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Regioselective and stereoselective oxidation of thiacalix[4]arene tetraacetate: synthesis of all possible sulfinylcalix[4]arenes

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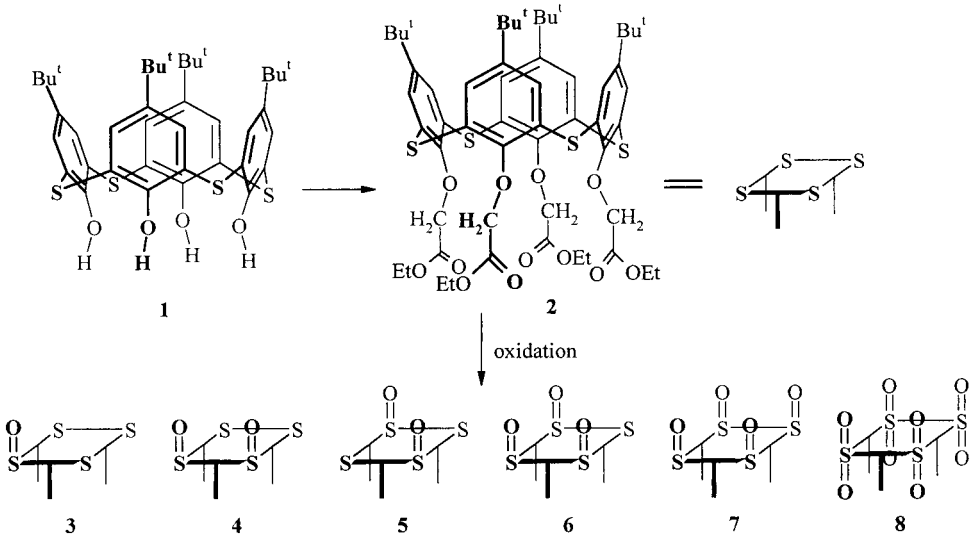
Abstract—Thiacalix[4]arene tetraacetate in the cone conformation was used as the starting point for regio- and stereoselective oxidation. Using various oxidation agents, all corresponding sulfinyl (mono-, di-, tri-, tetra-) and appropriate tetrasulfonyl derivatives were prepared and characterised by spectral methods. The pinched cone—pinched cone interconversion of tetrasulfonylcalix[4]arene was studied using dynamic ^{1}H NMR spectroscopy. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Calixarenes[1] are frequently used as suitably preorganised building blocks for the construction of more elaborate structures, receptors and molecular assemblies. The recently reported thiacalix[4]arene **1**, having four sulphur atoms instead of methylene bridges, represents a new member of the calixarene family.[2] The presence of sulphur imposes some novel interesting features on thiacalix[4]arene molecules if compared with the chemistry of 'classical' calixarenes.[3,4] Thus, oxidation of **1** can lead to tetrasulfinyl-[5] or tetrasulfonyl-[6] derivatives, possessing as bridging moieties four SO and SO_2 groups, respectively. In this paper we report the synthesis and characterisation of all possible sulfinylcalix[4]arenes prepared by the direct oxidation of thiacalix[4]arene derivatives fixed in the *cone* conformation.

2. Results and discussion

During our attempts to carry out *ipso*-nitration of thiacalix-[4]arene derivative **2** under similar conditions described for classical calix[4]arene derivatives[7] (100% HNO_3, CH_2Cl_2/



Scheme 1.

Keywords: calixarenes; oxidation; conformation; NMR analysis.

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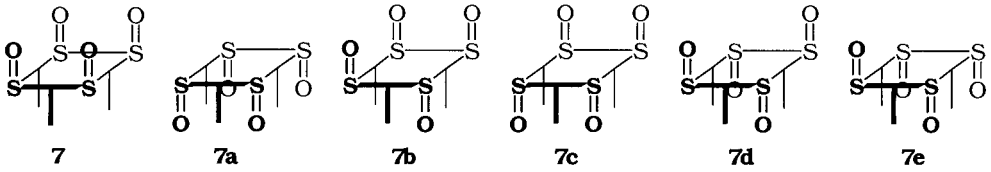

Figure 1. Schematic representation of all possible stereoisomers of **7**.

Table 1. Splitting pattern, multiplicity and population of signals in ^{1}H NMR spectra of derivatives **3** to **8**.

Derivative	Aromatic signals	-O-*CH*$_2$-COOEt	*tert*-butyl groups
3	d:d:d:d	d:d:d:d	s:s
	2:2:2:2	2:2:2:2	18:18
4	s:d:d:s	s:d:d:s	s:s:s
	2:2:2:2	2:2:2:2	9:18:9
5	d:d	d:d	s
	4:4	4:4	36
6	d:d:d:d	d:d:d:d	s:s
	2:2:2:2	2:2:2:2	18:18
7	s	s	s
	8	8	36
8	s	s	s
	8	8	36

CH_3COOH), we found that the expected nitration did not work at all. On the other hand, the products from the above reactions were identified as partly oxidised products containing S═O groups. These compounds represent novel building blocks that could find many possible applications in supramolecular chemistry. Consequently, we have focused our interest on the development of methods leading to the regioselective oxidation of **2** in acceptable yields.

Several oxidation agents were used in our study: (i) 65% HNO_3 in CH_2Cl_2 or CH_2Cl_2/CH_3COOH mixture, (ii) 100% HNO_3 in CH_2Cl_2 or CH_2Cl_2/CH_3COOH mixture, (iii) 35% aqueous. H_2O_2, (iv) pyridinium chlorochromate, (v) $NaClO_3$, (vi) H_2O_2-urea complex and (vii) MCPA (3-chloroperoxybenzoic acid). Tetrasulfinyl derivative **7** is smoothly formed in almost quantitative yield (93% isolated) using an excess of hydrogen peroxide in acetic acid (16 h) or excess of 100% HNO_3 in dichloromethane (2 h) at room temperature. Both reactions are very selective and gave pure **7** after simple extraction and evaporation to dryness. Surprisingly, no products of over-oxidation to SO_2 groups were found in the reaction mixture. By contrast, tetrasulfonyl derivative **8** was obtained in 70% yield using an excess of MCPA in boiling 1,2-dichloroethane, again after simple crystallisation of crude product from AcOEt (Scheme 1).

The preparation of partly oxidised products **3** to **6** is not as easy as the above-described synthesis of tetrasubstituted compounds **7** and **8**. Reaction mixtures always contain several compounds that must be isolated by column or

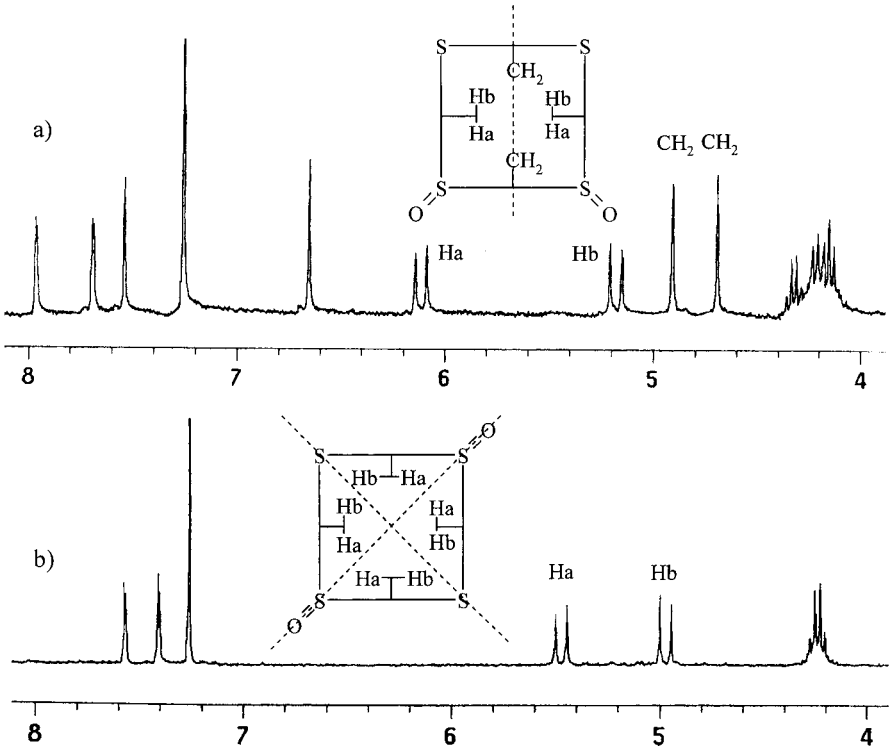

Figure 2. Partial ^{1}H NMR spectra ($CDCl_3$, 298 K, 300 MHz) of derivatives **4** and **5** together with symmetry consideration of -O-*CH*$_2$-COO- regions.

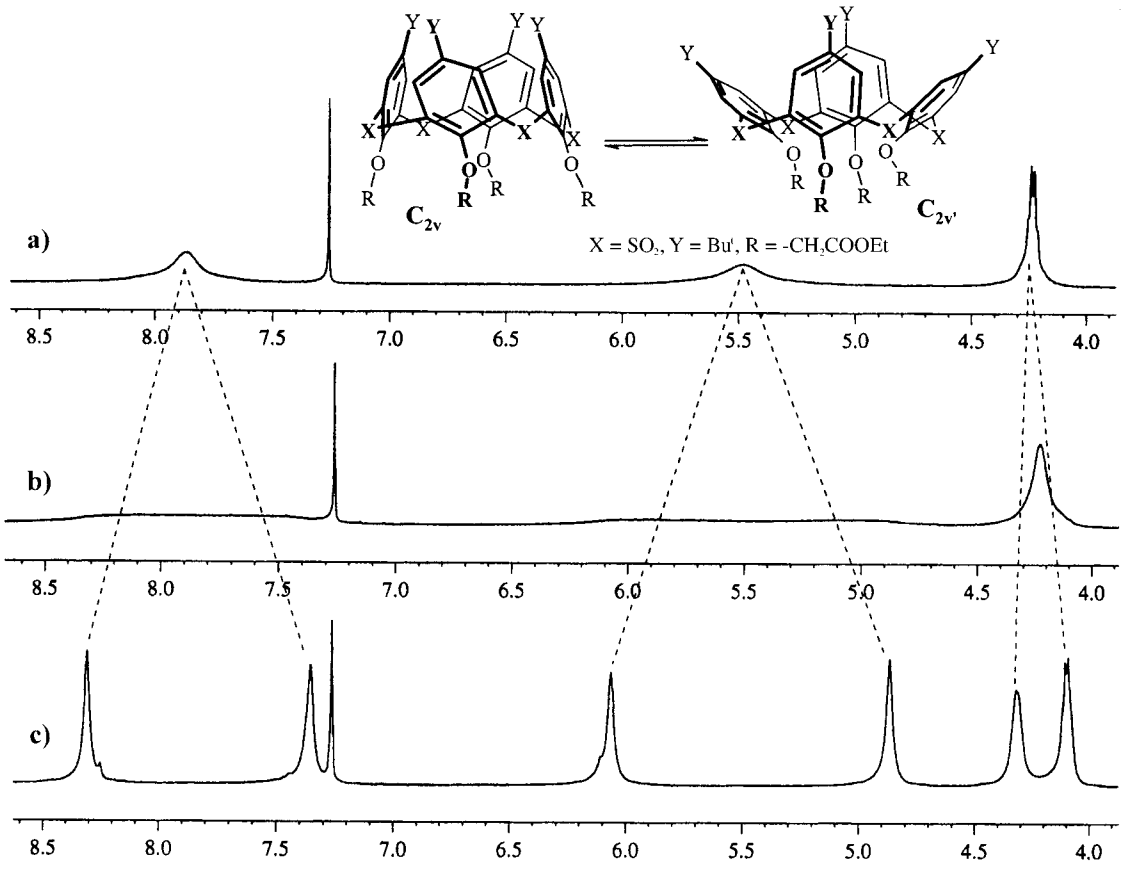

Figure 3. Partial ^{1}H NMR spectrum of **8** (500 MHz, $CDCl_3$) measured (a) at 298 K, (b) at 273 K, (c) at 233 K.

preparative thin layer chromatography on silica gel. The highest yield of monosulfoxide **3** (54%) was obtained using 5 equiv. of pyridinium chlorochromate (PCC) in CH_2Cl_2 (rt, 16 h). Similar reaction with 15 equiv. of PCC gave a mixture of monosulfoxide and both disulfoxides from which derivatives **4** and **5** were isolated in 28% and 24% yield, respectively. Finally, 100% HNO_3 in CH_2Cl_2/CH_3COOH mixture at room temperature led to trisulfoxide **6** in 26% yield after preparative TLC.

The relative orientation of the sulfoxide oxygens (S=O) and the substituents on the lower rim of thiacalix[4]arene can potentially lead to several stereoisomers. As shown in Fig. 1, tetrasulfinylcalix[4]arene **7** in the *cone* conformation could possess up to six isomers. On the other hand, during our study we have always isolated only one stereoisomer possessing C_4 symmetry, consistent with either structure **7** or **7a**. Furthermore, the recently published X-ray structure of the *cone* conformation of the tetrabenzyloxy tetrasulfoxide derivative[8] revealed, that this compound exists as a single isomer corresponding to structure **7**. Hence, one can anticipate that the oxidation agent preferentially attacks the thiacalix[4]arene skeleton from the other site to minimise steric hindrance with substituents on the lower rim. In other words, oxidation of tetrasubstituted *cone* thiacalix[4]arenes proceeds stereoselectively and all sulfoxides **3** to **7** were thus assigned structures with acetate and sulfoxide groups pointing in opposite directions (Scheme 1).

The structures of products were determined using a combination of FAB MS and NMR spectroscopy. Taking into account the different symmetry of particular isomers one can envisage the different sets of signals in three characteristic ^{1}H NMR regions, corresponding to *tert*-butyl groups, -O-*CH*$_2$-COO- groups and aromatic hydrogens. Table 1 summarises the splitting pattern, multiplicity and population of appropriate regions in isomers **3** to **8**. Thus, considering the -O-*CH*$_2$-COO- region the distal disulfoxide **5** exhibits two doublets (4.97 and 5.47 ppm) with typical geminal interaction constant (J=15.9 Hz), while proximal derivative **4** shows two doublets (5.18 and 6.11 ppm, J=16.5 Hz) together with two singlets (4.69 and 4.91 ppm) due to its lower symmetry (Fig. 2).

The ^{1}H NMR spectrum of tetrasulfone derivative **8** exhibits very broad signals indicating some additional conformational motion under the conditions used (500 MHz, $CDCl_3$, 298 K). The temperature dependant ^{1}H NMR spectra (Fig. 3) revealed that this can be ascribed to the C_{2v}-$C_{2v'}$ interconversion between two pinched cone conformations of derivative **8**. This so-called pinched cone—pinched cone interconversion exhibits a coalescence point at 273 K, a temperature that is indicative of a much higher activation energy than that of classical calix[4]arenes. Although this phenomenon was already described[4,9] for other thiacalix[4]arene derivatives, compound **8** represents the first example of a thiacalixarene derivative bearing *tert*-butyl groups. No such

behaviour was observed in the case of tetrasulfoxide derivative **7**.

In conclusion, thiacalix[4]arene **2** was stereoselectively and regioselectively oxidised to all possible sulfoxide derivatives, offering a collection of novel building blocks with many potential applications in supramolecular chemistry. The complexation properties of novel compounds and their usage for the synthesis of more complicated structures are currently under investigation.

3. Experimental

Melting points were determined with a Boetius Block apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini 300 and a Bruker AMX3 400 spectrometers using tetramethyl silane as an internal standard. FAB MS were measured on ZAB-EQ VG Analytical spectrometer.

Compound **2** was prepared according to known procedure by the reaction of **1** with ethyl bromoacetate in boiling acetone in the presence of Na_2CO_3.[9]

3.1. Synthesis of derivative 3

A solution of compound **2** (100 mg) and PCC (110 mg) in 5 ml of CH_2Cl_2 was stirred at room temperature for 16 h and then poured into water. After extraction with $CHCl_3$, the organic layer was dried with $MgSO_4$ and evaporated to dryness. The crude product was purified by preparative TLC (silica gel, $CHCl_3$) to yield compound **3** (54%) as a white solid. Mp: 170–172°C (EtOH). ^{1}H NMR ($CDCl_3$): δ 1.02 (s, 18H, Bu^t), 1.18 (s, 18H, Bu^t), 1.28 (m, 12H, CH_3), 4.22 (m, 8H, O*C*H_2CH$_3$), 5.10 (m, 6H, *C*H_A*H*$_B$-COOEt, *C*$H_{A'}$H$_{B'}$-COOEt), 5.50 (d, 2H, CH$_{A'}$*H*$_{B'}$-COOEt, *J*=16.5 Hz), 7.21 (brs, 4H, arom-H), 7.47 (d, 2H, arom-H, *J*=2.2 Hz), 7.64 (d, 2H, arom-H, *J*=2.2 Hz). EA calcd. for $C_{56}H_{72}O_{13}S_4$: C, 62.20; H, 6.71; S, 11.86; Found: C, 62.54; H, 6.62; S, 11.69. FAB MS *m/z* (rel. int.) 1081.2 [M+1]$^+$ (100).

3.2. Synthesis of derivatives 4 and 5

Reaction carried out similarly as for derivative **3** using 300 mg of PCC. Purification on preparative TLC (silica gel, $CHCl_3$) gave derivative **4** (R_f=0.13) and **5** (R_f=0.20) as white solids. Compound **4**: Yield 28%, mp: 203–206°C (EtOH). ^{1}H NMR ($CDCl_3$): δ 0.64 (s, 9H, Bu^t), 1.06 (s, 9H, Bu^t), 1.25 (m, 12H, CH_3), 1.35 (s, 9H, Bu^t), 4.24 (m, 6H, O*C*H_2CH$_3$), 4.32 (q, 2H, O*C*H_2CH$_3$, *J*=7.2 Hz), 4.69 (s, 2H, *C*H_2-COOEt), 4.91 (s, 2H, *C*H_2-COOEt), 5.18 (d, 2H, *C*H_AH$_B$-COOEt, *J*=16.5 Hz), 6.11 (d, 2H, CH$_A$*H*$_B$-COOEt, *J*=17.0 Hz), 6.65 (s, 2H, arom-H), 7.54 (s, 2H, arom-H), 7.69 (d, 2H, arom-H, *J*=2.2 Hz), 7.97 (d, 2H, arom-H, *J*=2.2 Hz). FAB MS *m/z* (rel. int.) 1097.5 [M+1]$^+$ (100). Compound **5**: Yield 24%, mp: 197–200°C (AcOEt). ^{1}H NMR ($CDCl_3$): δ 1.12 (s, 36H, Bu^t), 1.29 (t, 12H, CH_3, *J*=6.9 Hz), 4.24 (q, 8H, O*C*H_2CH$_3$, *J*=6.6 Hz), 4.97 (d, 4H, *C*H_AH$_B$-COOEt, *J*=15.9 Hz), 5.47 (d, 4H, CH$_A$*H*$_B$-COOEt, *J*=15.9 Hz), 7.41 (d, 4H, arom-H, *J*=2.2 Hz), 7.57 (d, 4H, arom-H, *J*=2.2 Hz). EA calcd. for $C_{56}H_{72}O_{14}S_4$: C, 61.29; H, 6.61; S, 11.69; Found: C, 61.45; H, 6.62; S, 11.43. FAB MS *m/z* (rel. int.) 1097.4 [M+1]$^+$ (100).

3.3. Synthesis of derivative 6

A mixture of compound **2** (100 mg), 100% HNO_3 (0.3 ml), dichloromethane (5 ml) and glacial acetic acid (5 ml) was stirred at room temperature for 4 days and then poured into water. The extraction, drying over $MgSO_4$ and evaporation gave crude product, that was purified using preparative TLC (silica gel, $CHCl_3$: AcOEt=10:1) to yield **6** (26%) as a white solid. Mp: 225–230°C (ethanol). ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 18H, Bu^t), 1.20 (s, 18H, Bu^t), 1.31 (m, 12H, CH_3), 4.23 (m, 8H, O*C*H_2CH$_3$), 5.01 (d, 2H, *C*H_AH$_B$-COOEt, *J*=16.5 Hz), 5.06 (d, 2H, *C*$H_{A'}$H$_{B'}$-COOEt, *J*=17 Hz), 5.14 (d, 2H, CH$_{A'}$*H*$_{B'}$-COOEt, *J*=16.7 Hz), 5.46 (d, 2H, CH$_A$*H*$_B$-COOEt, *J*=15.9 Hz), 7.36 (d, 2H, arom-H, *J*=2.2 Hz), 7.46 (d, 2H, arom-H, *J*=2.2 Hz), 7.78 (d, 2H, arom-H, *J*=2.2 Hz), 7.82 (d, 2H, arom-H, *J*=2.2 Hz). FAB MS *m/z* (rel. int.) 1113.4 [M+1]$^+$ (100).

3.4. Synthesis of derivative 7

Hydrogen peroxide (35%, 1 ml) was added to a suspension of compound **2** (100 mg) in 5 ml of glacial acetic acid and the mixture was stirred at room temperature for 16 h. The reaction mixture was then poured into a solution of sodium hydrogencarbonate and extracted with chloroform. The organic layer was washed with water, dried over $MgSO_4$ and evaporated to yield crude product (105 mg) in the form of white solid. The crystallisation from ethanol gave glossy rhombic crystals (93%), that within several minutes decayed to white powder. Mp: 273–275°C (EtOH). ^{1}H NMR ($CDCl_3$): δ 1.16 (s, 36H, Bu^t), 1.31 (t, 12H, CH_3, *J*=7.1 Hz), 4.26 (q, 8H, O*C*H_2CH$_3$, *J*=7.1 Hz), 5.11 (s, 8H, *C*H_2-COOEt), 7.74 (s, 8H, arom-H). EA calcd. for $C_{56}H_{72}O_{16}S_4$: C, 59.55; H, 6.43; S, 11.36; Found: C, 59.37; H, 6.62; S, 11.48. FAB MS *m/z* (rel. int.) 1129.6 [M+1]$^+$ (100).

3.5. Synthesis of derivative 8

A mixture of compound **2** (100 mg) and MCPA (1.00 g) in 10 ml of 1,2-dichloroethane was heated to reflux for 5 days. After being cooled, the reaction was evaporated to dryness and the residue was distributed between chloroform and a saturated aqueous solution of $NaHCO_3$. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The crystallisation from AcOEt gave the title compound (70%) as white platelets. Mp: 334–337°C (AcOEt). ^{1}H NMR ($CDCl_3$): δ 1.14 (brs, 36H, Bu^t), 1.32 (t, 12H, CH_3, *J*=7.1 Hz), 4.24 (q, 8H, O*C*H_2CH$_3$, *J*=7.1 Hz), 5.48 (brs, 8H, *C*H_2-COOEt), 7.87 (brs, 8H, arom-H). EA calcd. for $C_{56}H_{72}O_{20}S_4$: C, 56.36; H, 6.08; S, 10.75; Found: C, 56.57; H, 6.12; S, 10.58. FAB MS *m/z* (rel. int.) 1193.6 [M+1]$^+$ (100).

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