson and F. Hamada, *Supramol. Chem.*, 1993, **2**, 309.

6 G. S. Prasad and M.Vijayan, *Acta Crystallogr.*, 1991, **B47**, 927.

7 S. Capasso, C. A. Mattia, L. Mazzarella and A. Zagari, *Acta Crystallogr.*, 1983, **C39**, 281.

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