Stereoselective oxidation of thiacalix[4]arenes with the NaNO₃/CF₃COOH system

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Abstract—A series of alkyl substituted thiacalix[4]arene derivatives (being conformationally mobile or immobilised in the *cone* conformation) was used as the starting point for this study. It was demonstrated that the NaNO₃/CF₃COOH system can serve as an excellent oxidising agent. The oxidation of the bridging sulphur atoms smoothly leads to the corresponding tetrasulfoxides where alkyl and sulfoxide groups are oriented in the opposite directions in a stereoselective manner. © 2003 Elsevier Ltd. All rights reserved.

Thiacalix[4]arenes **1** and **2** are novel members of the calix[*n*]arene[1] family. As they are easily accessible on multi-gram scale,[2] thiacalixarenes represent promising candidates for use as molecular scaffolds or as building blocks for the synthesis of more sophisticated systems. The introduction of four sulphur atoms instead of -CH₂- groups imposes novel and interesting features on the thiacalix[4]arene derivatives compared to the chemistry of 'classical' calixarenes. Consequently, some reactions unknown in the chemistry of calix[4]arene have been described.[3,4]
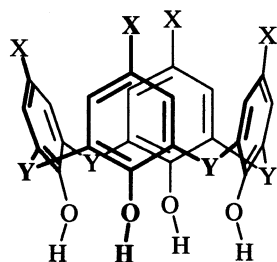
1, Y = S, X = Buᵗ
2, Y = S, X = H
3, Y = SO, X = Buᵗ
4, Y = SO₂, X = Buᵗ

The presence of sulphur atoms in the thiacalixarene skeleton offers another pathway for derivatisation of these molecules: reactions on the bridging moieties. While these reactions are still rare in classical calixarene chemistry,[1] the chemical transformation (e.g. oxidation) of sulphur is much easier. Thus, the oxidation of the parent thiacalixarene **1** (H₂O₂/trifluoroacetic acid or excess NaBO₃/CHCl₃–acetic acid) leads to the corresponding tetrasulfone derivative **4** while an equivalent amount of oxidising agent (NaBO₃) gives tetrasulfoxide **3**.[5–8]

The introduction of four sulfoxides imparts a novel type of stereoisomerism in the thiacalixarene series, which originates from the mutual positions of the oxygen atoms. For instance, assuming free rotation of the phenolic subunits, derivative **3** could adopt the four different configurations depicted in Figure 1.

During our on-going research[9] on thiacalix[4]arene derivatisation we found that using the nitration agents (conc. HNO₃ or 100% HNO₃ in CH₂Cl₂ or acetic acid), frequently used for aromatic substitution reactions in 'classical' calixarene chemistry, led to the oxidation of the sulphur bridges. Subsequently, the above-mentioned systems were used in some cases as oxidising agents for the synthesis of tetraalkylated sulfones or sulfoxides.[10]
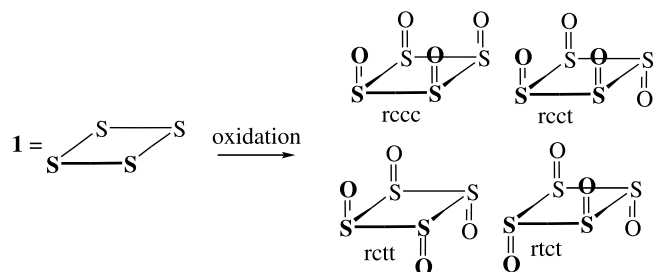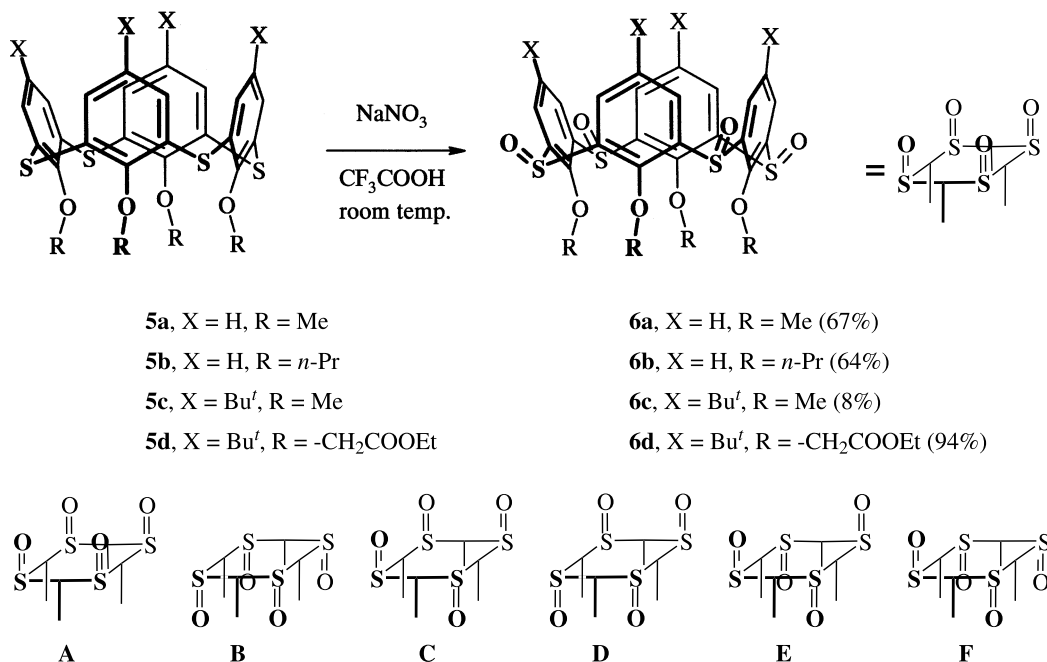

Figure 1. Four stereoisomers of thiacalixarene **3**, r = reference group, c = *cis* configuration to r, t = *trans* configuration to r.

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5a, X = H, R = Me   **6a**, X = H, R = Me (67%)

5b, X = H, R = *n*-Pr   **6b**, X = H, R = *n*-Pr (64%)

5c, X = Bu*t*, R = Me   **6c**, X = Bu*t*, R = Me (8%)

5d, X = Bu*t*, R = -CH₂COOEt   **6d**, X = Bu*t*, R = -CH₂COOEt (94%)

A   **B**   **C**   **D**   **E**   **F**

Scheme 1. General overview of thiacalix[4]arene oxidation with all six theoretically possible stereoisomers of the *cone* conformation (**A–F**).

We report herein another 'nitration' agent[11] (NaNO₃/ CF₃COOH) which can be used for the stereoselective oxidation of thiacalixarene derivatives.

The thiacalixarene derivatives **5b** and **5d** (being immobilised in the *cone* conformation) react smoothly with NaNO₃ in trifluoroacetic acid at room temperature to yield the corresponding tetrasulfoxides **6b** and **6d**. The reaction was carried out[12] using an excess of NaNO₃ (12 equiv.); however, no products of over-oxidation to sulfones were found in the reaction mixtures. In all cases, the pure oxidation product was isolated in high yields (64–94%) by simple precipitation of the crude reaction mixture with CHCl₃–MeOH. Similarly, starting from non-immobilised thiacalixarene derivatives **5a** and **5c** the corresponding tetrasulfoxides **6a** and **6c** were obtained, albeit in the case of **6c** in lower yield. To the best of our knowledge, the NaNO₃/CF₃COOH system has never been used for the oxidation of sulphur derivatives.[13] The overall oxidation procedure is very simple from a practical point of view, moreover, the mild conditions (room temp.) are compatible with the presence of ester groups (no hydrolysis observed).

To prove the general usefulness of this synthetic procedure we have carried out the oxidation of diphenyl sulfide **7** as a model compound under the same conditions (Scheme 2). Both sodium nitrate and potassium nitrate gave the diphenyl sulfoxide **8** in very high yields (94 and 87%, respectively), while the corresponding sulfone was not isolated at all.[14]

Theoretically, for the thiacalix[4]arenes, the relative orientation of sulfoxide groups and alkyl substituents can give rise to up to six different stereoisomers **A–F** (Scheme 1). Hovever, the NMR spectra of the sulfox-

ides **6** indicates the presence of a single stereoisomer in each case possessing a highly symmetric structure. Thus, the ¹H NMR spectrum of **6b** exhibited one set of signals for the propyl groups (δ 1.06, 1.47, and 4.27 ppm) together with two signals 7.17 ppm (t) and 7.49 ppm (d) in the aromatic region with typical vicinal coupling contants ($J = 7.70$ Hz). This splitting pattern and the multiplicity of the signals indicated C_{4v} symmetry, which excluded the structures **C–F**. Unfortunately, distinguishing between the structures **A** and **B** was impossible based on the NMR measurements alone.

Evidence for the tetrasulfoxide structure was obtained by single-crystal X-ray diffraction analysis.[16] Suitable single crystals of **6a** were grown by slow evaporation of an ethyl acetate solution. As shown in Figure 2, the sulfoxide groups (S=O) in compound **6a** are in the rccc mutual positions (cf. Fig. 1) and they are pointing in the opposite direction to the alkyl groups on the lower rim of the thiacalixarene. Based on this structure, we conclude that the oxidation of tetrasubstituted thiacalix[4]arenes proceeds stereoselectively. The nitrate (oxidising agent) preferentially attacks the thiacalix[4]arene molecule from the direction of the upper rim to minimise possible steric repulsions with substituents present on the lower rim. As a result, the stereoisomers **A** are formed as the main products. Sim-
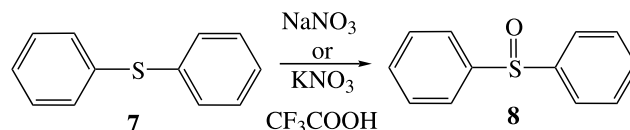
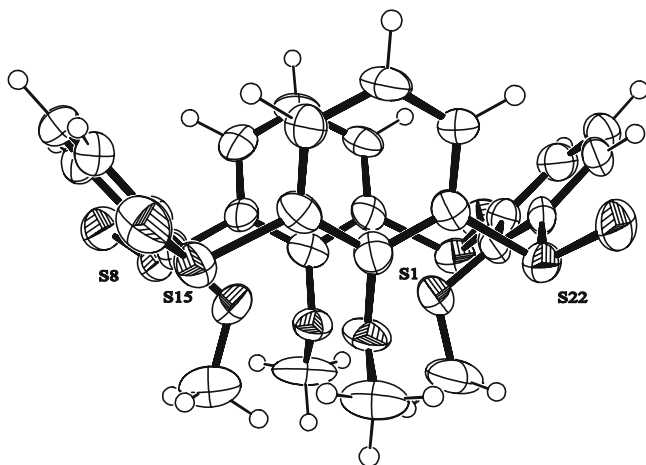**Scheme 2.** Oxidation of diphenyl sulfide **7**.

Figure 2. ORTEP drawing of derivative **6a**.

ilar solid-state structures were found for the tetraacetate compound **6d** and for the tetramethoxy-tetrasulfoxide **6c**.

Very recently, oxidation of the tetrabenzyloxy derivative of thiacalix[4]arene using NaBO₃·4H₂O was described.[19] The oxidation of the corresponding *cone* conformer leads to the same stereoisomers as in the case of our immobilised derivatives **6b** and **6d**, e.g. the rccc configuration. To compare the stereochemical outcomes of both oxidation systems, we carried out several experiments using the reaction conditions reported[19] (CHCl₃/acetic acid, 50°C, overnight, 1.05 equiv. of NaBO₃·4H₂O per S atom). Using **5d** as the starting material, the sulfoxide **6d** exhibiting the same stereochemistry (**A**) was isolated in high yield (94%). On the other hand, the tetramethoxy derivative **5a** which is conformationally mobile led to a very complicated reaction mixture where we were unable to identify stereoisomer **6A**. This indicated that the stereochemical preferences of both systems are different in the case of non-immobilised compounds.

Tetramethoxy derivative **6a** also possesses very interesting molecular packing shown in Figure 3. Molecules of **6a** are connected with each other via CH-π interactions of the methoxy group with the aromatic subunits of neighbouring molecules. This structural motif leads to the formation of infinite lines along the Y axis with the methoxy groups being immersed in the cavity of the adjacent thiacalixarene.
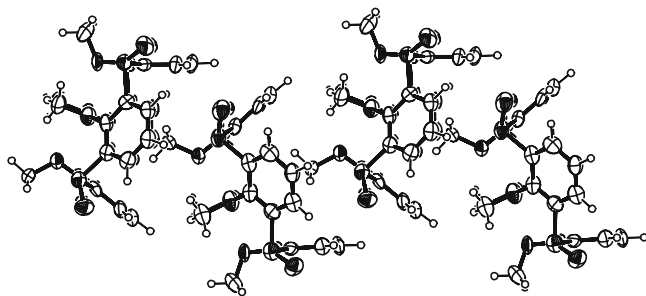

Figure 3. Crystal packing of **6a**.

In conclusion, we have demonstrated that tetraalkylated thiacalix[4]arenes **5** can be transformed into the corresponding tetrasulfoxides **6** which are novel building blocks with many potential applications in supramolecular chemistry. The *cone* stereoisomers of type **A** are accessible by direct stereoselective oxidation of the starting materials using NaNO₃ in trifluoroacetic acid. Stereochemical outcomes of this new oxidation agent for other thiacalixarene conformers (*partial cone*, *1,3-alternate*) are currently under investigation.

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11. Tetraalkylated derivatives of classical calix[4]arene were nitrated using the NaNO₃/CF₃COOH system in 60% yield. See: Arduini, A.; Mirone, L.; Paganuzzi, D.; Pinalli, A.; Pochini, A.; Secchi, A.; Ungaro, R. *Tetrahedron* **1996**, *52*, 6011.
12. **General procedure for the oxidation of thiacalixarenes**. Sodium nitrate (3.37 mmol, 12 equiv.) was added to the

suspension of alkylated thiacalixarene **5a–d** (0.28 mmol) in 30 ml of trifluoroacetic acid and the mixture was stirred at room temperature for 6.5 h. The reaction mixture was then poured into 60 ml of water and extracted with chloroform. The separated organic layer was washed with water, dried over $MgSO_4$ and evaporated to yield the crude product. The pure compound was obtained by precipitation from $CHCl_3$–MeOH. **Sulfoxide 6a**. Yield 67%, light yellow crystalline solid, mp 158–160°C. ^{1}H NMR (300 MHz, CD_2Cl_2, 0°C) δ 4.15 (s, 12 H, OCH_3), 7.25 (t, 4 H, $J=7.70$, H-arom), 7.57 (d, 8 H, $J=7.70$, H-arom). ^{13}C NMR (20°C, 75 MHz) 64.42, 125.84, 128.64, 139.10, 153.34. MS MALDI-TOF (1,8,9-trihydroxyanthracene matrix), m/z (%): 617 (100) $[M+H]^+$. **Sulfoxide 6d**. Yield 94%, white crystals, mp 264–266°C (lit.[10] 273–275°C). ^{1}H NMR (500 MHz, $CDCl_3$, 25°C) δ 1.18 (s, 36 H, *t*-Bu), 1.34 (t, 12 H, $J=7.00$, -CH_2CH_3), 4.29 (q, 8 H, $J=7.00$, -CH_2CH_3), 5.14 (s, 8 H, -OCH_2COOEt), 7.77 (s, 8 H, H-arom). IR (KBr, cm^{-1}) 1760, 1741 (ester). MS MALDI-TOF (1,8,9-trihydroxyanthracene matrix), m/z (%): 1131 (100) $[M+H]^+$. Anal. calcd for $C_{56}H_{72}O_{16}S_4$: C, 59.55; H, 6.43; S, 11.36. Found: C, 59.17; H, 6.21; S, 11.08. The same product was obtained using KNO_3 instead $NaNO_3$. Yield 74%.

13. The $NaNO_3$/HF system was used for the oxidation of 1,4-dithiino[2,3-*c*:6,5-*c*]diisothiazole to the corresponding disulfoxide. See: Vladuchick, S. A.; Fukunaga, T.; Simmons, H. E.; Webster, O. W. *J. Org. Chem.* **1980**, *45*, 5122.

14. **Preparation of diphenyl sulfoxide 8**: Sodium nitrate (7.50 mmol, 12 equiv.) was added to a solution of diphenyl sulfide **7** (0.62 mmol) in 10 ml of trifluoroacetic acid and the mixture was stirred at room temperature for 6.5 h. The reaction mixture was then poured into 60 ml of water and extracted with chloroform. The separated organic layer was washed with water, dried over $MgSO_4$ and evaporated to yield a crude product. The pure title compound **8** was obtained by precipitation from $CHCl_3$–MeOH. Yield 94%, white crystals, mp 69–71°C (lit.[15] 69–71°C). The identical compound was obtained using KNO_3 as the oxidising agent. Yield 87%.

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16. X-Ray data for **6a**: $C_{28}H_{24}O_8\cdot C_4H_8O_2$, $M=704.84$ g/mol, monoclinic system, space group $P2_1/c$, $a=11.602(1)$, $b=12.470(1)$, $c=22.477(1)$ Å, $\beta=91.51(1)°$, $Z=4$, $V=3250.9(4)$ Å^3, $D_{calcd}=1.44$ g cm^{-3}, μ (Cu Kα) $=3.18$ mm^{-1}, crystal dimensions of 0.1×0.1×0.4 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 methods.[17] The whole structure was refined anisotropically by full-matrix least-squares on F values[18] to final $R=0.1083$ and $R_w=0.1107$ using 2799 independent reflections ($\theta_{max}=67.9°$). Ethyl acetate solvent molecule was localised from the difference Fourier map. Hydrogen atoms were located from expected geometry and were not refined. Ψ-scan was used for absorption correction. Crystallographic data were deposited in CSD under CCDC registration number 196007.

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