

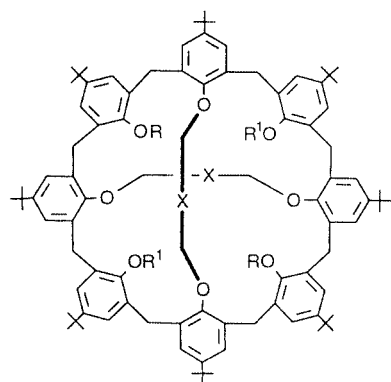
Interplay between cone and partial-cone geometry in doubly-bridged calix[8]arenes investigated by X-ray and 2D NMR

Corrada Geraci,^a Alessandra Bottino,^a Mario Piattelli,^a Enrico Gavuzzo^b and Placido Neri^{*c}^a Istituto per lo Studio delle Sostanze Naturali di Interesse Alimentare e Chimico-Farmaceutico, C.N.R., Via del Santuario 110, I-95028 Valverde (CT), Italy^b Istituto di Strutturistica Chimica "G. Giacomello", C.N.R., Area della Ricerca di Roma, Montelibretti (RM), Italy^c Dipartimento di Chimica, Università di Salerno, Via S. Allende, I-84081 Baronissi (SA), Italy

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X-Ray crystallography proves the occurrence in 1,5:3,7-doubly-bridged calix[8]arenes of a $\frac{3}{4}$ -cone geometry which can be transformed, in analogy to calix[4]arenes, to an unprecedented $\frac{3}{4}$ -partial-cone arrangement by proper alkylation of the free OH groups.

One of the most peculiar features of calix[4]arenes is their atropisomerism, which gives rise to four discrete conformers (*cone*, *partial-cone*, *1,3-alternate*, *1,2-alternate*) when groups bulkier than ethyl are appended at the lower rim.^{1†} A similar clear-cut picture cannot be drawn for the homologous calix[6]arenes, in which the complete blockage of *through-the-annulus* conformational interconversion can hardly be obtained because of the larger dimension of the macrocycle.^{2a} However, in this case two commonly adopted conformations have also been characterized: the *pinched-cone*^{2b} and the *1,2,3-alternate*.^{2c} The situation is even worse for the larger calix[8]arenes, for which the *pleated-loop*^{3a} and the *chair-like*^{3b} conformations have been characterized only in the solid state. In fact, it was recognized that the shaping of the calix[8]arene framework requires a mandatory intrabridging step.⁴ Using this approach highly preorganized D_{2d} -symmetrical 1,5:3,7-doubly-bridged calix[8]arenes have been prepared by both Shinkai⁵ and our⁶ groups, for which molecular modeling predicts an intriguing structure composed by four $\frac{3}{4}$ -cone clefts. In this communication we wish to report the first X-ray evidence for this geometry and also to prove that an unprecedented $\frac{3}{4}$ -partial-cone local arrangement can be generated by proper alkylation of the free OH groups.



- 1 X = CH₂CH₂; R = R¹ = H
 2 X = CH₂OCH₂; R = R¹ = H
 2a X = CH₂OCH₂; R = *p*-CH₂C₆H₄Bu^t; R¹ = H
 2b X = CH₂OCH₂; R = R¹ = Me
 2c X = CH₂OCH₂; R = R¹ = Et

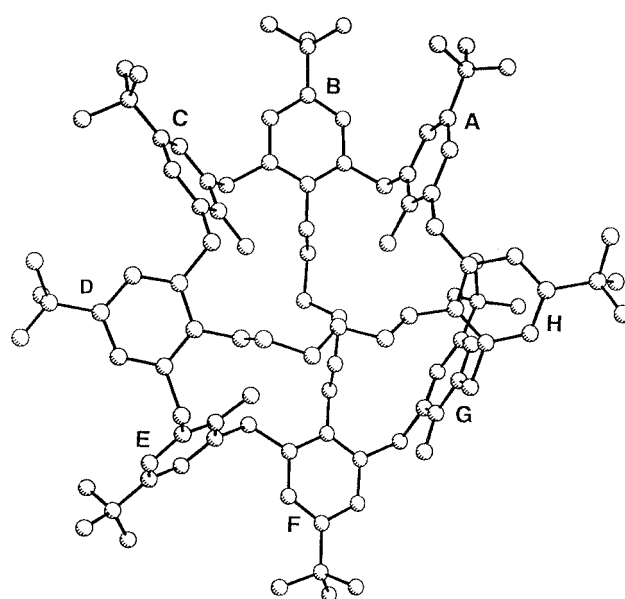


Fig. 1 Crystal structure of 1. The labeling of aromatic rings is indicated while solvent molecules are omitted.

Single crystal X-ray analysis[‡] was performed on 1,5:3,7-bis(tetramethylene)-bridged calix[8]arene 1,[§] which was synthesized, in analogy with 1,5:3,7-calix[8]bis-crown-3 2,⁶ in 68% yield by a two-step alkylation (Cs₂CO₃ followed by NaH) of *p*-tert-butylcalix[8]arene with 1,4-diiodobutane. The crystal structure of 1 (Fig. 1), which represents the first X-ray analysis of a bridged-calix[8]arene, shows two well defined $\frac{3}{4}$ -cone clefts (rings ABC and CDE), locally very similar to a typical calix[4]arene C_{2v} -cone.¹ Each of them is characterized by the inclination of the rings (canting angle) with respect to the mean planes of the four methylenes [A(71°), B(50°), C(53°) and C(23°), D(76°), E(49°)]. The EFG triad of aromatic rings forms a $\frac{3}{4}$ -partial-cone geometry in which G is the "inverted" ring. This inversion is obtained at expense of the self-filling⁷ of the fourth $\frac{3}{4}$ -cone (GHA triad), which consequently is very distorted. The ϕ and χ dihedral angles used for the symbolic representation of the molecular conformation of calixarenes according to Uguzzoli and Andreotti are reported in Table 1.⁸ The "inversion" of the G ring is evidenced by the — — symbol for F–G junction, which breaks the regular succession of — +, — +, + —, + —, — +, — +, — +, + —, corresponding to the D_{2d} conformation composed of four $\frac{3}{4}$ -cone clefts. Solvent molecules (one CH₂Cl₂ and two H₂O) are found within the $\frac{3}{4}$ -cone clefts (see Fig. 2). The CH₂Cl₂ molecule is disordered

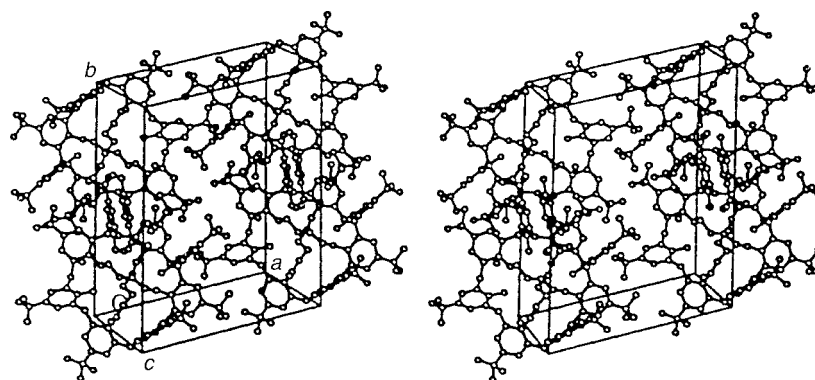


Fig. 2 Stereoview of the crystal packing of **1** including solvent molecules.

Table 1 The φ and χ torsion angles values ($^{\circ}$) which define the conformation of **1** (according to ref. 7), esd in the range 1.0–1.5 $^{\circ}$

| Joined rings | $\varphi/^{\circ}$ | $\chi/^{\circ}$ |
|--------------|--------------------|-----------------|
| A–B | –73.6 | +68.8 |
| B–C | –80.7 | +92.2 |
| C–D | +91.4 | –47.4 |
| D–E | +78.8 | –101.0 |
| E–F | –96.8 | +36.9 |
| F–G | –120.0 | –132.3 |
| G–H | +15.5 | –97.6 |
| H–A | +76.1 | –106.1 |

with the two chlorine atoms occupying four positions and the carbon atom, with its partial positive charge, positioned at 3.66 and 3.68 Å from the aromatic centroids of A and B rings, respectively, giving rise to probable CH– π interactions. Three strong hydrogen bonds are present: between the phenolic oxygens of the B and C rings (2.79 Å), D and E rings (2.71 Å), A and H rings (2.76 Å). The phenolic oxygen of the “inverted” G ring forms a weak hydrogen bond with a water molecule (3.04 Å) placed in the EFG triad of aromatic rings. The other water molecule, placed in the CDE cleft, seems to form a weak hydrogen bond with the phenolic oxygen of the C ring (3.26 Å). There are no other hydrogen bonds besides these and the molecular packing is mainly governed by van der Waals forces. The cavity formed by the two tetramethylene bridges and the three phenolic oxygens, pointing towards the centroid of the molecule, is not large enough to host any solvent probably because it is collapsed in the solid state. In fact, the shortest distance between carbon atoms of the two chains is only 4.4 Å, *ca.* 1.0 Å above the van der Waals distance.

On the basis of the NMR data [a well spaced AX system (δ 3.37 and 4.22, J = 14.0 Hz) for protons and a triplet at δ 32.3 for the carbon in ArCH₂Ar groups] it must be assumed that compound **1** (as well as **2**) in solution adopts an ideal time-averaged D_{2d} conformation with four $\frac{3}{4}$ -cone clefts. Therefore, the ring inversion has to be attributed to favorable interactions which take place in the crystal (mainly the *tert*-butyl self-filling and OH \cdots O bonding). In any case this brings to light the possibility that, in analogy with calix[4]arenes,¹ this inversion may be blocked when hydroxy groups are alkylated with sufficiently bulky groups. In order to test this hypothesis we subjected **2**⁶ to alkylation with *p*-*tert*-butylbenzyl bromide in the presence of Cs₂CO₃ which afforded in 20% yield the 1,5-dibenzyl derivative **2a**.[‡] Interestingly, this compound displays *inter alia* a tight AB system and a typical resonance at 38.9 ppm for the protons and carbon, respectively, of an ArCH₂Ar group which, in accordance with canonical rules, clearly indicates the presence of an inverted ring. This was confirmed by a conformational study, based on a complete 2D NMR analysis combined with ROE-restrained Molecular Dynamics calculations,⁹ which gave the structure depicted

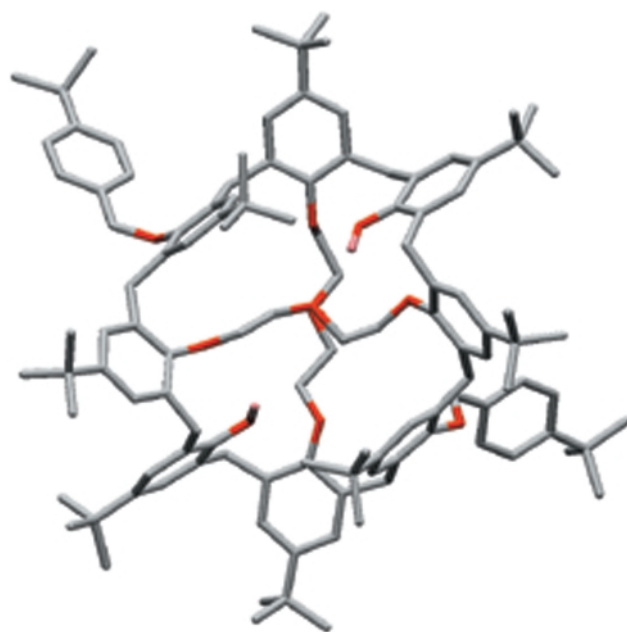


Fig. 3 Polytube model of the conformation of **2a** obtained by ROE-restrained MD calculations.

in Fig. 3. Therefore, compound **2a** represents the first example of a calix[8]arene with aryl rings blocked in an *anti* orientation.

The structure of 1,5-dibenzyl derivative **2a** is dissymmetric since it possesses only a C_2 symmetry axis and hence it is inherently chiral.¹⁰ This was confirmed by the splitting of several signals in the ¹H NMR spectrum upon addition of Pirkle's reagent. This result prompts a close scrutiny of the three-dimensional features of **1** or **2** which reveals that several chiral derivatives can be obtained from 1,5:3,7-doubly-bridged calix[8]arenes by a proper combination of regio- and *syn/anti* stereoisomerism when enough bulky substituents are appended at the lower rim.¹¹ How bulky these substituents have to be can be estimated from the observation that tetramethyl compound **2b**⁶ is conformationally mobile while tetraethyl derivative **2c**[‡] (obtained by ethylation of **2** using EtI–NaH–DMF) is conformationally hindered. In fact, **2c** gives simple NMR spectra at high temperatures (350 K, C₆D₆) compatible with a D_{2d} symmetry while at rt it gives rise to more complicated spectra compatible with an S_4 symmetry. In particular, the presence in the ¹³C NMR spectrum (295 K, CDCl₃) of an ArCH₂Ar resonance at δ 39.3 demonstrates the *anti* orientation of ethylated rings. In conclusion, in the case of bis-crown **2**, a substituent larger than propyl has to be used to block the *syn/anti* interconversion of aryl rings.

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Notes and references

† These conformations have been well characterized by X-ray crystallography and can be easily ascertained by NMR spectroscopy using ^1H and ^{13}C chemical shifts of ArCH_2Ar groups in accordance, respectively, to Gutsche and de Mendoza rules (ref. 1).

‡ Crystal data for **1**: $\text{C}_{96}\text{H}_{124}\text{O}_8 \cdot \text{CH}_2\text{Cl}_2 \cdot 2\text{H}_2\text{O}$, $M = 1527.0$, triclinic, space group $P\bar{1}$ (no. 2), $a = 17.739(6)$, $b = 21.050(9)$, $c = 16.878(8)$ Å, $\alpha = 108.70(3)^\circ$, $\beta = 103.60(4)^\circ$, $\gamma = 72.70(4)^\circ$, $U = 5631(4)$ Å³, $Z = 2$, $D_c = 0.90$ g cm⁻³, $\mu(\text{Cu-K}\alpha) = 8.72$ cm⁻¹, $F(000) = 1652.0$. Data were collected at room temperature to give 18436 measured reflections, 17748 considered unique. Among them, 7350 reflections with $F_o > 6.0\sigma(F_o)$ were considered as observed: $R = 0.147$, $R_w = 0.154$, $\Delta\rho_{\text{max}} = 2.2$ and $\Delta\rho_{\text{min}} = -0.6$ e Å⁻³. Large voids are present in the structure probably due to highly disordered solvent molecules, which are very difficult to model, and which account for residual peaks in the final difference Fourier map. CCDC reference number 188/208. See <http://www.rsc.org/suppdata/p2/a9/a909410e> for crystallographic files in .cif format.

§ Satisfactory microanalytical, FAB(+) MS and NMR spectral data were obtained for all new compounds. Compound **2a**: ^1H NMR (250 MHz, CDCl_3) δ 0.82, 0.97 [18 H each, s, $\text{Ar-C}(\text{CH}_3)$], 1.31 [18 H, s, $\text{Bn-C}(\text{CH}_3)$], 1.33, 1.36 [18 H each, s, $\text{Ar-C}(\text{CH}_3)$], 1.94 (2 H, br m, $\text{OCH}_2\text{-CH}_2\text{O}$), 3.18 and 4.36 (4 H, AX, J 15.3, ArCH_2Ar), 3.56 and 4.03 (4 H, AX, J 13.0, ArCH_2Ar), 3.38 and 4.08 (4 H, AX, J 17.2, ArCH_2Ar), 3.38 (2 H, m, $\text{OCH}_2\text{CH}_2\text{O}$), 3.56, 3.75 (4 H each, m, $\text{OCH}_2\text{CH}_2\text{O}$), 3.93 and 4.08 (4 H, AB, J 14.8, ArCH_2Ar), 4.09, 4.62 (2 H each, m, $\text{OCH}_2\text{-CH}_2\text{O}$), 4.59 and 4.94 (4 H, AB, J 11.7, OCH_2Bn), 5.77 and 7.24 (4 H, AX, J 2.1, ArH), 6.81 and 7.02, (4 H, AX, J 2.2, ArH), 6.95 and 7.46 (4 H, AX, J 2.2, ArH), 7.14 and 7.21 (4 H, AB, J 2.2, ArH), 7.16 (2 H, s, ArOH), 7.29 and 7.33 (8 H, AB, J 8.5, BnH); ^{13}C NMR (62.9 MHz, CDCl_3) δ 29.8, 32.0, 32.5, 38.9 (t, ArCH_2Ar), 31.0, 31.2, 31.4×2 , 31.6 [q, $\text{C}(\text{CH}_3)_3$], 33.8, 33.9×2 , 34.3, 34.5 [s, $\text{C}(\text{CH}_3)_3$], 67.0, 69.1, 69.3, 71.4 (t, $\text{OCH}_2\text{CH}_2\text{O}$), 73.2 (t, OCH_2Bn), 123.9, 124.1, 125.0 (d, C_{ArH}), 125.1×2 (d, C_{BnH}), 126.0, 126.2, 126.8 (d, C_{ArH}), 127.3×2 (d, C_{BnH}), 128.1, 128.5 (d, C_{ArH}), 127.0, 128.3, 131.5, 132.9, 133.2, 133.6, 134.0, 134.7 (s, C_{ArCH_2}), 135.1 (s, C_{BnCH_2}), 142.2, 144.9, 146.3, 148.6 (s, $\text{C}_{\text{Ar-}}$

Bu'), 150.5 (s, $\text{C}_{\text{BnBu}'}$), 148.9 (s, C_{ArOH}), 151.4, 153.0, 153.6 (s, $\text{C}_{\text{ArOCH}_2}$).

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