Conformational extremes in the supramolecular assemblies of *para*-sulfonato-calix[8]arene

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Received (in University of Durham, UK) 24th March 2006, Accepted 5th April 2006
First published as an Advance Article on the web 24th April 2006
DOI: 10.1039/b604349f

Two complex solid state structures of *para*-sulfonato-calix[8]arene are described, showing extremes in the macrocyclic conformation; one is planar and nearly circular, the other an inverted double cone. The differences in the molecular conformations lead to highly different packing arrangements in the structures.

Calixarenes[1] show a remarkable facility for chemical modification due to the highly different chemistries of the aromatic rings and the phenolic hydroxyl functions. Over the last decade, we[2] and other groups[3] have undertaken a number of studies on the biological and biopharmaceutical properties of their water soluble derivatives, and in particular the *para*-sulfonato-calixarenes. These derivatives have been shown to have anti-thrombotic, [4] anti-viral[5,6] and enzyme inhibition properties.[7] In general, the biological activity of the *para*-sulfonato-calix[*n*]arenes increases with the size of the macrocyclic ring; with *para*-sulfonato-calix[8]arene and its derivatives showing stronger binding to peptides, higher anticoagulant activity and stronger interaction with the Prion Protein PrP.[8] However, the binding to Bovine Serum Albumin (BSA)[9–10] shows reversed effects due to the steric blocking of the interaction of *para*-sulfonato-calix[8]arene with the strong binding pocket available in the protein. This biological activity is probably related to both an increased charge, leading to tighter electrostatic binding, and the higher conformational flexibility of the eight- macrocycle. This higher conformational flexibility has had a converse effect on our knowledge of the structural properties of *para*-sulfonato-calix[*n*]arenes. Therefore, while over 80 structures are known for *para*-sulfonato-calix[4]arene and 12 structures are known for *para*-sulfonato-calix[6]arene,[11] it was only in 2005 that Raston *et al.* reported the first structural study of a *para*-sulfonato-calix[8]arene **1**.[12]

In this paper we report on the structures of two complexes of *para*-sulfonato-calix[8]arene **1** that represent two conformational extremities in the molecular structure of **1**, one being an almost planar macrocyclic ring and the other showing a double partial cone structure, with each four-membered partial cone directed at 180° in relation to each other. The differences in the molecular structure are reflected in the highly divergent nature of the assemblies observed in the packing of the two complexes.

Suitable crystals for X-ray analysis were grown by aqueous solvent diffusion between a solution of *para*-calix[8]arene sulfonic acid **1**, and an alcoholic solution of 1,4-butanediamine or 1,2-*cis*-cyclohexanediamine, yielding the complexes **1A** and **1B**, respectively.†

With regard to complex **1A**, as shown in Fig. 1a, the *para*-sulfonato-calix[8]arene molecule adopts an almost planar conformation, in which all sulfonate groups are pointing out from the cavity; each phenolic hydroxyl group forming hydrogen bonds with its vicinal neighbors (2.63(7) Å to 2.76(1) Å). The aromatic rings are inclined to the plane of the eight oxygen atoms of the hydroxyl groups by 5.6(8) to 13.0(5)°. The C_{Ar}–CH_2–C_{Ar} angles are between 107.4(3) and 112.1(3)°. Four orthogonal grooves are present on the face of the macrocycle, which are occupied by butanediammonium cations, Fig. 2b. The macrocycle has an external diameter (S···S) of 18.83 Å and a height of 3.25 Å. The average internal diameter between opposing oxygen atoms is 6.63 Å.

In the case of **1B**, Fig. 1b, the *para*-sulfonato-calix[8]arene anion adopts an ‘inverted double partial cone’ conformation, in which four sulfonate groups are pointing up and the other four are pointing down from the mean plane of the molecule.

The size of molecule **1B** (19.97 × 6.23 × 5.91 Å) is clearly highly different from that observed for **1A**. Hydrogen bonds exist not only between vicinal hydroxyl groups (2.74(1) and 2.67(1) Å), but also between the sulfonate group of one inverted *para*-sulfonato-phenol group and the hydroxyl group of the neighbouring inverted cone (2.59(2) Å). The dimensions of the two partial cones are identical, 10.40(1) and 4.24(2) Å, and are similar to those observed for the *para*-sulfonato-calix[4]arene cone (9.28 × 4.21 × 5.89 Å) in relation to their external diameter, internal diameter and height, respectively.

The differences in the conformations of macrocycles **1A** and **1B** are translated into two highly different modes of assembly in the packing motifs of the structures.

The unit cell of **1A** consists of the following stoichiometry 1 : 3 : 1 : 2 (*para*-sulfonato-calix[8]arene) : (1,4-butanediammonium) : (methanol) : (water). Two of the butanediammonium cations are complexed within the macrocycle (shown in black in Fig. 2), while the third is situated external to the cavity and linked *via* hydrogen bonds (N···O 2.60(9)) Å). In a similar manner to that observed by Raston *et al.* in the structure of complex **1**,[12] in a ‘pleated loop’ conformation with

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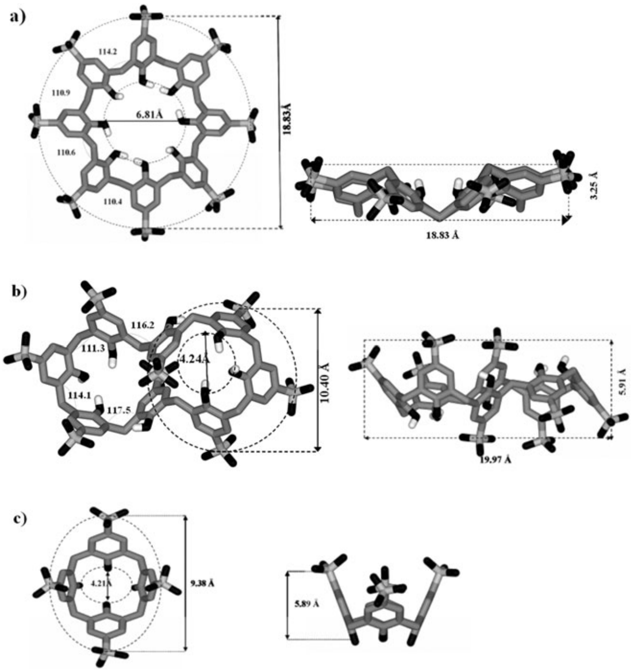

Fig. 1 (a) Top and side views of structure **1A**. (b) Top and side views of structure **1B**. (c) For comparison, the cone dimensions of *para*-sulfonato-calix[4]arene.

4,4′-dipyridine-*N*,*N*′ dioxide, each groove of the macrocycle contains a butanediammonium cation, with the head groups hydrogen bonded to the sulfonate groups (N···O 2.90 and 2.75 Å) (Fig. 2). Complex **1A** assembles with channels along the *b* axis; these channels being occupied by disordered methanol molecules, in light blue in Fig. 3a. However, the view perpendicular to the *b* axis reveals the complexity of the packing. It now becomes apparent that two sets of interaction cavities are generated (Fig. 3b).

The first set of cavities represent channels of an oval geometry with dimensions of 10.6×6.7 Å, and which contain one butanediammonium cation in a folded conformation. The cavity walls are formed mainly of sulfonate groups and are therefore highly hydrophilic. The second set of cavities intersect and connect the first set, and are of dimensions 3.5×5.2 Å. The butanediammonium cations in an elongated form are located within these cavities, with the ammonium head groups pointing out of them. Hydrogen bonds between the ammonium groups and sulfonate groups of the two different calixarenes effectively close the two cavities (N···O 2.90 Å and 2.75 Å). Calixarene molecules are bonded together *via* hydrogen bonds between sulfonate groups and phenolic hydroxyl groups (O···O 2.93 and 2.80 Å), and short contacts between sulfonate groups and methylenic bridges (O···C 3.37 Å).

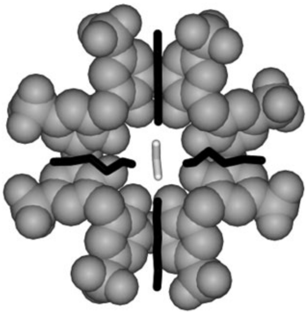

Fig. 2 The inclusion complex of butanediammonium cations in the grooves of **1A**. The calixarene molecule is colored in grey, the butanediammonium cations in black and the disordered methanol molecules in white. Water molecules have been deleted for clarity.

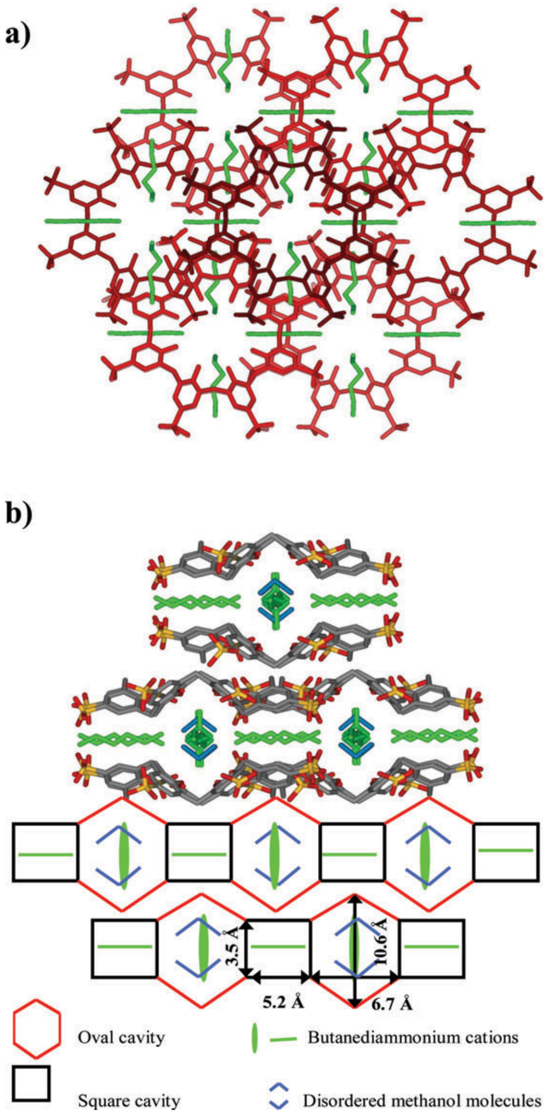

Fig. 3 (a) View along the *b* crystal axis of the 'channels' of complex **1A**. Calixarenes are colored in a nuance of red, butanediammoniums cations in green. Methanol and water molecules have been deleted for clarity. (b) View along the [101] direction and schematisation of the zeolite type of packing, showing the two different cavities. Calixarenes are colored by element, butanediammoniums cations in green, methanol molecules in blue. Water molecules have been deleted for clarity.

For structure **1B** (Fig. 4), the packing is very different to **1A**. The unit cell of **1B** has the stoichiometry 1 : 2 : 4 (*para*-sulfonato-calix[8]arene) : (cyclohexanediammonium) : (water). Whereas the calixarene in **1A** lies about a two-fold axis, the calixarene in **1B** lies about an inversion centre. The rippled bilayer arrangement (Fig. 5a) is formed by four aromatic interactions between four neighbouring calixarenes: two π–π interactions with the 'upper partial cone' (3.64 and 3.68 Å) and two π–π interactions with the 'lower partial cone' (3.63 and 3.67 Å) (Fig. 5b).

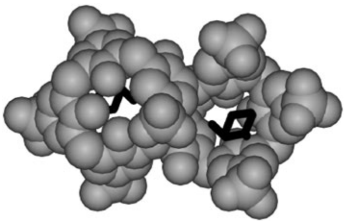

Fig. 4 Inclusion complex of cyclohexanediammonium cations in **1B** cavities. The calixarene molecule is colored in grey and the cations in black. Water molecules have been omitted for clarity.

Moreover, hydrogen bonds between sulfonate groups and phenolic hydroxyl groups of two calixarenes molecules (O···O 2.68(3) Å), and hydrogen bond interactions between calixarene molecules and solvent molecules contribute to the stabilisation of this packing.

The inclusion of the 1,2-cyclohexanediammonium cation is similar to that reported for the complex of this dication with *para*-sulfonato-calix[4]arene.[13] As is seen in Fig. 5a, cyclohexanediammonium cations are complexed in two different manners. The first one (shown in green in Fig. 5a) has its hydrocarbon ring included into the molecular cavity of the calixarene, with one ammonium head group interacting with sulfonate functions *via* hydrogen bonds (N···O 2.77(1) Å), and the other interacts with the sulfonate group of an adjacent calixarene (N···O 2.82(1) Å). The second cyclohexanediammonium cation, shown in grey in Fig. 5a, is included between two calixarenes, and interacts *via* hydrogen bonds (N···O 2.87(1), 2.91(1) and 2.81(1) Å) and short contacts (C···O 2.98(1), 3.14 and 3.30 Å, C···C 3.90(2) Å).

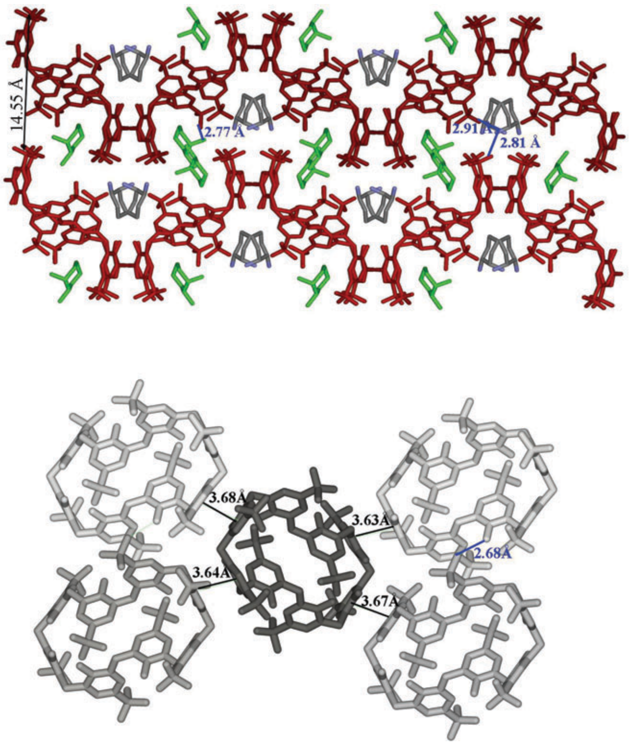

Fig. 5 (a) View along the *a* crystal axis of the rippled bilayer of cyclohexanediammonium complex of **1B**. Cyclohexanediammonium cations, colored in green, are complexed inside the cavity. The others, in grey, are complexed outside of the cavity. (b) View along the *b* crystal axis (π–π interactions are colored in black, hydrogen bond colored in blue.

In conclusion, depending on the structure of the complexed molecule, *para*-sulfonato-calix[8]arene adopts conformational extremes; from a planar to an inverted double partial cone conformation. This confirms the fact that this octameric calixarene is much more flexible than tetrameric or hexameric calixarenes. This capacity of the *para*-sulfonato-calix[8]arene to adapt its conformation to the targeted interaction site confirms the strong utility of this molecule for biomedical applications.

Acknowledgements

The authors wish to acknowledge the financial support of CNRS (F. P. Post-doc CNRS SC22). K. S. thanks the Polish MEiN Grant 4 T09A 068 25 for support.

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† *Crystallographic data*: Crystals were obtained by slow evaporation of *para*-calix[8]arene sulfonic acid from a methanol/water solution containing the relevant amine. Crystal data: **1A**: $C_{56}H_{48}O_{32}S_8 \cdot 3(C_4H_{12}N_2) \cdot 2(H_2O) \cdot CH_3OH$, M_r = 1822.01, colorless, 0.30 × 0.20 × 0.07 mm, monoclinic, $C2/c$, a = 24.3724(9), b = 22.2422(8), c = 23.340(1) Å, β = 119.279(2)°, V = 11 035.9(8) Å^3, Z = 4, ρ_{calc} = 1.065 Mg m^{-3}, θ_{max} = 18.79°, μ(Mo-Kα) = 0.230 mm^{-1}, 16 344 independent reflections, 3518 $> I > 2\sigma(I)$]. R = 0.189, wR = 0.483, (R = 0.206, wR = 0.499 for all data), GOF = 2.21. **1B**: $C_{56}H_{48}O_{32}S_8 \cdot 4C_6H_{14}N_2 \cdot 8H_2O$, M_r = 2090.46, colorless, 0.25 × 0.20 × 0.05 mm, monoclinic $P2_1/a$, a = 12.522(1), b = 25.679(3), c = 14.547(2) Å, β = 102.421(1)°, V = 4568.14(9) Å^3, Z = 2, ρ_{calc} = 1.508 Mg m^{-3}, θ_{max} = 27.92°, μ(Mo-Kα) = 0.293 mm^{-1}, 10 809 independent reflections, 7548 [$I > 2\sigma(I)$]. R = 0.235, wR = 0.617, (R = 0.264, wR = 0.624 for all data), GOF = 2.69. Intensity data were collected at 100(2) K on a Nonius KappaCCD diffractometer using Mo-Kα radiation (λ = 0.71073 Å). Data corrected for Lorentz and polarisation effects but not for absorption. The structures were solved by direct methods and Fourier techniques (SHELXS-86) and refined on $|F|^2$ (SHELX-97). For compound **1A**, only S and hydroxyl O atoms were refined anisotropically due to bad diffraction data, caused both by small, plate-shaped crystals and low resolution due to a high degree of disorder. Data were corrected using the PLATON SQUEEZE procedure for disordered solvent molecules, which were not located in the electron density maps. The butanediammonium cations were modelled using SHELXL-97 DFIX and DANG commands in order to retain their geometry. For compound **1B**, the crystals were fine, plate-shaped and probably twinned. In electron density maps we may have seen a 'shadow' of the second component, especially 4 large peaks of 6 e Å^{-3}. Under such conditions, refinement did not converge, and the R factors are very large. We have decided to publish the structure anyway because resolution of the most important information, concerning the mutual interactions of the host and guest molecules, and complex formation, was achieved. All H-atoms were included in geometric positions and refined as 'riding' atoms with isotropic thermal parameters based on the corresponding bonding carbon atom [U_{iso} = 1.2 U_{eq} (U_{iso} = 1.5 U_{eq} for CH_3, NH_3 and OH hydrogens)]. Crystallographic data (excluding structure factors) have been deposited at the CCDC. CCDC 294462 (**1A**) and CCDC 294462 (**1B**). For crystallographic data in CIF or other electronic format see DOI: 10.1039/b604349f

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