

One methylene too far: The solid state structure of the *para*-sulfonatomethylcalix[4]arene

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Abstract

We report here, the first crystallographic structure of the new water soluble calixarene, *para*-sulfonatomethylcalix[4]arene. Anchoring a methylene group between the aromatic core of the calixarene and sulfonate groups extended the hydrophobic cavity but led to a more flexible macromolecule allowing formation of hydrogen bonds between vicinal sulfonate groups, causing the groups to point towards the cavity and effectively close it, with S...S distances of $9.7 \text{ \AA} \times 7.9 \text{ \AA}$. The packing motif consists of bilayers of *para*-sulfonatomethylcalix[4]arene along both the *a* and *b* axis.

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1. Introduction

Water soluble calixarene derivatives have been well studied since 1984, when the first one was synthesised.[1] Among them, the *para*-sulfonatocalix[n]arenes are the most widely studied, both in solution and in the solid state. A large body of work has been carried out in aqueous media on the biochemistry of the *para*-sulfonatocalix[n]arenes and they have been found to have interesting bioactivities.[2] Concerning the solid state, the first structure of the sodium salt of *para*-sulfonatocalix[4]arene was published by Atwood et al. in 1988.[3] Since then, work has been carried out to study the solid state complexation of these calixarenes with various molecules including organic ammonium cations,[4–9] amino-acids [10–14], lanthanide cations,[15]. Depending on the nature of guest molecules, they can adopt different conformations leading to various kinds of packing: classic bilayers [10,12,16], zig-zag bilayers [13], stepped bilayers[17], capsules, and tubes [18]. In order to

both increase the flexibility of the sulfonate group at the upper rim of the calixarene and to extend the depth of the hydrophobic cavity, we have inserted methylene groups between the aromatic core and the ionisable functions, leading to the *para*-sulfonatomethylcalix[4]arene **1** [19,20] (Fig. 1). Here, we describe the first crystallographic study of this new water soluble calixarene, the results are cautionary as effectively the cavity is no longer open and hence inclusion is blocked.

2. Experimental

2.1. Synthesis

para-Sulfonatomethylcalix[4]arene, **1**, has been synthesised as previously reported [19,20].

The first step consists of the synthesis of the 5,11,17,23-tetrachloromethyl-25,26,27,28-tetrahydroxycalix[4]arene : to a solution of *p*-H-calix[4]arene (3.0 g; 7 mmol) and chloromethyl-*n*-octylether (46.75 mL; 240 mmol) in 300 ml CHCl₃, cooled at -10°C , was added SnCl₄ (14.1 mL, 12 mmol) in about 15 min. The cooling bath was removed and the

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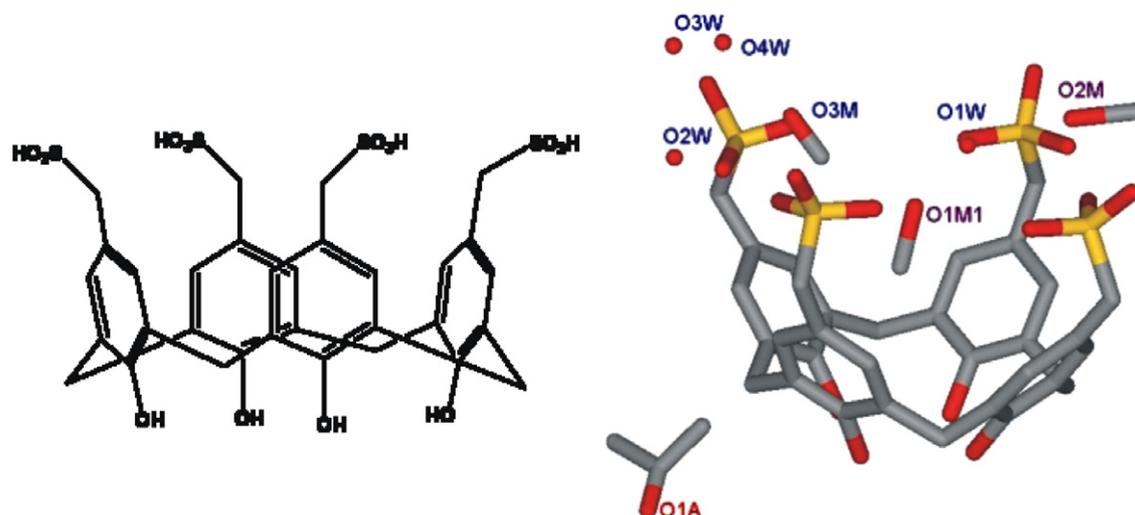


Fig. 1. Structural formula of the *p*-sulfonatomethyl-calix[4]arene 1, and molecular structure of the complex.

Table 1
Crystallographic data for *para*-sulfonatomethyl-calix[4]arene–triethylammonium complexes

Empirical formula	$C_{32}H_{32}O_{16}S_4 \cdot 2CH_3OH \cdot C_3H_6O \cdot 4.5H_2O$
Formula weight	1004.08
Temperature (K)	100(2)
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	
<i>a</i> (Å)	10.866(2)
<i>b</i> (Å)	10.947(2)
<i>c</i> (Å)	18.245(2)
α (°)	94.344(7)
β (°)	97.722(8)
γ (°)	100.933(7)
Volume (Å ³)	2100.1(6)
<i>Z</i>	2
Calculated density (Mg · m ⁻³)	1.567
Absorption correction	None
<i>F</i> (000)	1032
Crystal size (mm ³)	0.10 × 0.10 × 10
θ range for data collection (°)	2.98–20.30
Limiting indices	$-10 \leq h \leq 10, -10 \leq k \leq 10,$ $-17 \leq l \leq 17$
Reflections collected/unique	7318 / 3934 [$R_{int} = 0.101$]
Completeness to $\theta = 20.30^\circ$	96.8%
Refinement method	Full-matrix least-squares on F^2
Data/restraint/parameters	3934/0/625
Goodness-of-fit on F^2	0.980
Final <i>R</i> indices [$I > 2\sigma(I)$]	$R = 0.210, wR = 0.315$
Final <i>R</i> indices [all data]	$R = 0.114, wR = 0.267$

reaction mixture stored at room temperature for additional 50 min. Water was then added slowly and the two phases separated. The organic layer was washed twice with distilled, dried on Na_2SO_4 and evaporated to give a residue which was treated with *n*-hexane and filtered. A white powder is obtained and dried. Yield 67%. ¹H NMR (293 K, CDCl₃) 3.60 and 4.20 ppm (2 bs, 8H, Ar-CH₂-Ar); 4.43 ppm (s, 8H, Ar-CH₂-Cl); 7.10 ppm (s, 4H, Ar-H); 10.1 ppm (s, 4H, Ar-

Table 2
Hydrogen bonds (Å and °)

D–H ... A	d(D–H)	d(H ... A)	d(D ... A)	<(DHA)
O1–H1 ... O2	0.84	2.07	2.66(1)	126.6
O1–H1 ... O4 ¹	0.84	2.64	3.22(1)	127.3
O2–H2 ... O3	0.84	1.99	2.68(1)	138.7
O3–H3A ... O4	0.84	2.14	2.69(1)	123.3
O3–H3A ... O1A ²	0.84	2.54	3.18(2)	134.6
O4–H4 ... O1	0.84	1.99	2.66(1)	136.1
O11M–H11M ... O6	0.84	2.04	2.87(4)	168.8
O12M–H12M ... O3W ³	0.85	1.35	2.17(3)	160.2
O2M–H2M ... O7 ³	0.84	1.66	2.21(2)	120.4
<i>Possible hydrogen bonds to water molecules</i>				
O5 ... O3W ³			2.50(1)	
O6 ... O3W ³			2.73(2)	
O6 ... O5W ³			2.72(2)	
O8 ... O3W ³			2.13(2)	
O9 ... O2W ⁴			3.03(1)	
O10 ... O1W			2.50(2)	
O10 ... O3W ³			3.05(2)	
O10 ... O4W ³			2.26(2)	
O11 ... O1W			2.68(2)	
O11 ... O4W ³			2.08(2)	
O12 ... O1W ⁵			2.67(2)	
O12 ... O2W			2.86(2)	
O13 ... O5W			2.25(2)	
O14A ... O5W			2.36(2)	
O14B ... O1W ³			2.82(2)	
O14B ... O1W ⁶			2.44(2)	
O15 ... O1W ³			2.84(2)	
O15 ... O3W			2.09(2)	
O15 ... O4W			1.99(2)	
O16 ... O5W			2.47(1)	
O16 ... O5W ³			2.24(1)	
O11M ... O3W ³			2.20(4)	
O11M ... O4W ³			2.40(3)	
O12M ... O3W ³			2.17(3)	
O12M ... O4W ³			1.95(3)	
O1W ... O4W ³			2.19(2)	
O3W ... O4W			2.14(2)	

Symmetry transformations used to generate equivalent atoms: (1) $-x+1, -y, -z+1$; (2) $-x+1, -y+1, -z+1$; (3) $-x+1, -y, -z$; (4) $x, y-1, z$; (5) $-x+2, -y, -z$; (6) $x-1, y, z$.

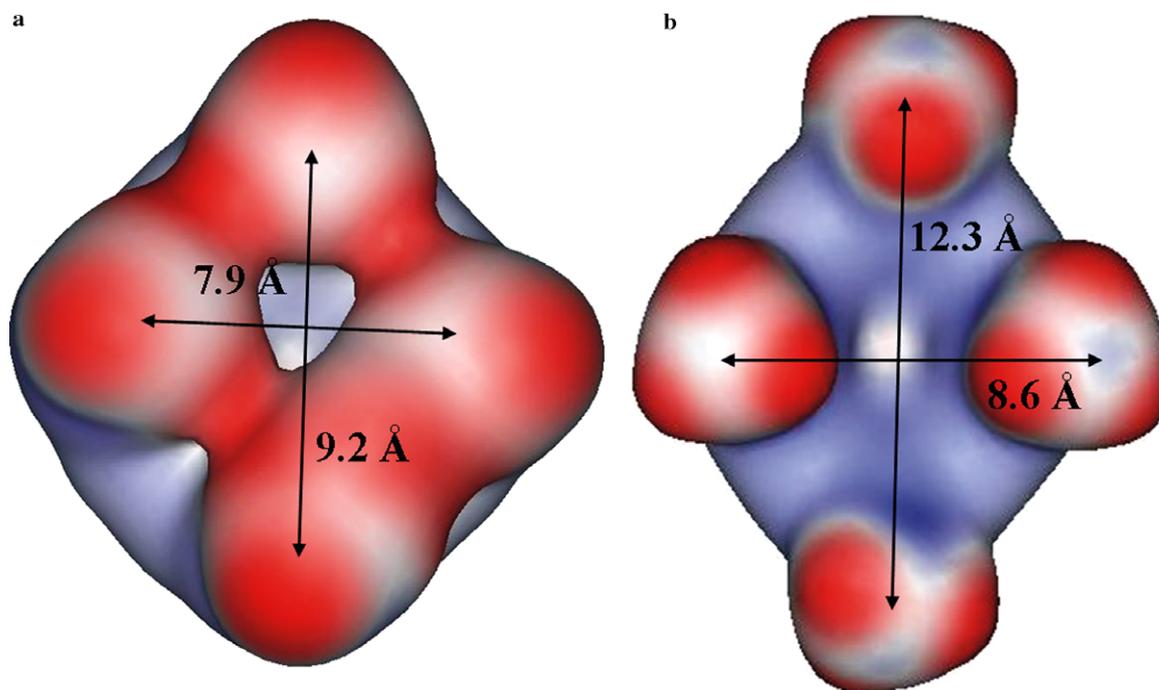


Fig. 2. (a) Top view of *para*-sulfonatocalix[4]arene **1** showing that its cavity is less accessible than the one of *para*-sulfonatocalix[4]arene **2** (b).

OH). ^{13}C NMR (293 K, CDCl_3) 31.6 (t, Ar- CH_2 -Ar); 45.8 (t, Ar- CH_2 -Cl); 128.3 (s, Ar-*ortho*); 129.5 (d, Ar-*meta*); 131.4 (s, Ar-*para*); 148.9 (s, Ar-O).

To a solution of 5,11,17,23-tetrachloromethyl-25, 26, 27,28-tetrahydrocalix[4]arene (1.54 g, 2.5 mmol) in EtOH (10 mL), an aqueous solution of Na_2SO_3 (2 M, 11 mmol) was added. After refluxing overnight, the solvent was evaporated until the obtention of a precipitate which was then washed with brine. After purification on an Amberlit IR-120 column, the residue is recrystallised from methanol to give pure compound **1** as a white powder. Yield 60%. ^1H NMR (293 K, D_2O) 3.70 ppm (s, 8H, Ar- CH_2 -Ar); 4.60 ppm (s, 8H, Ar- CH_2 - SO_3Na); 6.90 ppm (s, 8H, Ar-*H*). ES-MS (negative field, m/z): 865 ($\text{M}-\text{Na}^+$), 421 ($(\text{M}-2\text{Na}^+)/2$).

Crystals were obtained by recrystallisation of the crude reaction product from an acetone/methanol mixture.

2.2. X-ray crystallography

X-ray data were collected on a Nonius KappaCCD diffractometer. Data were corrected for Lorentz and polarisation.

Table 3

Comparison of the apparent stability constants K calculated for the complexes formed between the *p*-sulfonatocalix[4]arene **1** and *p*-sulfonatocalix[4]arene **2** with arginine and lysine in water at pH 7.5 (phosphate buffer) and 298.15 K^a [23]

Compound	K^b	
	1	2
Arginine	40 (± 10)	1780 (± 220)
Lysine	100 (± 20)	740 (± 60)

^a K deduced from the non-linear least-squares fit of the data using a 1:1 binding model.

^b Molar scale. ^c Shifts of the lysine.

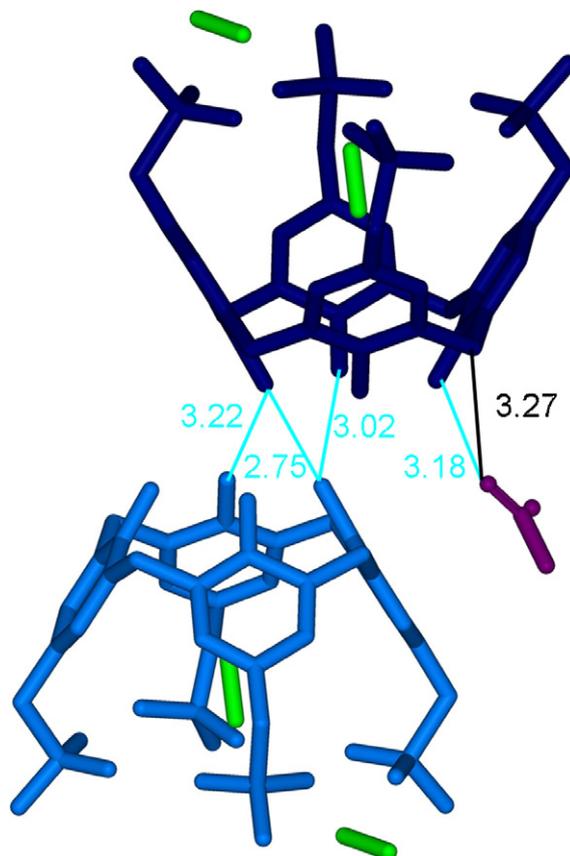


Fig. 3. Calixarene packing via hydrogen bonds (blue lines) between phenolic hydroxyl groups and short contacts (dark line) with acetone molecules (purple). Hydrogen bonds with water molecules are not shown for clarity. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this paper.)

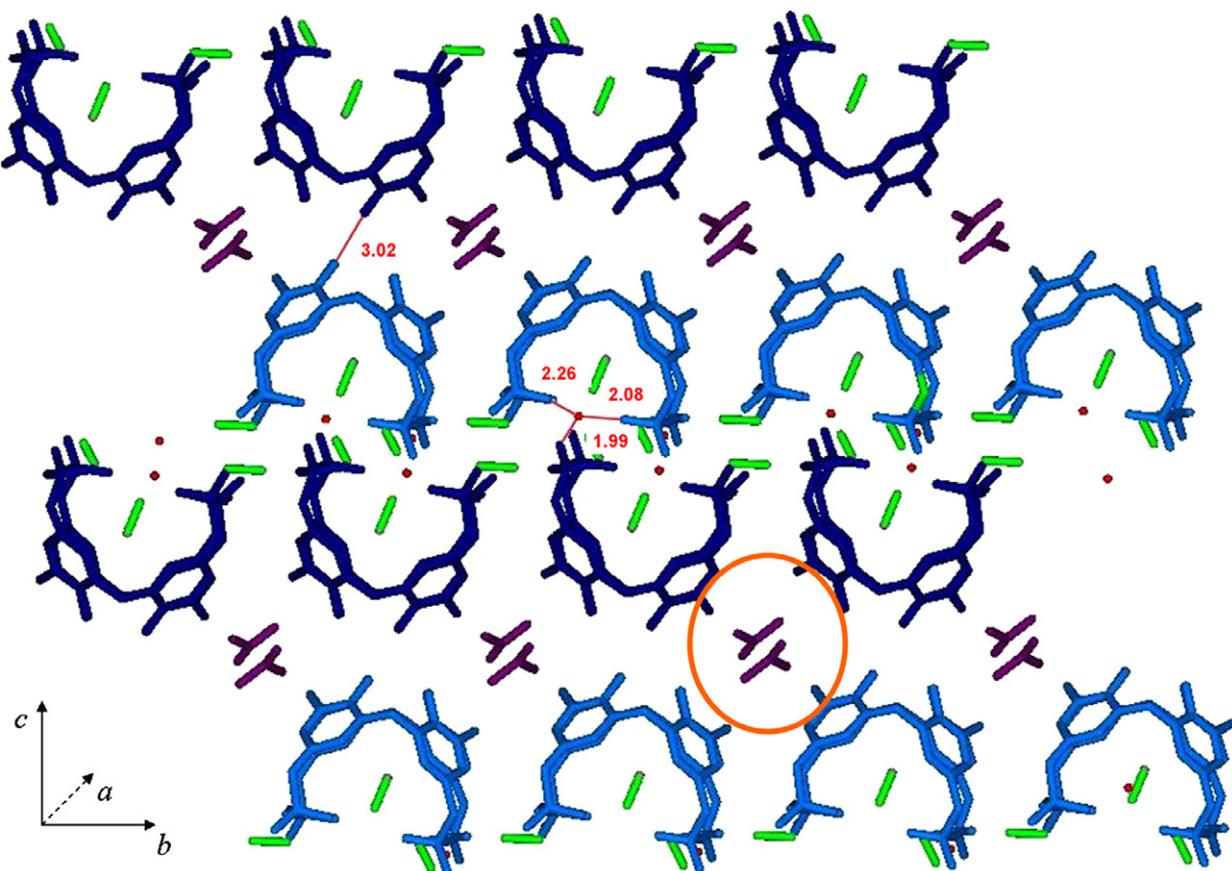


Fig. 4. View along the *a* axis of the structural bilayer packing motif; acetone channels are marked in orange. Calixarene molecules are colored in dark and light blue, methanol molecules in green, acetone in purple and water molecules as red spheres. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this paper.)

tion effects but not for absorption. The structure was solved by direct methods and Fourier techniques (SHELXS-86, [21]) and refined, on $|F|^2$ (SHELX-97, [22]). All non-hydrogen atoms were refined anisotropically. H-atoms were included in geometric positions and refined as ‘riding’ atoms with isotropic thermal parameters based upon the corresponding bonding carbon or oxygen atom [$U_{\text{iso}} = 1.2U_{\text{eq}}$, $U_{\text{iso}} = 1.5U_{\text{eq}}$ for CH_3 and OH hydrogens]. Experimental details for the structure determination are presented in Table 1, hydrogen bond lengths and cone angle are listed in Table 2.

3. Result and discussion

para-Sulfonatomethylcalix[4]arene **1** adopts a very slightly flattened cone conformation (cone angles between the opposite aromatic rings are 78.7° and 62.4°). Hydrogen bonds occur not only between the four phenolic hydroxyl groups at the lower rim as, usually seen in the structure of *para*-sulfonatocalix[4]arene **2**, but also between sulfonate groups at the upper rim causing them to be directed towards the interior of the cavity. Each sulfonate group also forms hydrogen bonds with either water or methanol molecules (for details see Table 2).

Comparing the structure of this water soluble calixarene with that of one of *para*-sulfonatocalix[4]arene in the struc-

ture of *para*-sulfonatocalix[4]arene – triethylamine complex [17] (Fig. 2), it can be clearly seen that the hydrophobic cavity is less accessible than that of the “traditional” *para*-sulfonatocalix[4]arene; the size of the upper rim ($7.9 \times 9.2 \text{ \AA}$) of the *para*-sulfonatomethylcalix[4]arene being noticeably smaller compared to the sulfonatocalixarene **2** ($8.6 \times 12.3 \text{ \AA}$). This observation is in agreement with the results we obtained on the complexation of **1** with lysine and arginine.[23] The association constants values were three orders of magnitude lower than those obtained for *para*-sulfonatocalix[4]arene **2** (Table 3), leading us to postulate that the cavity was not accessible for the lateral chains of these aminoacids.

The stoichiometry of the crystal is 1:2:1:4.5 for calixarene, methanol, acetone and water, respectively. Even though we have started with the acidic form of *para*-sulfonatomethylcalix[4]arene, in the crystal, the sulfonate groups are hydrated and probably deprotonated; four water molecules are probably protonated as hydroxonium cations to balance the charge.

The two methanol molecules found in the crystal are not chemically equivalent. One, disordered over two positions, is bound within the cavity and forms with the calixarene an inclusion complex with the methyl group pointing inside the cavity. The two partially occupied hydroxyl groups are

hydrogen bond donors; one to a sulfonate group and the second to a water molecule. In both orientations those hydroxyls may also act as the acceptors of hydrogen bonds from water molecules (for details see Table 2). The second methanol molecule, situated near the upper rim, interacts only with one of the sulfonate groups of *para*-sulfonatomethylcalix[4]arene via a hydrogen bond.

Water molecules are involved in a number of hydrogen bonds with calixarene sulfonate groups, methanol molecules as described above, and other water molecules forming a complex hydrogen bond network. The acetone molecule, which is also partially disordered, is not involved in this network.

The solid state structure is generated by a new kind of bilayer structural motif, different from typical bilayers [10,12,16] or zig-zag bilayers [13]. The bilayer is assumed by direct hydrogen bonds between phenolic hydroxyl groups of two calixarenes and strong hydrogen bonds between sulfonate groups and water molecules (Fig. 3). Between bilayers along crystallographic *a* axis, a hydrophobic channel filled with acetone molecules is formed (Fig. 4).

4. Conclusion

The first *para*-sulfonatomethylcalix[4]arene crystallographic structure has been solved. As might have been expected from solution complexation studies, the cavity of this calixarene derivative is less accessible for hydrophobic complexation than in the case of *para*-sulfonatocalix[4]arene.

5. Supplementary materials

Crystallographic data for this complex reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary materials (CCDC 607951). Copies of available material can be obtained free of charge on application to the director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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