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Synthesis and Conformation of *p-tert*-Butyltetramercaptocalix[4]arene[1]

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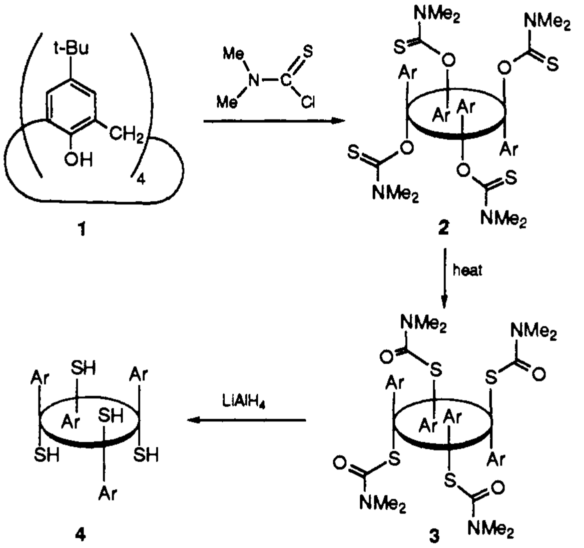
p-tert-Butylcalix[4]arene (**1**), easily prepared by the base-induced condensation of *p-tert*-butylphenol and formaldehyde, is a basket-shaped compound of potential utility as a complex-forming agent. Methods for enhancing this utility involve replacement of the *tert*-butyl groups on the upper rim with a variety of functionalities and affixing various moieties to the hydroxyl groups at the lower rim.[2] Another approach to altering the lower rim involves replacement of OH by a different atom or group such as hydrogen,[3] amino,[4] or mercapto.[5] Although one, two, three, or all four OH groups of **1** have been replaced by hydrogen, only one or two have been replaced by amino or mercapto groups. The present communication represents the first report of replacement of all four OH groups of **1** by four other heteroatom groups.



The transformation of **1** to its mercapto analog **4** was conceived in our laboratories in the 1980s and was based on the Newman–Kwart method for converting phenols to thiophenols.[6] Accordingly, the condensation of **1** with *N,N*-dimethylthiocarbamoyl chloride was carried out. However, no reaction conditions investigated at that time or since gave the tetrasubstituted compound **2** unmixed with various conformations of partially substituted analogs. Nevertheless, strenuous heating of the crude mixture in sulfolane produced a black tar from which a few crystals separated, and these were identified as **3** (1,2-alternate conformer) by X-ray crystallography.[7] Detailed publication[8] of this result was held in abeyance in anticipation of gaining a clearer understanding of the genesis of **3**. In the meantime, other examples of 1,2-conformations have been reported.[9,10] A careful reinvestigation of the reaction of **1** to **2** has now provided insight into the complexity of the reaction mixture and has yielded sufficient quantities of various *O*-dimethylthiocarbamato derivatives of **1** to allow a study of their conversion to the *S*-dimethylthiocarbamato derivatives and the corresponding mercapto compounds. Of particular interest is the conversion of **1** to **4**, employing the following procedures.

To a suspension of 3.84 g (96 mmol) of NaH (60% oil dispersion) in 300 mL of anhydrous, freshly distilled (from Na) diglyme[11] was added 8.9 g (12 mmol) of **1**,[12] and the mixture was heated to 130–135 °C for 1.5 h. A solution of 12.6 g (96 mmol) of *N,N*-dimethylthiocarbamoyl chloride in 60 mL of dry diglyme was added dropwise to the stirred mixture at a rate that maintained the temperature at 130 °C. Stirring was continued at 130–135 °C for 18 h, and the product was worked up to give 12.9 g of a mixture containing disubstituted, trisubstituted, and tetrasubstituted calixarenes. Flash chromatography[13] using gradient elution (CH_2Cl_2–petroleum ether to 100% CH_2Cl_2 in 10% incremental steps) afforded, after trituration with a small amount of MeOH, 5.2 g (43%) of **2** (1,2-alternate conformation).[14] A mixture of 5.0 g (5 mmol) of **2** and 100 g of *p*-tolyl ether was heated at gentle reflux for 24–30 h, cooled, diluted with petroleum ether–CH_2Cl_2 (80:20), suction filtered through a pad of silica gel, and worked up by flash chromatography with a gradient solvent system (100% CH_2Cl_2 to CH_2Cl_2–EtOAc, 95:5, in 1% incremental steps) to give, after trituration with a small amount of MeOH, 2.1 g (42%) of the rearranged tetrasubstituted compound **3** (1,2-alternate conformation).[15] Refluxing (8 h) a suspension of 2.0 g (2 mmol) of **3** in 150 mL of dry THF with

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[1] This communication is paper 31 in a series entitled Calixarenes. For paper 30, see: Reddy, P. A.; Kashyap, R. P.; Watson, W. H.; Gutsche, C. D. *Isr. J. Chem.* **1992**, *32*, 89.

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[7] We are indebted to Janet S. Rogers and George G. Stanley for the X-ray determination, which will appear in a forthcoming article.

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[11] Anhydrous diglyme from commercial sources gave inconsistent and erratic results, the tetrasubstituted calix[4]arene usually being a minor product.

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[14] Compound **2**: white solid on recrystallization from $CHCl_3$–MeOH; mp 378–379 °C; ^1H NMR ($CDCl_3$) δ 7.26 (d, 4 H, J = 2.0 Hz, ArH), 7.01 (d, 4 H, J = 2.2 Hz, ArH), 3.8 (s, 4 H, $ArCH_2Ar$), 3.64 (d, 2 H, J = 13.2 Hz, $ArCH_2Ar$), 3.35 (d, 2 H, J = 13.4 Hz, $ArCH_2Ar$), 3.20 (br s, 12 H, NCH_3), 2.11 (br s, 12 H, NCH_3), 1.34 (s, 36 H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 186.74 (C=S), 149.08, 147.63, 134.20, 133.49, 126.18, 126.04 (Ar), 43.43, 37.71 (NCH_3), 38.60, 29.47 ($ArCH_2Ar$), 34.42 ($ArCMe_3$), 31.60 ($C(CH_3)_3$), Anal. Calcd for $C_{56}H_{76}N_4O_4S_4$: C, 67.43; H, 7.68; N, 5.62. Found: C, 67.46; H, 7.70; N, 5.52.

[15] Compound **3**: white solid on recrystallization from $CHCl_3$–MeOH; mp 396.5–397.5 °C; ^1H NMR ($CDCl_3$) δ 7.36 (d, 4 H, J = 2.2 Hz, ArH), 7.23 (d, 4 H, J = 2.1 Hz, ArH), 4.58 (d, 2 H, J = 13.2 Hz, $ArCH_2Ar$), 4.12 (s, 4 H, $ArCH_2Ar$), 3.66 (d, 2 H, J = 13.3 Hz, $ArCH_2Ar$), 2.89 (br s, 12 H, NCH_3), 2.72 (br s, 12 H, NCH_3), 1.31 (s, 36 H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 167.15 (C=O), 150.49, 146.75, 146.05, 127.81, 125.19, 124.22 (Ar), 45.86, 39.04 ($ArCH_2Ar$), 36.77 (NCH_3), 34.35 ($ArCMe_3$), 31.27 ($C(CH_3)_3$). Anal. Calcd for $C_{56}H_{76}N_4O_4S_4$: C, 67.43; H, 7.68; N, 5.62. Found: C, 67.66; H, 7.75; N, 5.60.

[16] Compound **4**: white solid on recrystallization from petroleum ether–CH_2Cl_2; mp 406 °C (the melting point apparatus must be heated to just below the melting point prior to dropping in the sealed capillary; otherwise, compound **4** slowly polymerizes and then decomposes above 440 °C); ^1H NMR ($CDCl_3$) δ 7.30 (s, 8 H, ArH), 4.08 (s, 8 H, $ArCH_2Ar$), 2.32 (br s, 4 H, SH), 1.25 (s, 36 H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 146.56, 140.84, 130.42, 127.23 (Ar), 45.71 ($ArCH_2Ar$), 34.11 ($ArCMe_3$), 31.06 ($C(CH_3)_3$). Anal. Calcd for $C_{44}H_{56}S_4$: C, 74.10; H, 7.91; S, 17.98. Found: C, 74.30; H, 7.79; S, 18.24.

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1.28 g (32 mmol) of 95% $LiAlH_4$, followed by flash chromatography using petroleum ether–CH_2Cl_2 (80:20), gave 0.92 g (64%) of **4** (1,3-alternate conformation).[16]

The $ArCH_2Ar$ methylene protons in the ^1H NMR spectrum of **4** obtained from **3** (1,2-alternate conformer) show a singlet. This can arise either from a rapidly interconverting set of cone conformers or from a 1,3-alternate conformer. That the latter is the more likely is indicated by the invariance of the ^1H NMR spectrum down to −60 °C and by the X-ray crystallographic structure which shows **4** to be in the 1,3-alternate conformation in the solid state.[17] By the use of a protocol similar to the one described above, the 1,3-alternate and partial cone conformers of **2** have also been converted to the tetramercapto compound **4**. In both cases a product identical with that obtained from the 1,2-conformer of **2** was obtained, reinforcing the conclusion that the 1,3-alternate conformer of **4** is preferred. Of the three conformers of **2** investigated, the 1,2-alternate conformer rearranges most smoothly, providing a rationale for why it was the one isolated in the earlier experiments. Although the cone conformer of **2** has been isolated and characterized, it is not yet available in sufficient quantity to explore its rearrangement.

p-tert-Butylcalix[4]arene (**1**) exists almost exclusively in the cone conformation both in solution and in the solid state. This is attributed to the very strong intramolecular hydrogen-bonding among the OH groups on the lower rim. The SH groups in **4** are stronger donors but much weaker acceptors than the OH groups in **1**, and intramolecular hydrogen-bonding is less effective. Although this effect is finite, it appears to be counteracted by the larger size of SH, which favors the 1,3-alternate conformation. A detailed report will be published concerning the conformational consequences of replacing OH with SH and will also include the mono-, di-, and trimercaptocalix[4]arenes.

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[17] We are indebted to William H. Watson and Mariucz Krawiec for the X-ray determination, which will appear in a forthcoming publication.