



NMR and X-ray analysis of 25,27-dimethoxythiacalix[4]arene: unique infinite channels in the solid state

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Abstract

The conformational behaviour of 25,27-dimethoxythiacalix[4]arene was studied using NMR techniques and X-ray analysis. The title compound prefers a *cone* conformation in solution, while in the solid state it adopts a unique 1,2-*alternate* conformation thus creating a novel type of molecular channel held together by π - π interactions. © 2000 Elsevier Science Ltd. All rights reserved.

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Thiacalix[4]arenes¹ **1** and **2** have emerged very recently as a new part of the well-known calixarene family.^{2,3} Because of the presence of four sulphur atoms instead of methylene groups, thiacalix[4]arenes possess some interesting features when compared with the chemistry of ‘classical’ calixarenes. For example, the preparation of appropriate tetrasulphoxide⁴ or tetrasulphone⁵ derivatives can be achieved very easily by direct oxidation of sulphur. Unfortunately, the use of thiacalix[4]arenes as a molecular scaffold for the synthesis of more sophisticated systems is still restricted by the almost unknown conformational preferences of these compounds. As we found recently, simple alkylation of **1** and **2** by alkyl iodides/ K_2CO_3 in boiling acetone leads to the tetraalkylated products⁶ that demonstrate interesting conformational behaviour both in solution and in the solid state.⁷ In this paper we report on the synthesis of partly methylated thiacalix[4]arenes **3–5** and the conformational behaviour of these compounds.

We attempted the preparation of monoalkyl **3**, dialkyl **4**, and trialkyl **5** derivatives (Fig. 1) by the direct alkylation of **2** with methyl iodide using various molar ratios between the thiacalix-

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arene and a base (K_2CO_3). The alkylation of the parent compound **2** with an excess of methyl iodide in the presence of K_2CO_3 (1 equiv.) in refluxing acetone (5 days) smoothly gave the dialkylated derivative⁸ **4** in 64% yield. The use of acetonitrile as a solvent gave a comparable result (57%). Similarly, trimethoxy derivative **5** is directly accessible using 1.5 equiv. of K_2CO_3 , albeit in lower yield (29%) and only after chromatographic isolation by preparative TLC. Analogous attempts at monoalkylation (0.5 equiv. of K_2CO_3) of **2** led to a complex reaction mixture from which desired product **3** was obtained in low yields (15%). Derivative **3** was also prepared by the dealkylation reaction of **6** with $(CH_3)_3SiBr$ (3 equiv., CH_2Cl_2 , 1 week reflux) in 25% yield.

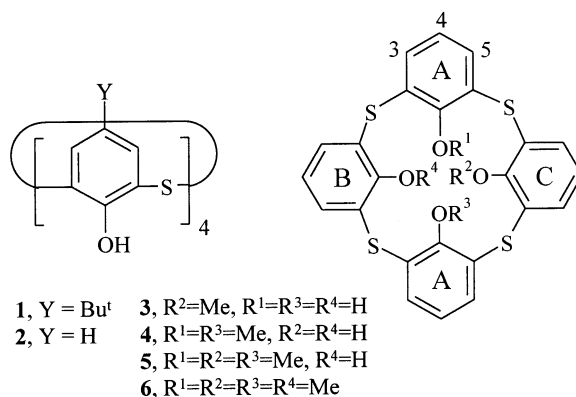


Figure 1. Definition of the compounds studied with indexing of the rings (A, B, C) and atom numbering used for the NMR assignment

The conformational behaviour of methoxy derivatives **3–5** has been studied in detail using $^1H/^{13}C$ NMR spectroscopy⁹ and X-ray crystallography. As shown in Figs. 2(a) and 3(a), the signals in 1H NMR spectra of the trimethoxy and dimethoxy derivatives **5** and **4** are broadened indicating a conformational exchange under the conditions used (500 MHz, $CDCl_3$, 298 K). The temperature-dependent 1H spectra of **5** confirmed the presence of two conformations at 203 K ($CDCl_3$) in an approx. 5:4 ratio (Fig. 2b). The major conformer was assigned using the NOE experiments as the *partial cone* (*paco*), with the methoxylated ring C inverted, while the minor signals were attributed to the *cone* conformer. The presence of two conformations (5.5:1 ratio, 213 K, $CDCl_3$) was also observed in the case of the dimethoxy thiocalixarene **4** (Fig. 3b). The 1H (203–333 K) and ^{13}C (213 K) spectral multiplicity of the prevailing conformer corresponds to the effective C_{2v} symmetry. The observed NOE contacts between aromatic protons of adjacent rings and between the substituents on the lower rim (OH, OCH_3) thus prove that the major isomer adopts the *cone* conformation. *Eventual* assignment as 1,2-*alt* is also eliminated by the lack of an NOE between the lower rim substituents and the aromatic protons, besides the high spectral symmetry. The assignment of the minor conformer was not a trivial problem due to the severe overlaps with the signals of the *cone* conformer. The number of signals indicates C_{2v} effective symmetry of the molecule, however, the analysis is still in progress. The behaviour described above of compounds **4** and **5** is substantially different from the corresponding methyl substituted classical calix[4]arenes where only *cone* conformations were observed under similar conditions.^{10–12}

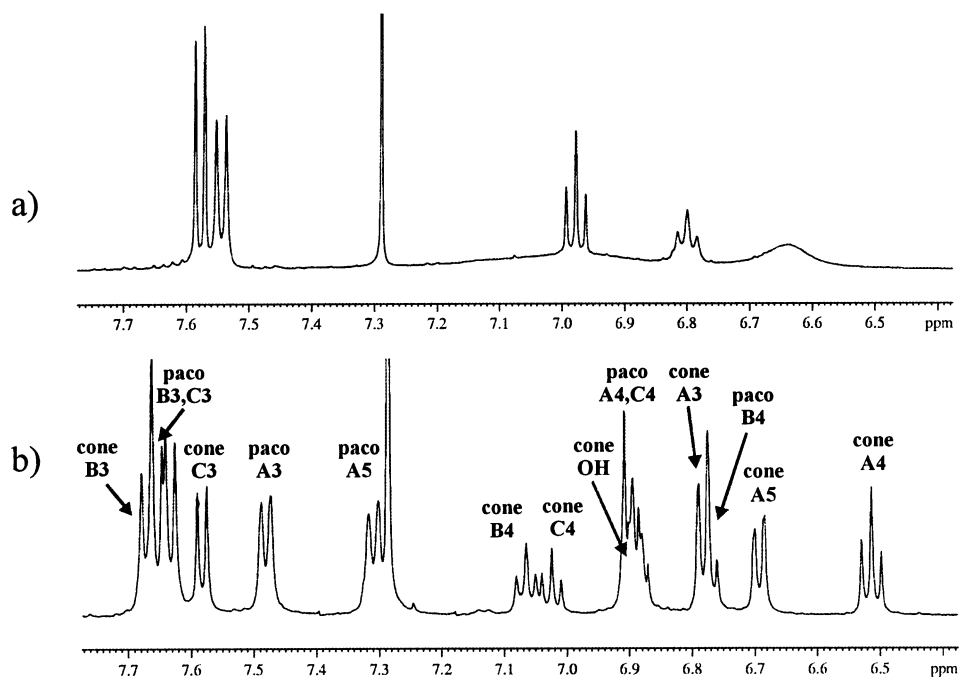


Figure 2. Partial ^1H NMR spectrum of **5** (500 MHz, CDCl_3) measured at (a) 298 and (b) 203 K

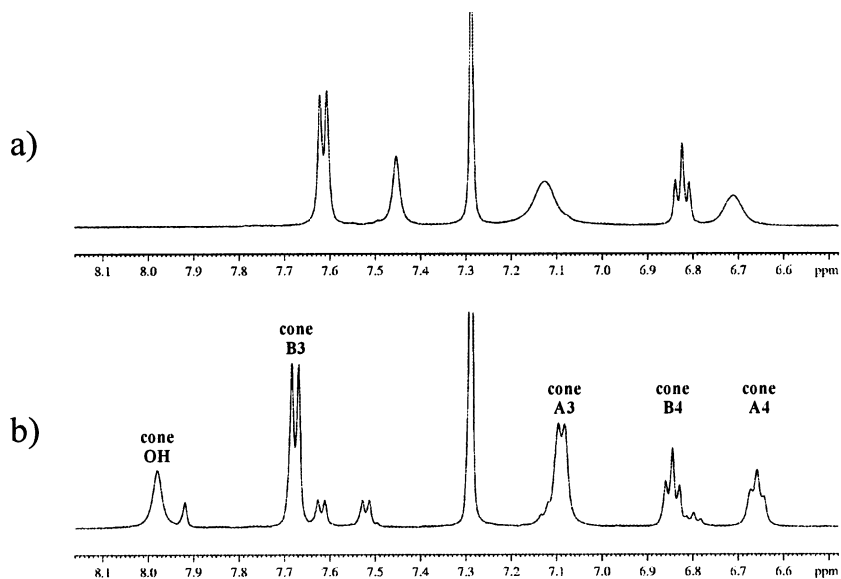


Figure 3. Partial ^1H NMR spectrum of **4** (500 MHz, CDCl_3) measured at (a) 298 and (b) 213 K

The peculiar conformational behaviour of dimethoxy derivative **4** was demonstrated using a single crystal X-ray diffraction¹³ (suitable monocrystals were obtained by slow evaporation of an EtOAc solution). It is known from the chemistry of 'classical' calix[4]arenes that distal dialkyl derivatives always prefer the *cone* conformation in the solid state.¹¹ Surprisingly, derivative **4** adopts a very unusual 1,2-*alternate* conformation, that is fixed by two hydrogen bonds (between

the adjacent methoxy and OH groups) on the opposite sites of the main molecular plane (Fig. 4). The non-ideal geometry of hydrogen bonds ($O29-H30-O30=146.8^\circ$) together with the short distance of the neighbouring sulphur atom ($H30-O29=1.99 \text{ \AA}$, $H30-S2=2.49 \text{ \AA}$) indicates possible electrostatic interactions with sulphur. The average distances between two adjacent (S2–S8) and two opposite (S8–S20) sulphur atoms are approximately 5.55 and 8.22 \AA , respectively, while the typical distances between the corresponding CH_2 groups in calix[4]arene 1,2-*alternate*¹⁴ are 5.13 and 7.40 \AA . The larger cavity of thiocalixarene probably enables better minimisation of electrostatic repulsion of methoxy groups via 1,2-*alternate* rather than via *cone* derivatives.

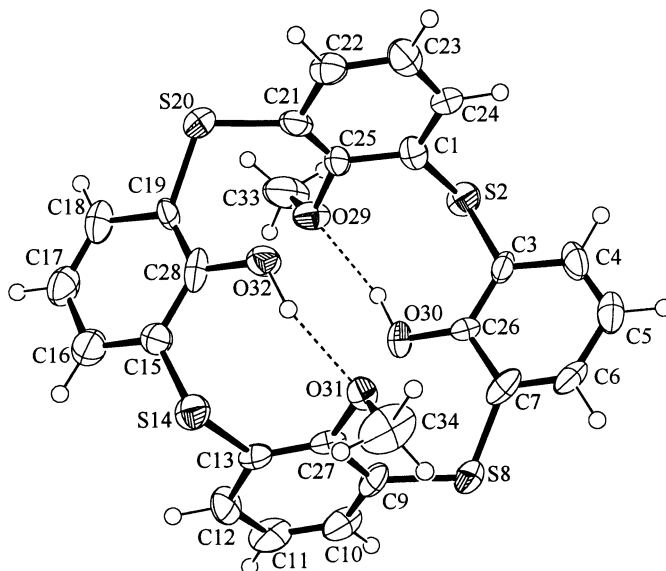


Figure 4. X-ray structure (ORTEP drawing) of **4** demonstrating intramolecular hydrogen bonds

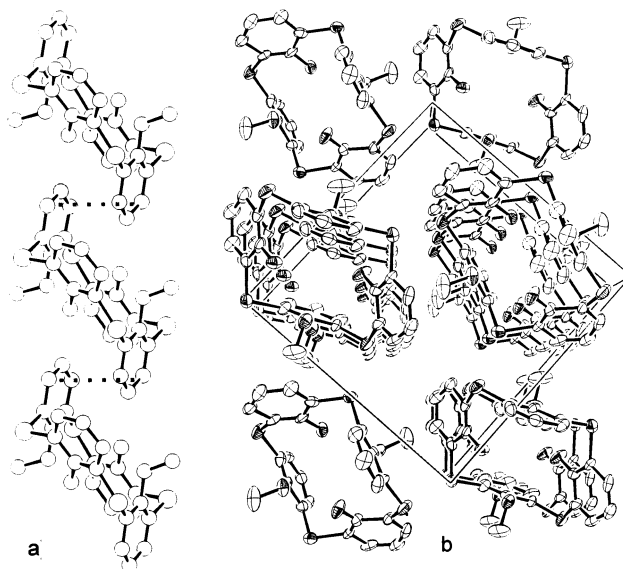


Figure 5. Crystal packing of **4**: (a) view along the y -axis, and (b) view along the x -axis

The most interesting feature of the derivative **4** is represented by its molecular packing. The thiacalix[4]arene molecules are arranged along the x -axis in such a way that they create infinite channels in the crystal (Fig. 5b). The network of molecules is held together by the intermolecular π - π interactions between the aromatic part (upper rims) of the methoxy substituted rings. The average distance of the two coplanar rings is 3.41 Å (Fig. 5a). To the best of our knowledge this arrangement of 1,2-*alternate* molecules is completely unknown in the chemistry of calixarenes (Cambridge Structural Database).

In conclusion, the partly methoxylated thiacalix[4]arenes possess interesting conformational behaviour both in the solution and in the solid state. The X-ray diffraction of dimethoxythiacalix[4]arene **4** revealed a novel type of molecular channels, held together by the π - π interactions. The conformational preferences of other partly alkylated thiacalixarenes are under current investigation.

References

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8. The mixture of derivative **2** (1 mmol), potassium carbonate (1 mmol) and methyl iodide (20 mmol) was stirred under reflux in 20 ml of acetone for 5 days. The reaction mixture was poured into diluted hydrochloric acid and extracted with chloroform. The organic layer was washed with water, dried over MgSO₄ and evaporated to yield crude product. The crystallisation from an CHCl₃-methanol mixture gave pure derivative **4** (65%) as white crystals, mp: 256–257°C. ¹H NMR spectrum (CDCl₃, 213 K, 500 MHz): (major conformer—*cone*): δ 4.15 (s, 6H, -OCH₃), 6.69 (brt, 2H, H4-arom A), 6.84 (t, 2H, $J=7.6$, H4-arom B), 7.10 (d, 4H, $J=6.8$, H3-arom A), 7.67 (d, 4H, $J=7.6$, H3-arom B), 7.97 (brs, 2H, OH), rings B, C are equivalent (Fig. 1). EA calcd for C₂₆H₂₀O₄S₄: C, 59.52; H, 3.84; S, 24.44%. Found: C, 59.17; H, 3.72; S, 24.87%.
9. Compound **3** (*cone*): ¹H NMR (500 MHz, 298 K, CDCl₃): δ 4.27 (s, 3H, -OCH₃), 6.67 (t, 1H, $J=7.7$, H4-arom B), 6.77 (t, 2H, $J=7.7$, H4-arom A), 6.94 (t, 1H, $J=7.7$, H4-arom C), 7.46 (d, 2H, $J=7.7$, H3-arom B), 7.53 (d, 2H, $J=7.7$, H3-arom C), 7.64 (d, 4H, $J=7.7$, H3-arom A), 8.63 (brs, 3H, OH). Compound **5**, ¹H NMR (500 MHz, 203 K, CDCl₃): (major conformer—*partial cone*): δ 3.70 (s, 3H, -OCH₃ C), 3.89 (s, 6H, -OCH₃ A), 6.78 (t, 1H, $J=7.7$, H4-arom B), 6.89 (m, 3H, H4-arom A, C), 7.31 (d, 2H, $J=7.7$, H5-arom A), 7.48 (d, 2H, $J=7.7$, H3-arom A), 7.64 (m, 4H, H3-arom B, C), 8.40 (brs, 1H, OH). ¹H NMR (500 MHz, 203 K, CDCl₃): (minor conformer—*cone*): δ 3.92 (s, 3H, -OCH₃ C), 3.94 (s, 6H, -OCH₃ A), 6.51 (t, 2H, $J=7.5$, H4-arom A), 6.69 (d, 2H, $J=7.5$, H5-arom A), 6.78 (d, 2H, $J=7.5$, H3-arom A), 6.91 (brs, 1H, OH), 7.03 (t, 1H, $J=7.7$, H4-arom C), 7.07 (t, 1H, $J=7.6$, H4-arom B), 7.58 (d, 2H, $J=7.7$, H3-arom C), 7.67 (d, 2H, $J=7.6$, H3-arom B). The assignment is based on ¹H NOE, COSY, ¹H-¹³C HMQC, and HMBC experiments.
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13. Crystallographic data for **4**: $C_{26}H_{20}O_4S_4$: $M=524.68\text{ g mol}^{-1}$, monoclinic system, space group $P2_1$, $a=7.579(1)$, $b=12.246(1)$, $c=13.108(1)\text{ \AA}$, $\beta=104.68(1)^\circ$, $Z=2$, $V=1176.9(2)\text{ \AA}^3$, $D_c=1.48\text{ g cm}^{-3}$, $\mu(\text{Cu K}\alpha)=3.92\text{ mm}^{-1}$, crystal dimensions of $0.1\times 0.1\times 0.4\text{ mm}$. Data were measured at 293 K on an Enraf–Nonius CAD4 diffractometer with graphite monochromated Cu K α radiation. The structure was solved by direct methods¹⁵ and anisotropically refined by full-matrix least-squares on F^{16} to final $R=0.0499$ and $R_w=0.0530$ using 1877 independent reflections ($\theta_{\text{max}}=69.93^\circ$). Hydrogen atoms were located from a Fourier map and from expected geometry and were not refined. Psi scan was used for the absorption correction.
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