



Evidence of Hydrogen Bonding in Stabilizing the Cone Conformation of a Monoalkylated Calix[4]arene. X-ray Structure of 25-[2-(ethoxy-1-*p*-toluene-sulfonate)phenyl]-26,27,28-trihydroxy calix[4]arene*

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(Received: 22 November 1999; in final form: 10 March 2000)

Key words: calix[4]arene, monoalkylated calix[4]arene, cone conformation, hydrogen bonding, X-ray structure

Abstract

The synthesis of 25-[2-(ethoxy-1-*p*-toluene-sulfonate)phenyl]-26,27,28-trihydroxy calix[4]arene **3** as a byproduct of the preparation of 1,3-dialkylated 25,27-di-[2-(ethoxy-1-*p*-toluene-sulfonate)phenyl]-26,28-dihydroxy calix[4]arene **2** is reported. Compound **3** is a monoalkylated calix[4]arene in the cone conformation. The X-ray structure of **3** showed that this conformation is stabilized by intramolecular hydrogen bonding.

Introduction

Calixarenes have attracted much interest because of their versatility in functionalization behaviour and their ability to adopt after functionalization four basic conformations: cone, partial cone, 1,2-alternate and 1,3-alternate [1, 2]. These different conformations which have been identified, differ in the orientation of the phenyl rings with respect to the mean plane of the four connecting methylene CH₂ atoms. The *cone conformation* is stabilized in parent calixarenes by the presence of circular arrays of intramolecular hydrogen bonds. The synthesis of monoalkylated calix[4]arenes is poorly documented and only two publications have appeared on their preparation [3, 4], only one of which discussed the conformation of the products obtained. As a consequence, very little is known about the factors stabilizing the conformation of monoalkylated calix[4]arenes.

In the present note we present the preparation of monoalkylated 25-[2-(ethoxy-1-*p*-toluene-sulfonate)phenyl]-26,27,28-trihydroxy calix[4]arene **3** as a by-product of the preparation of 1,3-dialkylated 25,27-di-[2-(ethoxy-1-*p*-toluene-sulfonate)phenyl]-26,28-dihydroxy calix[4]arene **2**. The X-ray structure of **3** indicated the cone conformation of the calix unit and showed evidence of hydrogen bonding in stabilizing this conformation.

Experimental

Materials for synthesis

2-(2-Hydroxyethoxy)-phenol, *p*-toluene-sulfonyl chloride, triethylamine, potassium carbonate and the solvents were commercial reagents and used without further purification. Calix[4]arene was prepared according to the literature [5].

Analytical procedures

The melting points (mps) were taken on a Büchi apparatus in capillaries sealed under nitrogen. Elemental analyses were performed at the Service de Microanalyse of the Institut de Chimie de Strasbourg. The ¹H-NMR spectra were recorded at 200 MHz on a Bruker AC 200 spectrometer. The FAB mass spectra were obtained on a VG-Analytical ZAB HF apparatus.

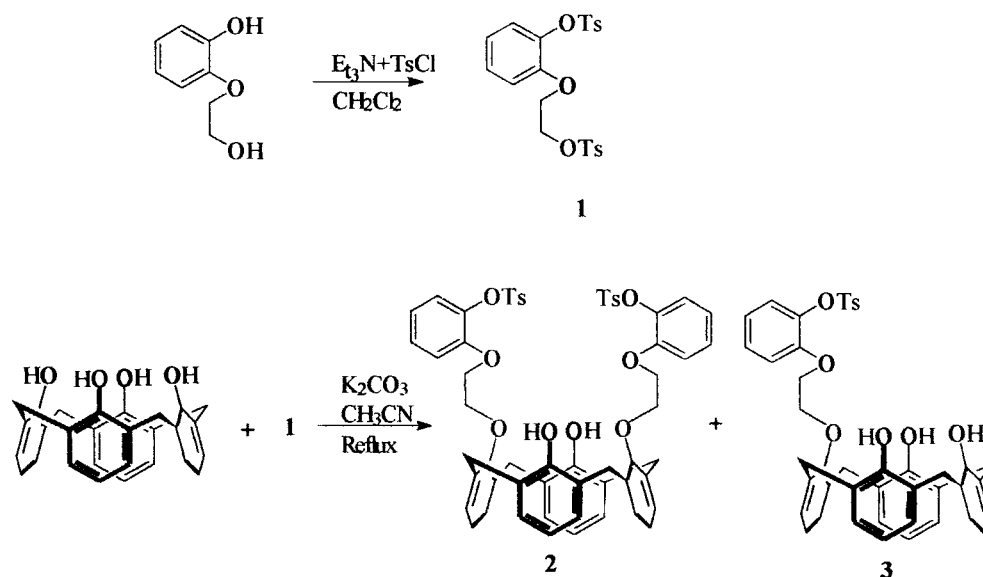
Synthesis of the calixarenes (2) and (3)

Preparation of the ditosylate of 2-(2-hydroxyethoxy)-phenol (1)

2-(2-Hydroxyethoxy)-phenol (3.00 g, 19.4 mmol) and *p*-toluene-sulfonyl chloride (7.43 g, 39.0 mmol) were dissolved in CH₂Cl₂ (150 mL). Triethylamine (11 mL, 77.0 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 24 h under a nitrogen atmosphere. On completion of the reaction, the solution was neutralized with 1N HCl. The organic phase was separated and the water layer was extracted twice with CH₂Cl₂. The combined extracts were dried over Na₂SO₄.

* **Supplementary Data** relevant to this publication have been deposited with the British Library, Boston Spa, Wetherby, Yorkshire, U.K as Supplementary Publication 82276 (63 pages).

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Scheme 1. Synthesis of calixarene derivatives **2** and **3**.

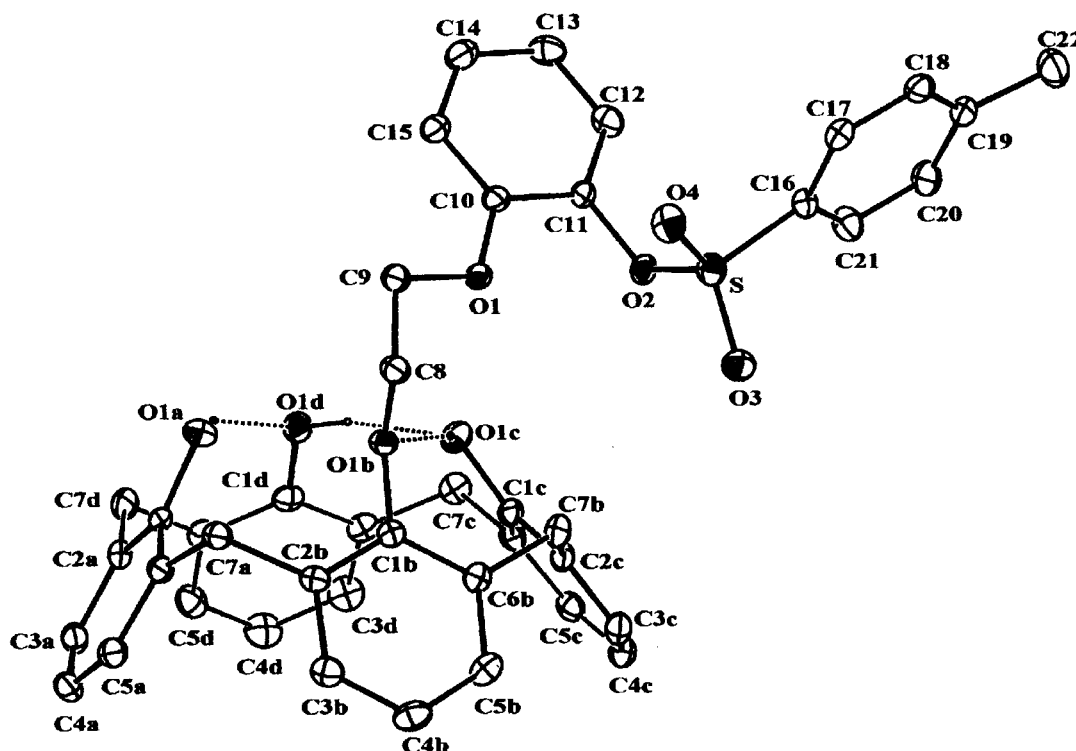


Figure 1. ORTEP III [8] view of the title compound with atomic numbering scheme. Unrefined H-atoms have been omitted for clarity.

The filtered solution was concentrated and precipitated with Et₂O to yield quantitatively pure **1** as a white powder. M.p. = 111–113 °C.

¹H-NMR (200 MHz, CDCl₃) δ 7.82 d (2 H, *J* = 8.3 Hz, TsH), 7.68 d (2 H, *J* = 8.3 Hz, TsH), 7.37 d (2 H, *J* = 8.3 Hz, TsH), 7.29–7.12 m (4 H, ArH and TsH), 6.96–6.75 m (2 H, ArH), 4.18–4.14 m (2 H, OCH₂), 3.97–3.93 m (2 H, OCH₂), 2.45 s (3 H, TsCH₃), 2.42 s (3 H, TsCH₃). *Anal. Calcd* for C₂₂H₂₂O₇S₂: C, 57.13; H, 4.79. Found: C, 57.03; H, 4.82.

Synthesis of the di and the monotosyl-calix[4]arenes (**2**) and (**3**) (Scheme 1)

Calix[4]arene (1.061 g, 2.5 mmol), K₂CO₃ (0.352 g, 2.55 mmol) were dissolved in CH₃CN (70 mL). After 2 h stirring at room temperature ditosylate **1** (2.36 g, 5.1 mmol) was added and the reaction mixture was refluxed for 48 h. After evaporation of the solvent, the residue was solubilized in CH₂Cl₂. The solution was neutralized with 1N HCl. The organic phase was separated and dried over Na₂SO₄. The filtered solution was evaporated and precipitated with CH₃OH to yield dialkylated calix[4]arene **2** as a white powder in 21% yield. M.p. = 146–147 °C. The filtrate of

Table 1. Crystallographic data for the monoalkylated calix[4]arene **3**

	Crystal parameters
Formula	C ₄₃ H ₃₈ O ₈ S
Formula weight	714.80
Crystal size (mm ³)	0.35 × 0.40 × 0.25
Crystal system	Monoclinic
Space group	P21/a
<i>a</i> (Å)	22.628(9)
<i>b</i> (Å)	10.406(4)
<i>c</i> (Å)	17.846(7)
β (deg)	121.60(4)
<i>V</i> (Å ³)	3579(3)
<i>Z</i>	4
<i>d</i> _{calc} (g/cm ³)	1.327
F(000)	1504
μ (Mo K α) (cm ⁻¹)	1.46
	Data collection
2 θ _{max} (deg)	48.0
Data collected (<i>hkl</i>)	±28, +15, +22
Scan speed (deg/sec)	0.01
Measured reflections	9641
Intensity decay (%)	4
Independent reflections	7676
Observed reflections	3453
Criterion for observed	1 > 2 σ (I)
<i>R</i> _{int}	0.016
	Refinement
Refinement on <i>F</i> ²	
Used reflections	7676
Number of restraints	0
Number of parameters	478
<i>R</i> ₁ (obs) (%)	7.20
<i>wR</i> ₂ (all) (%)	5.70
<i>S</i> (all)	1.23
(Δ/σ) _{max}	0.036
$\Delta(\rho)$ _{min-max} (e/Å ³)	-0.22; +0.23

$$R_{\text{int}} = \frac{\sum w|F_o^2 - \overline{F_o^2}|}{\sum w|F_o^2|}; R_r = \frac{\sum \|F_o - |F_c|\|}{\sum |F_o|}; wR_2 = \left[\frac{\sum w(F_o^2 - F_c^2)^2}{\sum w(F_o^2)^2} \right]^{\frac{1}{2}}; S = \left[\frac{\sum w(F_o^2 - F_c^2)^2}{n-p} \right]^{\frac{1}{2}}.$$

$\overline{F_o^2}$ is the average value of the equivalent reflection intensities, *n* is the number of independent reflections; *p* is the number of refined parameters; *w* = $\sigma^{-2}(F_o^2)$.

2 was evaporated and precipitated with CH₃OH to yield monoalkylated calix[4]arene **3** in 6% yield as microcrystals. M.p. = 128–129 °C.

¹H-NMR of **2** (200 MHz, CDCl₃) δ 7.63 d (4 H, *J* = 8.3 Hz, TsH), 7.47 s (2 H, ArOH), 7.18–6.88 m (20 H, ArH and TsH), 6.78–6.63 m (*H*, *Hpara* of calix), 4.31 d (4 H, *J* = 13.1 Hz, ArCH₂Ar) 4.14–4.12 m (8 H, CH₂), 3.36 d (4 H, *J* = 13.1 Hz, ArCH₂Ar), 2.34 s (6 H, TsCH₃). FAB (+) MS *m/z* = 1005.3. *Anal. Calcd* for C₅₈H₅₂O₁₂S₂·H₂O: C, 70.29; H, 5.49. *Found*: C, 70.21; H, 5.52.

¹H-NMR of **3** (200 MHz, CDCl₃) δ 9.71 s (1 H, ArOH), 9.12 s (2 H, ArOH), 7.66 d (2 H, *J* = 8.3 Hz, TsH), 7.35–6.84 m (15 H, ArH and TsH), 6.66 t (3 H, *J* = 7.5 Hz, *Hpara* of calix), 4.47–4.36 m (6 H, OCH₂CH₂O and ArCH₂Ar), 4.19 d (2H, *J* = 13.3 Hz, ArCH₂Ar), 3.48 d (2H, *J* = 13.0 Hz, ArCH₂Ar) 3.38 d (2 H, *J* = 13.3 Hz, ArCH₂Ar) 2.40 s (3H, TsCH₃). FAB (+) MS *m/z* = 715.2. *Anal. Calcd* for C₄₃G₃₈O₈S: C, 72.25; H, 5.67. *Found*: C, 72.28; H, 5.26.

Structure determination

Experimental details of the X-ray analysis of the monoalkylated calix[4]arene **3** presented here are given in Table 1. Single-crystal X-ray diffractometer data were collected on an Philips PW100 diffractometer with graphite-monochromated Mo K α radiation (λ = 0.71069 Å) using the ω – 2 θ scan technique at room temperature. Lattice parameters were obtained from least-squares analysis of 25 reflections. Three standard reflections recorded every two hours showed a decay in intensity of about 4% by the end of the data collection and so the data have been rescaled accordingly. The structure was corrected for Lorentz and polarisation effects but absorption and extinction effects were ignored.

The structure was solved by direct methods using SHELXS-86 [6] which revealed all the nonhydrogen atoms. Refinement was carried out on *F*² by full-matrix least-

Table 2. Selected bond lengths (Å) and angles (°) with e.s.ds.

Atom (1)—Atom (2)	Distance	Atom (2)—Atom (1)—Atom (3)	Angle
O(1a)—C(1a)	1.372(4)	C(6a)—C(7a)—C(2b)	111.8(2)
C(2a)—C(7d)	1.522(4)	C(6b)—C(7b)—C(2c)	112.3(2)
C(6a)—C(7a)	1.508(4)	C(6c)—C(7c)—C(2d)	114.2(2)
O(1b)—C(1b)	1.394(3)	C(6d)—C(7d)—C(2a)	112.3(2)
C(2b)—C(7a)	1.522(3)	O(1b)—C(8)—C(9)	107.3(2)
C(6b)—C(7b)	1.524(4)	C(8)—C(9)—O(1)	106.7(2)
O(1c)—C(1c)	1.388(3)	C(9)—O(1)—C(10)	117.9(2)
C(2c)—C(7b)	1.517(3)	O(1)—C(10)—C(11)	115.5(3)
C(6c)—C(7c)	1.499(4)	O(1)—C(10)—C(15)	125.9(3)
O(1d)—C(1d)	1.381(3)	C(11)—O(2)—S	119.3(2)
C(2d)—C(7c)	1.516(4)	O(2)—S—O(3)	102.8(2)
C(6d)—C(7d)	1.523(4)	O(2)—S—O(4)	109.7(2)
O(1b)—C(8)	1.437(3)	O(2)—S—C(16)	104.5(2)
C(8)—C(9)	1.493(4)	O(3)—S—O(4)	120.3(2)
C(9)—O(1)	1.419(3)	O(3)—S—C(16)	109.6(2)
O(1)—C(10)	1.371(3)	O(4)—S—C(16)	108.8(2)
C(11)—O(2)	1.409(3)	S—C(16)—C(17)	119.5(2)
S—O(2)	1.595(2)	S—C(16)—C(21)	120.3(2)
S—O(3)	1.428(2)		
S—O(4)	1.426(2)		
S—C(16)	1.746(3)		
C(19)—C(22)	1.497(4)		

Table 3. Hydrogen-bond geometry

Donnor—H...Acceptor	$d_{H...A}$ (Å)	$d_{D...A}$ (Å)	$d_{D-H...A}$ (Å)
O(1a)—H(1a)···O(1d)	2.09(6)	2.687(4)	145(6)
O(1c)—H(1c)···O(1b)	2.05(6)	2.708(5)	156(6)
O(1d)—H(1d)···O(1c)	1.73(4)	2.623(4)	167(4)

squares methods using SHELXL-97 [7]: the approximate atomic parameters were adjusted by several cycles first with isotropic and then with anisotropic temperature factors. Phenyl and methylene H atoms were inserted at calculated positions; the methyl group was treated as a rigid CH₃ unit with its original orientation taken from the strongest H atom peak on a difference Fourier synthesis. Hydroxyl hydrogen atoms were obtained from the $\Delta\rho$ synthesis and then refined. All hydrogen atoms were assigned an isotropic displacement factor corresponding to the U_{eq} value of the parent atom. The final wR_2 value was 0.056 ($w = 1/\sigma(F_o^2)$). The final difference electron-density map did not show residual peaks >0.23 e Å⁻³. Atomic scattering factors in the analytical forms were taken from the *International Tables for X-ray Crystallography*. All calculations were run on a Unix Digital Alpha Server 1000A.

Results and discussion

¹H-NMR of **2** showed that selective 1,3-O-dialkylation occurred and that the calix moiety adopted the cone conforma-

tion: an AB system at 3.36 ppm and 4.31 ppm with $J = 13.1$ Hz was observed for the ArCH₂Ar protons in the macroring. One also could observe a single signal as a singlet for the methyl groups of the tosyl residue.

Two AB systems were assumed in the ¹H-NMR spectrum of **3** at 3.38 ppm and 4.19 ppm with $J = 13.3$ Hz and at 3.48 ppm with $J = 13.0$ Hz (the second doublet being engaged in the multiplet from 4.36 to 4.47 ppm of OCH₂CH₂O) and led us to the conclusion of a cone conformation of **3**.

In order to ascertain the cone conformation we decided therefore to carry out the X-ray structure of **3**.

Selected bond lengths and angles are shown in Table 2. The conformation of the molecule shown in Figure 1, is mainly induced by the intramolecular hydrogen bond system (see Table 3), so the monoalkylated calix[4]arene **3** adopts a cone conformation although slightly distorted. The O···O contacts [O(1a)···O(1d) = 2.709(4), O(1c)···O(1b) = 2.713(4), O(1d)···O(1c) = 2.610(4) Å] indicate a significant strong hydrogen bonding system. The angles at the methylene carbon atoms are 111.8(2)°, 112.3(2)°, 114.2(2)°, and 112.3(2)°, respectively, for atoms C(7a) to C(7d). The inclination of the phenolic units with respect to the mean plane of the bridging methylene groups are 120.6(1)°, 116.1(1)°, 129.7(1)°, and 127.9(1)°, respectively for rings (C1a, ..., C6a) to (C1d, ..., C6d). The interplanar angles between opposite pairs of phenolic units are 109.6(1)° for rings (C1a, ..., C6a) and (C1c, ..., C6c), and 115.9(1)° for rings (C1b, ..., C6b) and (C1d, ..., C6d), while the interplanar angles between two adjacent phenolic rings are 101.5(2)°, 106.7(2)°, 113.1(2)°, and 109.3(1)°, respectively for (C1a,

..., C6a)–(C1b, ..., C6b), (C1b, ..., C6b)–(C1c, ..., C6c), (C1c, ..., C6c)–(C1d, ..., C6d), and (C1d, ..., C6d)–(C1a, ..., C6a).

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