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A new packing motif for *para*-sulfonatocalix[4]arene: the solid state structure of the *para*-sulfonatocalix[4]arene D-arginine complex†

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Received (in Columbia, MO, USA) 8th June 2004, Accepted 20th July 2004
First published as an Advance Article on the web 20th August 2004

The solid-state structure of the complex of *para*-sulfonatocalix[4]arene with D-arginine, contains a water channel diagonal to a zigzag bilayer of the host, within the bilayer six crystallographically independent molecules of arginine are present, four being included in the calix cavities.

The study of the biological properties of the calix[*n*]arenes is receiving growing interest,[1] with particular emphasis on the *para*-sulfonatocalix[*n*]arenes. Biological activities including ion channel blocking,[2] enzyme inhibition,[3] anti-viral[4] and antithrombotic properties[5] have been observed. In contrast to the cyclodextrins,[6] the *para*-sulfonatocalix[*n*]arenes show no hemolytic toxicity even at concentrations of 50 g L^{-1}.[7]

In order to better understand the mechanisms of these activities, knowledge of the interactions between the *para*-sulfonatocalix[*n*]-arenes and amino acids is a key element. A number of studies of complexation in solution have been carried by ourselves[8] and Ungaro *et al.*;[9] the strongest binding constants are observed with cationic amino acids, lysine, arginine and histidine,[10] electrostatic binding to these amino acids is probably the major feature in the interactions of the *para*-sulfonatocalix[*n*]arenes with proteins. Solid state structural studies have been reported on the complexes of *para*-sulfonatocalix[4]arene and lysine,[11] histidine, phenylalanine, tyrosine, alanine[12] and serine.[13] For all these systems the classical bilayer structure of *para*-sulfonatocalix[4]arene is present,[14] although in the case of the lysine complex a molecule of lysine was observed to traverse the bilayer.[11]

Here, we present the structure of *para*-sulfonatocalix[4]arene, **1**, complexed with D-arginine.‡ The overall stoichiometry of the complex is (*para*-sulfonatocalix[4]arenes)$_4$: (arginine)$_6$: (water)$_{26}$ with the solvent distributed over 44 sites, the guanidinium functions of the arginine molecules are present as cations, however the exact charge balance in the complex is difficult to define. Each of the four independent molecules of **1** includes an arginine molecule. A totally novel solid state motif is observed, where the four molecules of **1** delimit an inclusion region for six arginines. The packing of the structure also reveals a separate motif: an aqua-channel.

The packing is quite different with respect to the bilayer motif observed in other structures of **1**.[12] The characteristic planar bilayer is replaced by a zigzag bilayer arrangement, the stability of this arrangement being assured by a total of six π–π aromatic interactions. Four π–π aromatic interactions (3.72 Å, 3.69 Å, 3.58 Å and 3.52 Å), shown in red in Fig. 1, occur between molecules on opposite faces of the zigzag bilayer. Two other π–π interactions shown in blue in Fig. 1, of 3.61 Å and 3.64 Å, are found between neighbouring molecules of **1** in the same face of the bilayer, acting to laterally rigidify the structure (Fig. 1).

As seen in the Fig. 1, the four independent molecules of **1** form a cage that includes a total of six arginines, all with different lateral chain conformations (torsion angles are presented in the supplementary information†). Four of these have their lateral chains included into the molecular cavities of the calix molecules and the other two occupy independent sites in the cage.

A very complex network of hydrogen bonds is formed between all the polar groups of the arginine molecules with fully or partially occupied sites of water molecules and with sulfonate groups of **1**. The orientation of each host molecule, as well as the conformation the arginine guest depends strongly on these interactions. As a result of the different polar environment, no identical interactions occur for the four inclusion complexes (see Fig. 2).

One arginine (lower-left in Fig. 2) is hydrogen bonded only with its host molecule and interacts with five surrounding water molecules. Another arginine (upper-left), in addition to the hydrogen bonds that connect it to its host calix, interacts with three water molecules as well as with a neighbouring molecule of **1**. An even more complex network of hydrogen bonds occurs for a third arginine (upper-right) involving interactions with its host, with four water molecules, and also with the neighbouring host–guest system (hydrogen bonds between the carboxylate group with a sulfonate of **1** and with a nitrogen of the guanidinium lateral side of the guest arginine). The final arginine (lower-right) completes its hydrogen bond network by developing interactions with a molecule of **1** exterior to the cage.

The other two arginine molecules, included in the cage but exterior to the host–guest systems, interact with other three molecules of **1**; thus a total of eight calix molecules are involved in the caging of the six arginines. Two positions are found for one of the exterior arginines; consequently disorder is also found for the

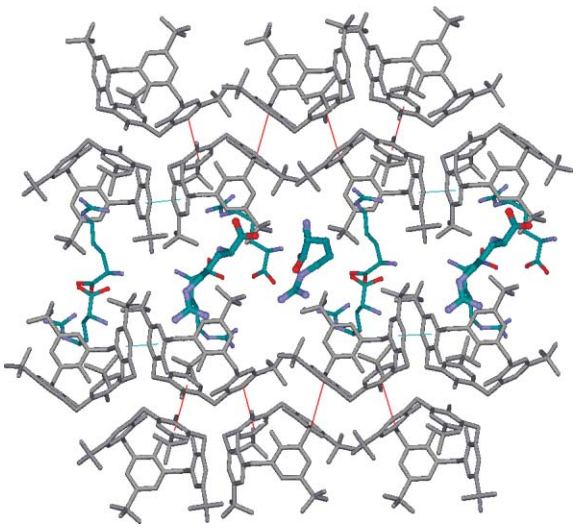

Fig. 1 View along the *a* crystal axis of the zigzag bilayer of the arginine complex of **1**, showing intermolecular π–π interactions between molecules of **1** and the interconnectiong arginine molecules. The arginine molecules are colored in blue, with oxygen atoms in red; the two molecules not included in the cavities of **1** are highlighted. Only one position of disordered sulfonate groups is shown for clarity.

† Electronic supplementary information (ESI) available: torsion angles and selected hydrogen bond distances. See http://www.rsc.org/suppdata/cc/b4/b408863h/

DOI: 10.1039/b408863h

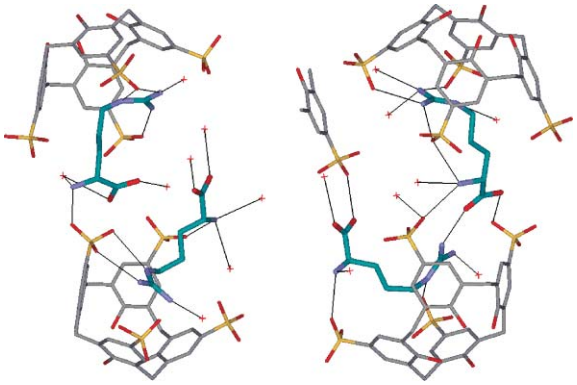

Fig. 2 The four different inclusion complexes *para*-sulfonatocalix[4]arene D-arginine found in the crystal. The hydrogen bonds between the arginines and their environment are shown in black. Ten of the water molecules represented have occupation factors lower than 1, probably arising from the numerous options to develop hydrogen bonds with the neighbouring host–guest systems.

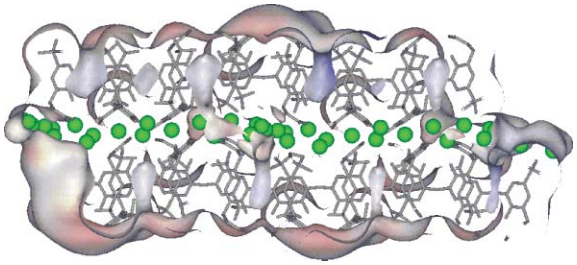

Fig. 3 Water channel—perpendicular views (all occupied water sites in the channel are illustrated).

water molecules in the cage and for the surrounding sulfonate groups.

Hydrogen bonds with either the hydroxyl groups of the phenolic rim of **1**, or with the disordered sulfonate groups are formed with water molecules lying along an "aqua-channel" parallel to the *ab* direction, Fig. 3.

Highly complex, the structure of *para*-sulfonatocalix[4]arene with arginine is characterized by three notable elements: a novel zigzag bilayer of calix molecules, six molecules of arginine, each having different conformations and an infinite water channel.

The authors would like to thank M. Nierlich, CEA-DRECAM, Saclay, for access to the KappaCCD difractometer.

Notes and references

‡ Crystal data for $4C_{28}H_{24}O_{16}S_4{\cdot}6C_6H_{14}N_4O_2{\cdot}26H_2O$: M_r = 4487.74, colorless, 0.22 × 0.20 × 0.10 mm^3, triclinic, P1, a = 12.306(3), b = 20.590(4), c = 21.349(4) Å, α = 79.750(4)°, β = 74.872(5)°, γ = 85.978(5)°, V = 5137.0(18) Å^3, Z = 1, ρ_{calc} = 1.451 g cm^{-3}, $2\theta_{max}$ = 49.4°, μ(Mo–Kα) = 0.275 mm^{-1}, 17695 independent reflections, 7617 with $I > 2\sigma(I)$. Intensity data were collected at 123 K on a Nonius KappaCCD diffractometer using Mo–Kα radiation (λ = 0.7107 Å). Data processing and internal scaling were carried out with DENZO and Scalepack programs.[15] Lorentz and polarisation corrections were applied, the diffraction data were not corrected for absorption. The structure was solved with the molecular replacement package AMoRe,[16] using 665 reflections (resolution: 7.7–2.5 Å) and as probe, the refined model of the *para*-sulfonatocalix[4]arene of the putrescine complex.[17] Five D-arginine molecules were positioned from $F_o - F_c$ maps. $3F_o - 2F_c$ maps were used as guides for manual rebuilding of the sixth arginine of the structure, occupying two positions (occupation factors 0.67 and 0.33). Seven sulfonate groups are disordered; 26 water molecules are distributed over 44 sites of which, 10 have full occupancy factors. The hydrogen atoms of the calix molecules and of the non disordered arginine molecules were placed in calculated positions and refined with isotropic thermal parameters based upon the corresponding riding atom [U(H) = 1.2 U_{eq}]. No hydrogen atoms of water molecules were found on difference maps. 2317 parameters were refined with 1110 restraints using the SHELXL-97 program,[18] no non-crystallographic restraints were imposed during refinements. R_1 = 0.097, wR_2 = 0.259. GoF = 1.09 for all data, residual electron density between 0.54 and −0.51 e Å^{-3}. The structure and the density maps were displayed and analyzed on a Silicon Graphics O2 station using TURBO FRODO[19] and DS ViewerPro[20] packages. CCDC 245594. See http://www.rsc.org/suppdata/cc/b4/b408863h/ for crystallographic data in .cif or other electronic format.

To a solution of D-arginine (0.01 M) in water, a solution of *para*-sulfonatocalix[*n*]arenes (0.01 M) in methanol was added so as to form interfacial layers of the two solutions. Crystals were obtained by slow diffusion of the solvents at room temperature after several weeks.

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