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Alkylation of thiacalix[4]arenes

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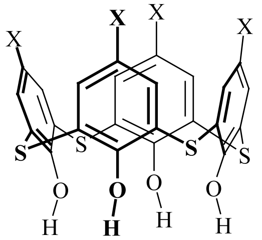
Abstract—Thiacalix[4]arenes were alkylated using procedures well established in 'classical' calixarene chemistry (PrI/K_2CO_3/acetone or PrI/NaH/DMF) to reveal conformational preferences in the thiacalixarene series. Surprisingly, the conformer distribution of tetraalkylated products is different from that of calix[4]arene. The *1,3-alternate* conformers are well accessible in high yields (>60%) while the *cone* conformation forms only in very low yields (<20%). Moreover, the conformational outcome of the alkylation strongly depends on the upper rim substitution (*tert*-butyl versus H). © 2002 Elsevier Science Ltd. All rights reserved.

Thiacalix[4]arenes **1a** and **1b** represent novel members of the calix[*n*]arene[1] family bearing sulphur atoms instead of the usual methylene bridging groups. As they are accessible in multi-gram scale using a simple synthetic procedure,[2] thiacalixarenes represent attractive candidates for applications as molecular scaffolds or as building blocks in the synthesis of more complicated systems. Unfortunately, the full scope utilisation of thiacalixarenes in supramolecular chemistry is somewhat limited by the lack of general methods for derivatisation, especially as far as conformational outcomes are concerned.



1a, X = Bu^t
1b, X = H

Tetraalkylation of the lower rim (phenolic functions) represents an usual procedure for shaping the calixarene skeleton.[2,3] Accordingly, we[4] and others[5] have studied the alkylation of thiacalixarenes **1a** and **1b** with ethyl-bromoacetate using the acetone/M_2CO_3 reaction systems (M = Li, Na, K and Cs). This reaction exhibits a pronounced template effect and smoothly leads to high yields (~60%) of the corresponding tetraacetates in various conformations (*cone*, *partial cone*, *1,3-alternate*) strictly depending on the cation used for the alkylation. On the other hand, the products are not compatible (due to the presence of the ester groups) with common organometallic reagents which partly hinders their utilisation in subsequent chemical transformations.

During our on-going research on thiacalix[4]arene derivatisation we demonstrated that the presence of four sulphur atoms implicates many novel features of the conformational behaviour[6] and the solid-state preferences[7] of this system. In this paper we report the first systematic study on the tetraalkylation of thiacalix[4]arene using a simple alkyl halide which is bulky enough to immobilise the product in a specific conformation which is isolable at room temperature. The conformer distribution of products indicates significantly different behaviour of thiacalixarenes **1a** and **1b** in comparison with 'classical' calix[4]arenes.

Tetrapropoxy derivatives of thiacalix[4]arenes are known to be infinitely conformationally stable at room temperature.[8] Consequently, to ensure the conformational stability of the alkylated products propyl iodide was chosen as the alkylating agent. The alkylations were carried out[9] using three different methods: A = PrI/K_2CO_3 in refluxing acetone, B = PrI/NaH in DMF at rt, and C = PrI/KH in DMF at rt. Theoretically, four basic conformations are accessible for thiacalix[4]arenes: (i) *cone*, (ii) *partial cone*, (iii) *1,2-alternate*, (iv) *1,3-alternate* (Scheme 1). In the classical calix[4]arene series, method A yields a mixture of *1,3-alternate* and *partial cone* conformers in various ratios depending on the alkylating agent (*partial cone* always being the main product). On the other hand, reaction

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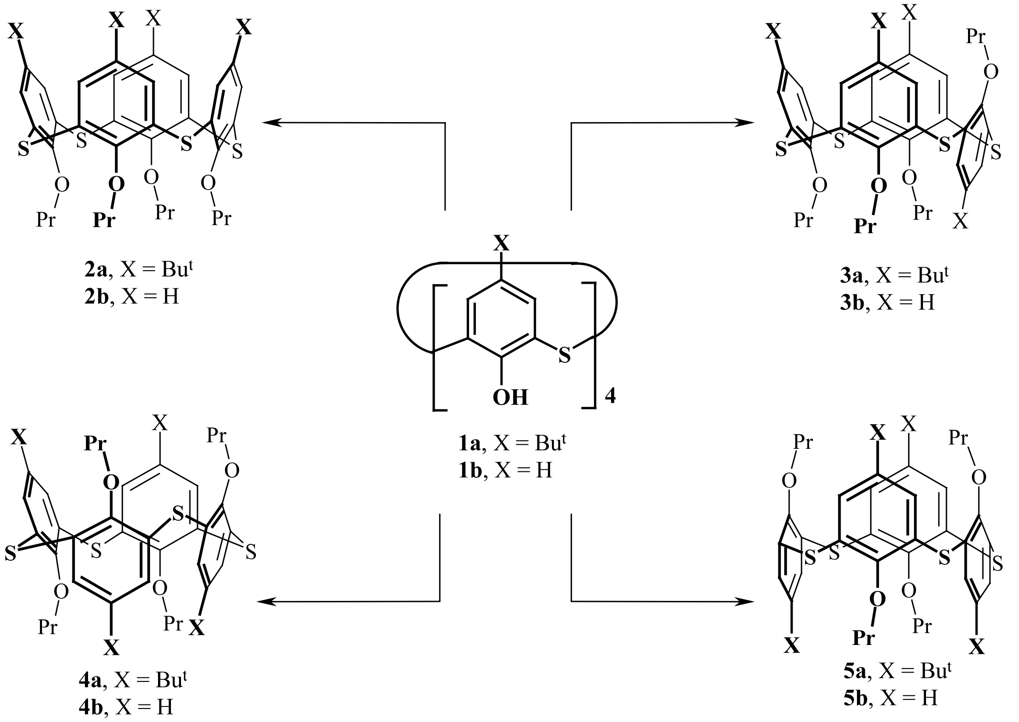

Scheme 1. General overview of thiacalix[4]arene conformers: **2** (*cone*), **3** (*partial cone*), **4** (*1,2-alternate*), **5** (*1,3-alternate*).

conditions B are known to yield preferentially the *cone* conformation.[1] The results obtained in the thiacalixarene series are collected in Table 1.

The alkylation of **1a**, carried out using procedure A, leads to the corresponding *1,3-alternate* **5a** accompanied by small amounts of **3a** and **4a**. Similarly, **1b** yields **5b** and *partial cone* **3b**. Hence, this method is suitable for a large scale (multi-gram amounts) preparation of the *1,3-alternate* conformers **5** which can be obtained in high yields (~60%) by simple precipitation from the crude reaction mixture in $CHCl_3$/methanol system.[10] Surprisingly, **1a** under reaction conditions B did not give the expected *cone* conformer **2a**. After 2 days stirring almost 50% of the starting material remained unreacted while only small amounts of **3a**, **4a** and **5a** were isolated from the reaction mixture. Neither a longer reaction time (4 days) nor elevated (80°C) temperature gave better results. A similar reaction with **1b** gave the desired *cone* conformer **2b** (in only 19% yield) accompanied by roughly the same amount of *partial cone* derivative **3b**. Substitution of NaH by KH (procedure C) gave no improvement as far as the yield of *cone* conformation was concerned: **2a** (0% yield), **2b** (2%). On the other hand, the least accessible *1,2-alternate* conformation (in the classical calix[4]arene series) **4a** is formed in unexpectedly high yield (21%). It is surprising that neither procedure B nor C is suitable for the synthesis of the *cone* conformation. Consequently, *cone* conformers bearing alkyl groups on the lower rim are so far almost unavailable for subsequent derivatisation in thiacalixarene series.[11] This is another example of the completely different conformational behaviour of thiacalix[4]arene as compared with the chemistry of classical calixarenes.

The structures of novel compounds were confirmed by ^{1}H NMR spectroscopy and in the cases of **2b**–**5b** also by comparison with original samples prepared by thermal isomerisation of **5b**.[8] The ^{1}H NMR spectra of **3a** and **4a** reflect the lower symmetry in comparison with *1,3-alternate*[10] **5a**. Thus, splitting of the $–O–CH_2–$ signals into two sets of multiplets ($\delta = 3.62$ and 3.77 ppm) due to H_A–H_B geminal interactions is a typical feature of the *1,2-alternate* conformation. Moreover, the presence of only two doublets ($\delta = 7.46$ and 7.58 ppm with the typical *meta* coupling $J = 2.5$ Hz) in the aromatic region of the spectrum, together with one singlet due to the *tert*-butyl groups, clearly indicates the structure **4a**. Another interesting point is an uncommon upfield shift of the terminal groups ($-CH_2–CH_3$ from O–Pr) that are

Table 1. Alkylation of thiacalix[4]arenes **1a** and **1b**

Comp.	Alkylation method	Isolated yields of conformers (%)			
		2	**3**	**4**	**5**
1a	A	–	5	9	66
1a	B	–[a]	7	9	12[b]
1a	C	–	–	21	50
1b	A	–[c]	17	–	61
1b	B	19[a]	16	–	–[d]
1b	C	2	25	–	10

[a] Under the same conditions classical calix[4]arene yields more than 80% yield of the *cone* conformation (82% for H, 88% for *t*-Bu).

[b] Starting compound (43%) was recovered from the reaction mixture.

[c] Classical calix[4]arene gives a mixture (82% yield) of partial *cone* and *1,3-alternate* conformations in a 4:1 ratio.

[d] Partly alkylated products were identified in the reaction mixture.

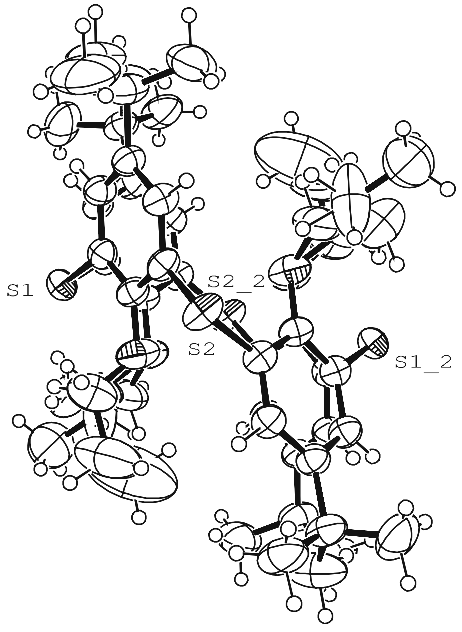

Figure 1. ORTEP drawing of the X-ray structure of **4a**.

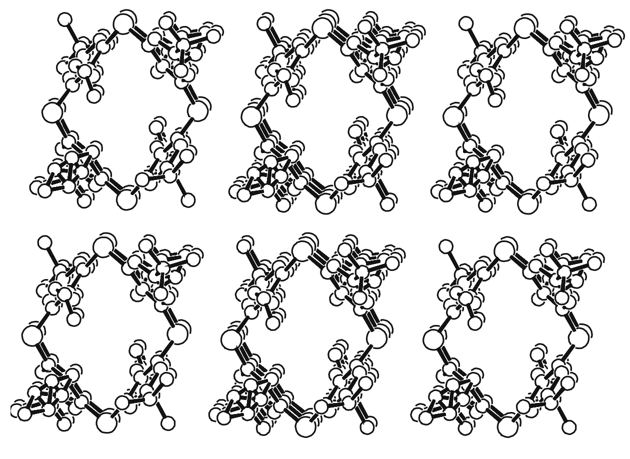

Figure 2. Crystal packing of **4a**.

shielded by magnetic anisotropy due to the inverted aromatic units being in close proximity. Similarly, splitting of the aromatic signals into two doublets (7.07 and 7.41 ppm) and two singlets (7.61 and 7.67 ppm) is peculiar to the *partial cone* conformation **3a**.

The structure of **4a** was unequivocally proven by X-ray crystallography.[12] Suitable single crystals were grown by slow evaporation of an ethyl acetate solution. The *1,2-alternate* conformation is centro-symmetrical with opposite inverted aromatic rings being coplanar (Fig. 1). Four sulphur atoms are placed in the corners of a lozenge with shorter (S1–S1_2) and longer (S2–S2_2) diagonals being 7.09 and 8.55 Å, respectively, while the distance between the two proximal sulphur atoms is approximately 5.55 Å. The box-shaped cavities of the *1,2-alternate* conformer **4a** are packed parallel to each other and form infinite channels within the crystal lattice (Fig. 2).

In conclusion, we have demonstrated that thiacalix[4]arenes **1a** and **1b** possess surprisingly different conformational preferences in the alkylation reaction compared with classical calix[4]arenes. While the *cone* derivatives can be obtained only in very low yields, the *1,3-alternate* conformations are easily accessible by direct peralkylation of the starting compounds. Synthetic procedures leading to other conformers are currently under investigation.

Acknowledgements

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9. Alkylation method **A**: The mixture of **1** (1 mmol), potassium carbonate (20 mmol) and propyl iodide (20 mmol)

was stirred under reflux in 20 ml of acetone for 48 h. The reaction mixture was cooled to rt, carefully neutralised with diluted hydrochloric acid and extracted with dichloromethane. The organic layer was washed with water, dried over $MgSO_4$ and evaporated to dryness. The semi-solid residue was purified by column chromatography on silica gel using petroleum ether/chloroform (gradient from 10:1 to 5:1) as eluent. Isolated yields of the corresponding conformers are collected in Table 1.

Alkylation method **B**: The mixture of **1** (0.15 mmol), NaH (0.9 mmol) and propyl iodide (2 mmol) was stirred at rt in 6 ml of anhydrous DMF for 24 h. The reaction mixture was worked up as described in method **A** and isolated using preparative TLC on silica gel.

Alkylation method **C**: The same procedure as in **B**, KH (0.9 mmol) was used instead of NaH.

Compounds **5a**, **2b**, **3b**, **4b** and **5b** were identical with samples previously prepared.[8,10]

Compound **3a**: mp: >350°C (ethyl acetate), ^1H NMR ($CDCl_3$, 298 K, 300 MHz): δ 0.72 (t, 3H, $J=7.4$ Hz, CH_3), 0.93 (t, 3H, $J=7.4$ Hz, CH_3), 1.04 (s, 18H, *t*-Bu), 1.04 (t, 6H, $J=7.5$ Hz, CH_3), 1.33 (s, 9H, *t*-Bu), 1.39 (s, 9H, *t*-Bu), 1.87 (m, 8H, $\text{-O-CH}_2\text{-}\underline{\text{CH}_2}\text{-}$), 3.82 (m, 4H, $\text{-O-}\underline{\text{CH}_2}\text{-}$), 3.96 (q, 2H, $J=7.5$ Hz, $\text{-O-}\underline{\text{CH}_2}\text{-}$), 4.03 (q, 2H, $J=7.7$ Hz, $\text{-O-}\underline{\text{CH}_2}\text{-}$), 7.07 (d, 2H, $J=2.5$ Hz, H-arom.), 7.41 (d, 2H, $J=2.5$ Hz, H-arom), 7.61 (s, 2H, H-arom), 7.67 (s, 2H, H-arom). EA calcd for $C_{52}H_{72}O_4S_4$: C, 70.22; H, 8.16; S, 14.42%. Found C, 70.01; H, 8.01; S, 14.04%.

Compound **4a**: mp: 346–348°C (ethyl acetate), ^1H NMR ($CDCl_3$, 298 K, 300 MHz): δ 0.65 (t, 12H, $J=7.2$ Hz, CH_3), 1.04 (m, 4H, $\text{-}\underline{\text{CH}_A}\text{H}_B\text{-CH}_3$), 1.31 (m, 4H, $\text{-CH}_A\underline{\text{H}_B}\text{-CH}_3$), 1.31 (s, 36H, *t*-Bu), 3.62 (m, 4H, $\text{-O-}\underline{\text{CH}_A}\text{H}_B\text{-CH}_2\text{-}$), 3.77 (m, 4H, $\text{-O-CH}_A\underline{\text{H}_B}\text{-CH}_2\text{-}$), 7.46 (d, 4H, $J=2.5$ Hz, H-arom), 7.58 (d, 4H, $J=2.5$ Hz, H-arom). EA calcd for $C_{52}H_{72}O_4S_4$: C, 70.22; H, 8.16; S, 14.42%. Found C, 69.93; H, 8.21; S, 14.11%.

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12. X-Ray data for **4a**: $C_{52}H_{72}O_4S_4$, M = 889.378 g/mol, triclinic system, space group P-1, $a=10.8477(7)$, $b=11.4720(7)$, $c=12.3694(6)$ Å, $\alpha=105.173(5)$, $\beta=115.401(4)$, $\gamma=94.932(5)°$, $V=1306.9(2)$ Å^3, $Z=2$ (half molecule in asymmetric unit), $D_c=1.13$ g cm^{-3}, μ(Cu Kα) = 19.755 cm^{-1}, crystal dimensions of 0.4×0.5×0.6 mm. Data were measured at 293 K on an Enraf–Nonius CAD4 diffractometer with graphite monochromated Cu Kα radiation. The structure was solved by direct method[13] and anisotropically refined by full matrix least-squares on F values[14] to final $R=0.0803$, $R_w=0.0736$ and $S=1.0737$ with 305 parameters using 3591 independent reflections ($\theta_{max}=69.89°$). Hydrogen atoms were located from expected geometry and were not refined, except those linked to carbon atoms of the aromatic rings (H1, H2, H3, H4), their positions and isotropic parameters were refined. ψ-scan was used for absorption correction. Crystallographic data were deposited in CSD under CCDC registration number 193202.
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