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Synthesis of a deep-cavity thiacalix[4]arene^{\pm}

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Abstract—A novel thiacalix[4]arene derivative bearing four phenyl groups on the upper rim was prepared by the direct condensation of biphenyl-4-ol with elemental sulphur. As revealed by X-ray diffraction analysis, this compound adopts the *cone* conformation in the solid state, thus creating a cavity with an extended π -aromatic system potentially applicable for solid-state inclusion of suitable molecules. Subsequent alkylation (RI/K₂CO₃/acetone, R=Me, Et, Pr) yielded tetraalkylated derivatives, which were studied for their conformational preferences using ¹H NMR spectroscopy. While the Me or Et derivatives are conformationally mobile and exhibit thermodynamic equilibria of several conformers in solution (CDCl₃ or CD₂Cl₂), the corresponding propoxy derivative is infinitely stable at room temperature. © 2003 Elsevier Ltd. All rights reserved.

Thiacalix[4]arenes have become easily accessible in multi-gram scales recently using simple synthetic procedures.¹ Because of the presence of four sulphur atoms, the system has many novel features if compared with classical calixarenes,² and thiacalixarenes represent very promising building blocks or molecular scaffolds for the synthesis of more complicated supramolecular systems.³ Despite some recently described procedures for thiacalix[4]arene derivatisation,^{4,5} the chemistry of these compounds is still rather underdeveloped. If we consider the basic thiacalix[4]arene skeleton, only a few basic derivatives **1a–d** are accessible so far.^{1,6}



Keywords: thiacalixarenes; X-ray crystallography; alkylation; conformational analysis.

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One of the major goals of calixarene chemistry has been the design of novel receptors possessing properties suitable for separation science and/or molecular recognition. Therefore, the construction of calixarenes with larger cavities is of interest, as these compounds can potentially find applications in neutral guest recognition.^{2,3} Due to its rigid hydrophobic cavity, the thiacalix[4]arene with extended π -systems **1f** could be a very attractive host molecule for host–guest chemistry. In this paper we report the first synthesis and characterisation of thiacalix[4]arenes with deep aromatic cavities.

It is known from the chemistry of classical calixarenes that the deep-cavity calix[4]arene **1e** is virtually inaccessible by the direct condensation reaction of biphenyl-4ol with formaldehyde.^{1,7} So far, this compound has been prepared either by a stepwise procedure⁸ or by coupling reactions starting from the corresponding tetrahalocalix[4]arenes.⁹ As the tetrabromo- or tetraiodothiacalix[4]arenes are not available, we focused our attention on the direct condensation of biphenyl-4-ol with elemental sulphur.

Unfortunately, heating (200–230°C) biphenyl-4-ol with sulphur in the presence of NaOH in tetraethylene glycol dimethyl ether, i.e. similar conditions to those used for the preparation of thiacalix[4]arene 1a,¹ led to very complicated reaction mixtures, which gave the required product only in very low yields after complicated isolation procedures (repeated column chromatography).

This extensive study revealed several important facts: (i) the most suitable solvent is diphenyl ether; (ii) the temperature profile used throughout the reaction seems to be of critical importance for the yield of the condensation; (iii) the deep-cavity calixarene **1f** can be isolated using a simple precipitation/crystallisation procedure on a multi-gram scale.¹⁰ In a typical procedure, starting from 140 g of biphenyl-4-ol the *p*-phenylthia-calix[4]arene **1f** was isolated as an off-white solid (mp >300°C) in approx. 22% yield (ca. 35 g).

The structure of **1f** was confirmed by ¹H NMR spectroscopy and mass spectrometry. The spectrum in CDCl₃ shows a typical splitting pattern with $C_{4\nu}$ symmetry corresponding to the *cone* conformation. The high resolution TOF ESI MS in acetonitrile revealed the molecular mass of 800.108 (exact mass=800.118) with a splitting pattern matching exactly an isotopic model. As no higher mass was observed, we can conclude that compound **1f** prefers intramolecular (δ_{OH} = 9.66 ppm in CDCl₃) instead of intermolecular hydrogen bonds.

The final evidence for the structure of **1f** was demonstrated using single crystal X-ray diffraction analysis¹¹ (single crystals were obtained by slow evaporation of an EtOAc/CHCl₃ solution). The molecule adopts a *cone* conformation held together by intramolecular hydrogen bonds on the lower rim (Fig. 1), thus representing a deep cavity suitable for inclusion.



Figure 1. ORTEP drawing of 1f.

Thiacalixarene 1f was alkylated using the procedure described for the alkylation^{4d,12} of **1a,b** (RI/K₂CO₃/acetone, reflux) yielding the corresponding tetraalkoxy derivatives 2-4 in good yields (55-77%) (Scheme 1). The conformational behaviour of the tetramethoxy derivative 2 was studied using dynamic ¹H NMR spectroscopy in the range of 173–298 K with CD₂Cl₂ as a solvent. This revealed that the simple set of signals at room temperature (e.g. the singlet at $\delta = 3.80$ ppm for the methoxy groups) is due to the fast chemical exchange of several conformers (2a-d). As demonstrated in Figure 2, lowering of the temperature leads to the appearance of new signals. However, the large line width of the resonances and overlapping nature of these signals did not allow us to prove exactly the structures and ratios of the corresponding conformers. The relatively low coalescence temperature indicated the much higher mobility of the thiacalixarene skeleton as com-



Scheme 1. Preparation of 1f and subsequent alkylation reactions: (i) S_8 , diphenyl ether, 230°C, 6 h (22%); (ii) $RI/K_2CO_3/acetone$, 24 h to 2 days reflux [R = Me, 2 (77%); R = Et, 3 (75%); R = Pr, 4a (55%); 4b (10%)].



Figure 2. ¹H NMR spectra of 2 (CD_2Cl_2 , 300 MHz) acquired at: (a) rt, (b) -40°C, (c) -90°C. Signal at approx. 5.3 ppm is solvent.

pared with classical calixarenes.² Similarly, the ¹H NMR spectrum of **3** at room temperature confirmed that several possible conformers were present in solution under slow exchange conditions (see Fig. 3). By means of conventional one- and two-dimensional NMR experiments (COSY, NOESY, etc.) the main signals were assigned as the *partial cone* **3b** and *1,3-alternate* **3c** conformers in an approximate 45:55 ratio. The spectrum probably contains minor signals (less than 5%) due to other conformers **3a** and/or **3d**, but their accurate assignment was prevented by overlapping with stronger signals.

In the case of the propyl derivative, the tetraalkylated products **4** are infinitely stable at the room temperature and the corresponding conformers can be isolated.



Figure 3. Partial ¹H NMR spectra of **3** (CD₂Cl₂, 300 MHz) (a) aromatic region, (b) -O-CH₂- signals; * = 1,3-alternate **3c**, # = partial cone **3b**.

Consequently, two main products were obtained by column chromatography: the 1,3-alternate 4c (55% yield) and the *partial cone* 4b (10%). This situation with the gradual freezing of conformers (Me \rightarrow Et \rightarrow Pr) resembles the behaviour of *tert*-butyl-thiacalix[4]arene 1a where the same general trend was found.¹³

In conclusion, we have prepared a novel thiacalix[4]arene derivative bearing four phenyl groups on the upper rim by a direct condensation of biphenyl-4-ol with elemental sulphur. This compound represents an interesting deep-cavity thiacalixarene with an extended π -aromatic system, and is potentially useful for solidstate inclusion of suitable molecules. The subsequent utilisation of this compound for the construction of more elaborate structures is currently under investigation.

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- 10. Preparation of 5,11,17,23-tetraphenylthiacalix[4]arene (1f): A mixture of biphenyl-4-ol (140 g, 0.823 mol) and elemental sulphur (51 g, 1.594 mol) was dissolved in 100 ml of diphenyl ether at 140°C in a 1000 ml three-necked flask. The mixture was stirred on a heating mantle equipped with magnetic stirring. The reaction flask was purged by a slow stream of nitrogen during the whole reaction to remove the evolving hydrogen sulphide. Solid NaOH (16 g) was added to the yellow solution and the mixture was maintained for 2 h at a temperature of 140–145°C. During this time the reaction mix-

ture changed from yellow to red and finally to almost a black colour. The temperature was elevated to 170°C over the next 30 min and the reaction mixture was maintained at 170-180°C for an additional 4.5 h. The reaction mixture was then warmed up to 230°C over 1 h and this temperature was maintained for a further 3 h. During this time the reaction mixture became thick and a precipitate appeared accompanied by a colour change from black to red to yellow. The reaction mixture was cooled to rt, diluted with 1.5 L of CHCl₃ and acidified by the addition of hydrochloric acid (50 ml conc. HCl+ 250 ml water). Insoluble material was removed by filtration, the two-phase mixture was separated and the aqueous layer was extracted with 200 ml of CHCl₃. The organic fractions were collected, washed with water and the chloroform was removed on a rotary evaporator. To this liquid residue ethyl acetate (175 ml) was added and the mixture was stirred overnight. The precipitate was filtered off and washed with ethyl acetate to yield 36 g (22%) of raw product as off-white crystals. Higher purity product can be obtained by crystallisation from dioxane and subsequent precipitation from a CHCl₃diethyl ether mixture. Mp >350°C with decomp. ¹H NMR (CDCl₃, 298 K, 300 MHz) δ (ppm): 9.66 (s, 4H, OH), 7.89 (s, 8H, ArH), 7.55–7.28 (m, 20H, ArH); IR (CHCl₃) v_{max} (cm⁻¹): 3311 (OH); EA calcd. for C48H32O4S4: C, 71.97; H, 4.03; S, 16.01%. Found C, 71.53; H, 3.98; S, 15.74%. HR TOF ESI MS = 800.108 (calc. 800.118).

- 11. X-Ray data for 1f: $C_{48}H_{32}O_4S_4$, M=801.018, monoclinic system, space group P1 $2_1/c$ 1, a=12.577(2), b=30.428(4), c=10.582(1) Å, $\beta=103.61(1)^\circ$, V=3935.9(9)Å³, Z=4, $D_{calcd}=1.35$ g cm⁻³, μ (Cu K α)=25.85 cm⁻¹, crystal dimensions of $0.1 \times 0.2 \times 0.5$ mm. Data were measured at 293 K on an Enraf-Nonius CAD4 diffractometer with graphite monochromated Cu K α radiation $(\lambda=1.54180$ Å). The structure was solved by direct methods¹⁴ and anisotropically refined by full matrix least-squares on F values¹⁵ to final R=0.098, $R_w=0.098$ and S=1.173 with 245 parameters using 1514 independent reflections ($\theta_{max}=59.97^\circ$). Hydrogen atoms were located from expected geometry (see supplementary data). Crystallographic data were deposited in CSD under CCDC registration number 213637.
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- 13. Alkylation example: 5,11,17,23-tetraphenyl-25,26,27,28tetrapropoxythiacalix[4]arene (4): A mixture of derivative 1f (5 g, 6.25 mmol), potassium carbonate (20 g, 145 mmol) and propyl iodide (12 ml, 195 mmol) was stirred under reflux in 150 ml of dry acetone for 48 h. The solvent was evaporated under reduced pressure and the residue was poured into dilute hydrochloric acid and extracted with chloroform. The organic layer was washed with water, dried over MgSO4 and evaporated to yield the crude product. Recrystallisation from ethyl acetate gave 2.40 g of pure derivative 4c (40%) as white crystals, mp 236–237°C. ¹H NMR (CDCl₃, 300 MHz) δ (ppm): 7.54 (s, 8H, ArH), 7.52–7.28 (m, 20H, ArH), 3.9 (t, 8H, OCH₂), 1.4 (m, 8H, C-CH₂-C), 0.54 (t, 12H, CH_3). The mother liquor after crystallisation was evaporated and purified by column chromatography (silica

gel, eluent petroleum ether– $CH_2Cl_2=4:1$) to yield an additional 0.9 g (overall 55%) of **4c** and 0.59 g of **4b** (10%) as a white crystalline solid, mp 211–212.5°C. ¹H NMR (CDCl₃, 300 MHz) δ (ppm): 8.06 (s, 2H, ArH), 7.85 (s, 2H, ArH), 7.72 (d, 2H, ArH, J=2 Hz), 7.11 (d, 2, ArH, J=2 Hz), 7.72 (m, 2H, ArH), 7.65 (m, 2H, ArH), 7.47 (m, 4H, ArH), 7.37 (m, 2H, ArH), 7.05 (m, 2H, ArH), 6.94 (m, 8H, ArH), 4.2–4.1 (m, 4H, OCH₂), 3.8–3.62 (m, 4H, OCH₂), 2.1–1.9 (m, 6H, CH₂), 1.36–1.22 (m,

2H, CH₂), 1.12 (t, 6H, CH₃, J=7.33 Hz), 1.03 (t, 3H, CH₃, J=7.33 Hz), 0.34 (t, 3H, CH₃, J=7.33 Hz).

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