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Synthesis and solid state structural analysis of 1,3-alternate conformer of tetrathiacalix[4]arene tetra-ester, -acid and -ether derivatives

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Abstract

Four new tetrathiacalix[4]arene derivatives blocked in 1,3-alternate conformation and bearing four ester, acid or ether groups were prepared and their 1,3-alternate conformation was established by X-ray diffraction methods on single-crystal. © 2000 Elsevier Science Ltd. All rights reserved.

The spectacular development of calixarenes¹ is related to the possibilities that this class of molecules offers in terms of structural and functional modifications. In particular, although some time ago the conformational mobility of calixarene derivatives could have been considered as a limitation, today the control of the conformational space is positively explored in the design of receptors, catalysts and building blocks. In our own hands, whereas the cone conformation of *p*-*tert*-butylcalix[4]arene derivatives was exploited in the design of building blocks for the formation of inclusion networks in the solid state,² the 1,3-alternate conformation was used, both in the case of calix³ and cyclophane⁴ based building blocks, for the design of coordination networks and molecular braids.⁵

Recently a new class of calix[4]arene derivatives such as **1**⁶ and **2**⁷ in which the CH₂ junctions between the phenolic moieties are replaced by S atoms, thus leading to thiacalixarenes was reported. The synthesis and the structural analysis of tetrathiatetramercaptocalix[4]arene in which the CH₂ junctions are replaced by S atoms and the OH groups by SH moieties has been also reported.⁸ In the case of **1**, its remarkable binding ability towards transition metals has been recently investigated by us.⁹ Furthermore, partial oxidation of the thio junctions in **1** affording the tetrasulfoxide derivatives¹⁰ or complete oxidation of the sulfur atoms leading to the tetrasulfone derivatives^{11,12} have been achieved. The synthesis of tetra

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ester derivatives of **1** in various conformations has been also investigated.¹³ The *O*-alkylation of **1** has been also reported.¹⁴

Dealing with sulfur containing calixarenes, the synthesis^{15–17} of di- and tetra-mercaptocalix[4]arenes, in which two or four OH moieties were replaced by SH groups, and their binding^{16,17} as well as extraction¹⁸ abilities towards mercury have been reported.

As for calix[4]arenes, in the case of thiacalixarenes four limit conformers (cone, partial cone, 1,2-alternate and 1,3-alternate) may be formed. Although in the solid state the cone conformation was observed for **1** and **2**,⁷ in solution, the interconversion between different conformers occurs rapidly above rt. Related to our investigations on molecular networks, we are interested in developing new building blocks. In this context, we have investigated the possibility of freezing of tetrathiacalix[4]arene derivatives conformation in 1,3-alternate conformation using bulky substituents at the lower rim which would block the interconversion processes between conformers.

In the present communication, we report the first synthesis and structural analysis of four new tetrathiacalix[4]arene derivatives **3–6** blocked in 1,3-alternate conformation (Fig. 1).

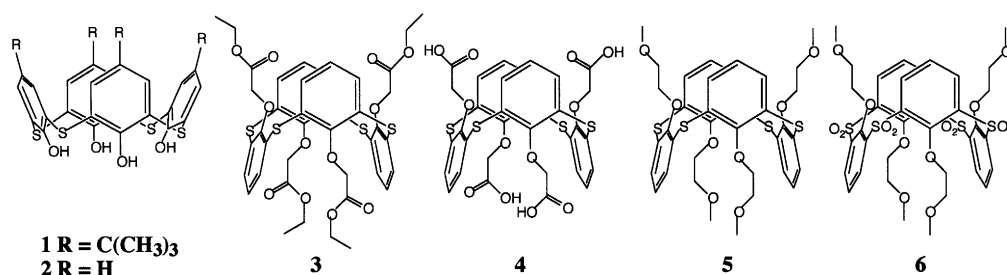


Fig. 1. Schematic representation of the cone conformation for the compounds **1** and **2** as well as the 1,3-alternate conformation for compounds **3–6**

The common starting material for the synthesis of **3–6** was the tetrathiacalix[4]arene **2**⁷ which was obtained by detertibutylation of *p*-tert-butyltetrathiacalix[4]arene **1**.⁶ Compound **3** was obtained in 85% yield upon refluxing a solution of **2** and ethylbromoacetate in dry acetone in the presence of Cs₂CO₃.¹⁹ Upon hydrolysis of the tetra ester **3** by LiOH in a THF/H₂O mixture, the tetra acid **4** was obtained in quantitative yield.¹⁹ On the other hand, treatment of **2** by 1-methoxy-2-(toluene-4-sulfonyloxy)ethane, freshly prepared following a reported procedure,²⁰ in DMF in the presence of Cs₂CO₃ afforded the tetra ether **5** in 58% yield.¹⁹ The complete oxidation of **5** to the tetra sulfone **6** was achieved in 59% yield using *m*-CPBA in CHCl₃.¹⁹

In solution, all four compounds **3–6** were studied by both ¹H and ¹³C NMR spectroscopy which showed sharp signals indicating the presence of conformationally blocked isomers. However, in marked contrast with calixarene derivatives for which both the ¹H and ¹³C NMR signals corresponding to the methylene groups are usually used for conformational assignment in solution, due to the absence of such an NMR probe for the thiacalix[4]arenes, their conformation cannot be unambiguously established using NMR techniques. Therefore, for all four compounds **3–6**, their 1,3-alternate conformation was assigned in the solid state by X-ray diffraction methods on single-crystal (Figs. 2–5).²¹ For compound **3**, suitable single crystals were obtained from a CH₂Cl₂/MeOH mixture. Compound **3** crystallises in a monoclinic form, space group C 1 2/c 1 (Fig. 2). No solvent molecules are found in the lattice. Compound **3** adopts the 1,3-alternate conformation. The average CS distance and CSC angle are 1.780 Å and 101.7°, respectively. The average C=O distance is 1.186 Å whereas the average C–O (arom) and C–O (ethyl) distances are found to be 1.420 Å and 1.328 Å, respectively. For compound **4**, suitable single crystals were obtained from a MeOH/H₂O mixture. Compound **4** in 1,3-alternate conformation, crystallises in a

triclinic form, space group P-1 (Fig. 3). In the lattice, in addition to two crystallographically different calix units, two H₂O and one CH₃OH molecules are present. The average CS distance and CSC angle are 1.782 Å and 105.7°, respectively. The average C=O and C–OH distances are 1.207 Å and 1.310 Å, respectively, whereas the average C–O (arom) and C–O (ethyl) distances are found to be 1.433 Å and 1.381 Å, respectively. For compound **5**, suitable single crystals were obtained from a CH₂Cl₂/MeOH mixture. Compound **5**, in 1,3-alternate conformation, crystallises in a rhombohedral form, space group P3 1 (Fig. 4). The lattice contains only the compound **5** and no solvent molecules. The average CS distance and CSC angle are 1.782 Å and 106.4°, respectively. The average C–OPh and C–OMe distances are 1.377 Å and 1.320 Å, respectively.

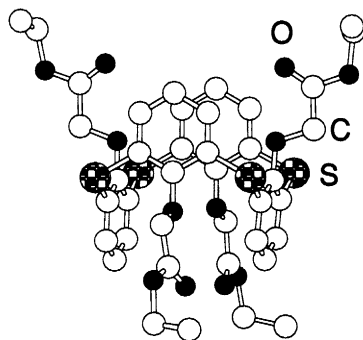


Fig. 2. X-Ray structure of **3** showing the 1,3-alternate conformation. H atoms and solvent molecules are not presented for sake of clarity

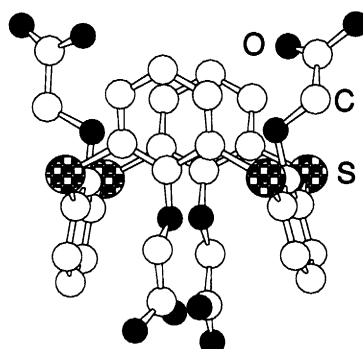


Fig. 3. X-Ray structure of **4** showing the 1,3-alternate conformation. H atoms and solvent molecules are not presented for sake of clarity

For compound **6**, suitable single crystals were obtained from a CHCl₃/MeOH mixture. Compound **6** in 1,3-alternate conformation, crystallises in a tetragonal form, space group P 42/n (Fig. 5). The lattice is exclusively composed of compound **6**. The average CS distance, CSC and OSO angle are 1.785 Å, 104.5° and 117.7°, respectively. The average C–OPh and C–OMe distances are 1.377 Å and 1.402 Å, respectively.

In conclusion, using tetrathiacalix[4]arene as a backbone, four new compounds bearing four ester, acid or ether groups were synthesised. The blocked conformation of all four compound was supported by ¹H NMR which showed sharp signals. For all four compounds, the 1,3-alternate conformation was demonstrated by X-ray diffraction methods on single-crystal. Elaboration on the reported compounds as building blocks is currently under investigation.

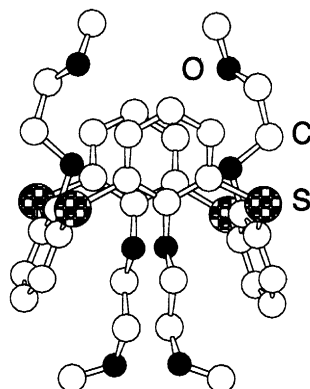


Fig. 4. X-Ray structure of **5** showing the 1,3-alternate conformation. H atoms and solvent molecules are not presented for sake of clarity

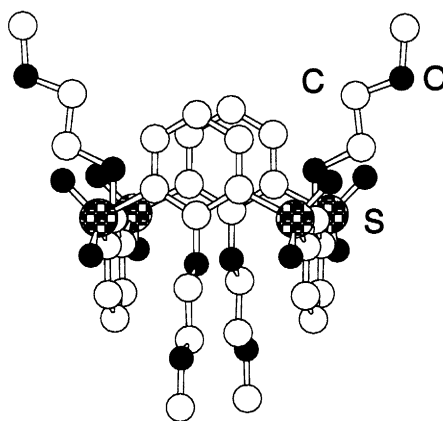


Fig. 5. X-Ray structure of **6** showing the 1,3-alternate conformation. H atoms are not presented for sake of clarity

Acknowledgements

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19. Compound **3**: A suspension of compound **2** (0.25 g, 50 μmol) in dry acetone (25 ml), Cs_2CO_3 (1 g, 3 mmol) and ethylbromoacetate (0.45 ml, 4 mmol) was refluxed overnight. After cooling to rt, the mixture was filtered and the solid thus obtained was washed with CH_2Cl_2 (2×10 ml). The filtrate and washes were combined and evaporated to dryness leaving a brownish oil. The treatment of the latter with methanol (5 ml) gave a precipitate which was filtered and crystallised from a $\text{CH}_2\text{Cl}_2/\text{MeOH}$ mixture affording the pure compound **3** in 85% yield (360 mg) as a light brown solid. Mp 186–187°C. Anal. calcd for $\text{C}_{40}\text{H}_{40}\text{O}_{12}\text{S}_4$: C, 57.13; H, 4.79. Found: C, 57.39; H, 4.64%; ^1H (300 MHz, CDCl_3 , 25°C): δ (ppm): 1.37 (t, $J=7.1$ Hz, 12H, CH_2CH_3), 4.32 (q, $J=7.1$ Hz, 8H, CH_2CH_3), 4.65 (s, 8H, OCH_2O), 6.82 (t, $J=7.8$ Hz, 4H, Ar), 7.58 (d, $J=7.8$ Hz, 8H, Ar); ^{13}C (75 MHz, CDCl_3 , 25°C): δ (ppm): 14.23 (CH_2CH_3), 60.82 (CH_2CH_3), 69.31 (CH_2OPh), 123.46, 128.44, 138.21, 159.80, 168.57; DEPT 135 (75 MHz, CDCl_3 , 25°C): δ (ppm): 14.23 (CH_2CH_3), 60.82 (CH_2CH_3), 69.31 (CH_2OPh), 123.46, 138.21. Compound **4**: To a solution of **3** (0.144 g, 0.17 mmol) in THF (25 ml) was added LiOH (0.04 g, 1.6 mmol) dissolved in water (8 ml) and the mixture stirred at rt overnight. Upon acidification to pH=1 using HCl (2.5 N), the pure compound **4** was obtained in quantitative yield as a precipitate. Mp 290°C (decomp). Anal. calcd for $\text{C}_{32}\text{H}_{24}\text{O}_{12}\text{S}_4$: C, 52.74; H, 3.32; found: C, 52.53; H, 3.24%; ^1H (300 MHz, MeOD, 25°C): δ (ppm): 4.54 (s, 8H, CH_2OPh), 6.85 (t, $J=7.8$ Hz, 4H, Ar), 7.56 (d, $J=7.8$ Hz, 8H, Ar); ^{13}C (50 MHz, MeOD, 25°C): δ (ppm): 69.19 (CH_2OPh), 125.47, 130.13, 137.30, 160.29, 172.25; DEPT 135 (50 MHz, MeOD, 25°C): δ (ppm): 69.19 (CH_2OPh), 125.47, 130.13, 137.30. Compound **5**: To a solution of compound **1** (100 mg, 0.2 mmol) in dry DMF (30 ml), Cs_2CO_3 (1.31 g, 4.02 mmol) was added and the mixture stirred for 1 h at 80°C. To the mixture 1-methoxy-2-(toluene-4-sulfonyloxy)ethane²⁰ (0.92 g, 4.02 mmol) was added and the mixture was stirred at 80°C overnight. After cooling to rt, the volatiles were evaporated and the residue was dissolved in CH_2Cl_2 (100 ml), washed with HCl 1 M (2×30 ml) and H_2O (30 ml). After evaporation of the solvent, to the yellowish liquid thus obtained, CH_3CN (50 ml), Et_3N (0.2 ml) and KI (200 mg) were added and the mixture refluxed for 3 h. After removal of volatiles, the residue was dissolved in CH_2Cl_2 (100 ml) and washed with HCl 1 M (20 ml), brine (20 ml) and H_2O (20 ml). After evaporation of the solvent, the viscous oil was treated with cold MeOH affording a white powder which was crystallised from a $\text{CH}_2\text{Cl}_2/\text{MeOH}$ mixture affording the pure compound **5** in 58% yield (86 mg) as colourless crystals. Mp 162°C. Anal. calcd for $\text{C}_{36}\text{H}_{40}\text{O}_8\text{S}_4$: C, 59.57; H, 5.57; found: C, 59.32; H, 5.32%; ^1H (200 MHz, CDCl_3 , 25°C): δ (ppm): 3.16 (s, 12H, $\text{OC}_2\text{H}_4\text{OCH}_3$), 3.27 (t, 8H, $J=5.8$ Hz, $\text{OCH}_2\text{CH}_2\text{OCH}_3$), 4.13 (t, 8H, $J=5.8$ Hz, $\text{OCH}_2\text{CH}_2\text{OCH}_3$), 6.89 (t, 4H, $J=7.4$ Hz, H arom.), 7.47 (d, 4H, $J=7.4$ Hz, H arom.); ^{13}C (50 MHz, CDCl_3 , 25°C): δ (ppm): 59.16 (ArOCH_2), 68.60 ($\text{CH}_2\text{CH}_2\text{OCH}_3$), 70.81 ($\text{CH}_2\text{CH}_2\text{OCH}_3$), 123.36, 129.10, 133.32, 159.75. Compound **6**: To a solution of compound **5** (50 mg, 0.068 mmol) in CHCl_3 (50 ml) *m*-CPBA 70–75% (252.3 mg) was added and the mixture was stirred for 4 days at rt. To the mixture H_2O (50 ml) was added and the organic layer was separated and washed with a 10% solution of NaOH (16 ml) and then H_2O (30 ml). The organic phase was dried (MgSO_4) before the solvent was removed leaving a solid which was recrystallised from a $\text{CHCl}_3/\text{MeOH}$ mixture affording thus the pure compound **6** as colourless crystals in 59% yield (35 mg). Mp >300°C. Anal. calcd for $\text{C}_{36}\text{H}_{40}\text{O}_{16}\text{S}_4$: C, 50.46; H, 4.70; found: C, 50.72; H, 4.81%; ^1H (200 MHz, CDCl_3 , 25°C): δ (ppm): 3.41 (s, 12H, $\text{OC}_2\text{H}_4\text{OCH}_3$), 3.68 (t, 8H, $J=4.4$ Hz, $\text{OCH}_2\text{CH}_2\text{OCH}_3$), 4.65 (t, 8H, $J=4.4$ Hz, $\text{OCH}_2\text{CH}_2\text{OCH}_3$), 7.33 (t, $J=8$ Hz, 4H, arom.), 8.44 (d, $J=8$ Hz, 4H, arom.); ^{13}C (50 MHz, CDCl_3 , 25°C): δ (ppm): 58.93 (ArOCH_2), 71.91 ($\text{CH}_2\text{CH}_2\text{OCH}_3$), 78.66 ($\text{CH}_2\text{CH}_2\text{OCH}_3$), 123.31, 136.16, 138.29, 155.4.
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21. X-Ray data for **3**: $\text{C}_{40}\text{H}_{40}\text{O}_{12}\text{S}_4$, $M=841.01$, monoclinic, $a=23.7190(9)$, $b=13.5220(4)$, $c=17.6030(7)$ Å, $\beta=131.800(1)$, $U=4208.8(5)$ Å³, space group C 1 2/c 1, $Z=4$, $D_c=1.33$ g cm⁻³, $\mu(\text{Mo-K}\alpha)=0.285$ mm⁻¹. Crystal dimensions 0.20×0.20×0.14 mm. Data were measured at 173 K. $R=0.063$, $R_w=0.078$ for 3964 independent observed reflections with $[\text{I}_o] > 3\sigma(\text{I}_o)$. X-Ray data for **4**: $2(\text{C}_{32}\text{H}_{24}\text{O}_{12}\text{S}_4) \cdot 2\text{H}_2\text{O} \cdot \text{CH}_3\text{OH}$, $M=1525.67$, triclinic, $a=10.7676(4)$, $b=17.118(1)$, $c=20.732(1)$ Å, $\alpha=72.407(5)$, $\beta=77.158(5)$, $\gamma=88.084(5)$, $U=3549.1(4)$ Å³, space group P-1, $Z=2$, $D_c=1.43$ g cm⁻³, $\mu(\text{Mo}$

$K\alpha$)=0.333 mm⁻¹. Crystal dimensions 0.20×0.12×0.04 mm. Data were measured at 173 K. $R=0.078$, $R_w=0.111$ for 5330 independent observed reflections with $[|F_o|>3\sigma(|F_o|)]$. X-Ray data for **5**: C₃₆H₄₀O₈S₄, $M=728.97$, rhombohedral, $a=b=11.3623(3)$, $c=24.869(1)$ Å, $\alpha=\beta=90$, $\gamma=120$, $U=2780.5(3)$ Å³, space group P3 1, $Z=3$, $D_c=1.31$ g cm⁻³, $\mu(\text{Mo-K}\alpha)=0.305$ cm⁻¹. Crystal dimensions 0.20×0.18×0.15 mm. Data were measured at 293 K. $R=0.050$, $R_w=0.068$ for 2115 independent observed reflections with $[|F_o|>3\sigma(|F_o|)]$. X-Ray data for **6**: C₃₆H₄₀O₁₆S₄, $M=856.97$, tetragonal, $a=12.9883(8)$, $b=12.9883(8)$, $c=12.2674(6)$ Å, $\alpha=\beta=\gamma=90.0$, $U=2069.5(4)$ Å³, space group P 42/n, $Z=2$, $D_c=1.38$ g cm⁻³, $\mu(\text{Mo-K}\alpha)=0.298$ mm⁻¹. Crystal dimensions 0.20×0.20×0.16 mm. Data were measured at 273 K. $R=0.054$, $R_w=0.068$ for 1218 independent observed reflections with $[|F_o|>3\sigma(|F_o|)]$. For all four structures, data were measured on a kapa CCD diffractometer with graphite monochromated Mo-K α radiation. All structures were solved by direct methods using OpenMoleN 2.2 and refined anisotropically using absorption corrected data. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.