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Novel molecular chirality in the calixarene family: formation of chiral disulfinyldithiacalix[4]arenes via partial oxidation of two adjacent sulfides of tetrathiacalix[4]arene

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Abstract

The first chiral disulfinyldithiacalix[4]arenes have been obtained by oxidation of two adjacent epithio groups of the tetramethyl ether of tetra(*p-tert*-butyl)tetrathiacalix[4]arene. The chiral resolution was achieved by HPLC using Chiralpak AD as a stationary phase. Furthermore, the absolute configuration of these compounds was determined by X-ray crystallography.

Keywords: calixarenes; oxidation; sulfinyl compounds; X-ray crystallography.

Calixarenes (e.g. **1**) have been widely used as three-dimensional building blocks for the construction of artificial molecular receptors capable of recognizing neutral molecules, cations, and anions.[1] Recently, increasing demand for molecular receptors with chiral discriminating abilities has prompted the design and synthesis of chiral calixarenes.[2] The most feasible synthetic strategy for chiral calixarenes is to anchor chiral residues at the lower (phenolic oxygens) or the upper (*p*-positions) rims of the calixarene skeleton.[3] A more sophisticated way to generate chiral calixarenes is to create dissymmetry or asymmetry within the molecule by introducing, at least, two kinds of achiral substituents into the upper and/or lower rims or *meta* positions of the phenol unit.[4] Since we reported a facile synthesis of tetra(*p-tert*-butyl)tetrathiacalix[4]arene (**2**),[5] in which the bridging methylenes of **1** are replaced by epithio groups, we have been engaged in the development of its novel functions and applications.[6] During the course of this study, we first showed that **2** can be

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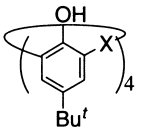
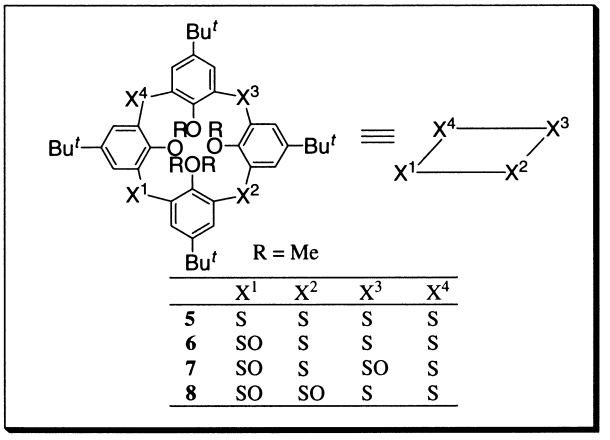
selectively oxidized to either tetra(*p-tert*-butyl)tetrasulfinylcalix[4]arene (**3**) or tetra(*p-tert*-butyl)-tetrasulfonylcalix[4]arene (**4**) by controlling the amount of $NaBO_3$ as the oxidizing agent.[7] From a stereochemical point of view, **3** has a quite interesting feature in that all four S=O groups oriented in a *trans* manner to each other.[7] Furthermore, we recently succeeded in controlling the direction of the four S=O groups in all *cis* relationship.[8] These results gave us the idea to construct chiral calixarenes; the stereo- and regioselective oxidation of the epithio groups should produce tetrathiacalix[4]arenes of molecular asymmetry, which is not attainable by the conventional methylene-bridged calix[4]arenes. To demonstrate this hypothesis, herein we report the synthesis of chiral disulfinyldithiacalix[4]arene (**8**), with the two adjacent S=O groups residing on the opposite side of the mean plane defined by the macrocycle, via oxidation of a pair of two adjacent epithio groups of a tetrathiacalix[4]arene tetramethyl ether (**5**).

First, we tried to partially oxidize the sulfide function of **2**, which resulted in the formation of a small amount of **3**, recovering most of **2** intact. The phenol moiety of **3** seemed to be vulnerable to decomposition by oxidation on silica gel during purification. Depending upon the oxidation conditions, TLC of the reaction indicated the presence of trace amounts of partially oxidized products of **2**, while it was very difficult to isolate them by chromatography because of their instability; it seemed necessary to protect the phenolic oxygens of **2** to isolate the partial oxidation products. Thus, **2** was treated with methyl iodide in acetone using K_2CO_3 as a base catalyst to give the corresponding tetramethyl ether **5** in a satisfactory yield (90%).[9]



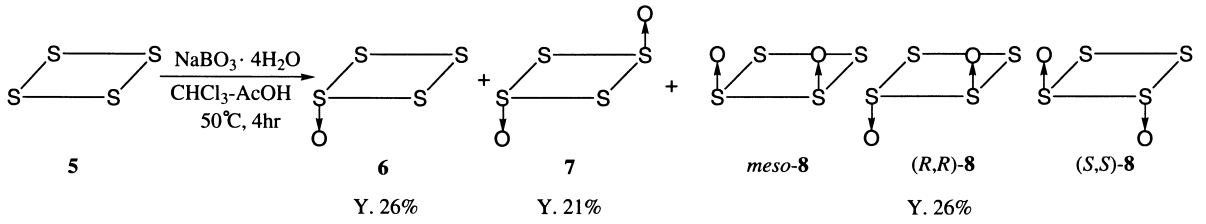
1 X = CH_2
2 X = S
3 X = SO
4 X = SO_2



	X^1	X^2	X^3	X^4
5	S	S	S	S
6	SO	S	S	S
7	SO	S	SO	S
8	SO	SO	S	S

Oxidation of **5** with twofold excess $NaBO_3$ in $CHCl_3$–acetic acid gave a mixture of the oxidation products, which was chromatographed on a silica gel column ($CHCl_3$/hexane) to give monosulfinyltrithiacalix[4]arene **6** (26%) and disulfinyldithiacalix[4]arenes **7** (21%) and **8** (26%), in which a pair of distal and proximal S atoms are oxidized, respectively (Scheme 1).[10] The configuration of two distal S=O groups of **7** was presumed by ^1H NMR to be in *trans* relationship. On the other hand, it was expected that **8** might be comprised of the stereoisomers of (*R*,*R*)-, (*S*,*S*)-, and *meso*-form depending upon the combination of the orientation of the two proximal S=O groups. In fact, ^1H NMR revealed that the obtained **8** consisted of a 1:4 mixture of (±)- and *meso*-isomers.

The resolution of (±)- and *meso*-**8** was accomplished by HPLC using chiral stationary phase Chiralpak AD (amylose tris-3,5-dimethylphenylcarbamate) coated on 10 μm silica gel (Fig. 1a).



Scheme 1. Oxidation of *p-tert*-butylthiacalix[4]arene tetramethyl ether **5**

Retention factor of the first-eluted enantiomer (k_1) and separation factor (α) calculated from the HPLC chromatogram are 3.24 and 2.07, respectively. Sufficient base line separation of the components enabled the isolation of both enantiomers as optically pure samples.[10] Specific rotations $[\alpha]_D^{24}$ of the first and third eluted components were measured to be –49.3° (*c* 0.52, $CHCl_3$) and +49.3° (*c* 0.51, $CHCl_3$), respectively. As shown in Fig. 1b, the CD spectra of (+)-**8** and (–)-**8** are quite symmetrical, whereas *meso*-**8** did not give any perceptible CD absorption. Although it is well known that sulfoxides are highly susceptible to isomerization under strongly acidic conditions, treatment of (+)-**8** with HCl did not show any indication of epimerization or racemization.[11]

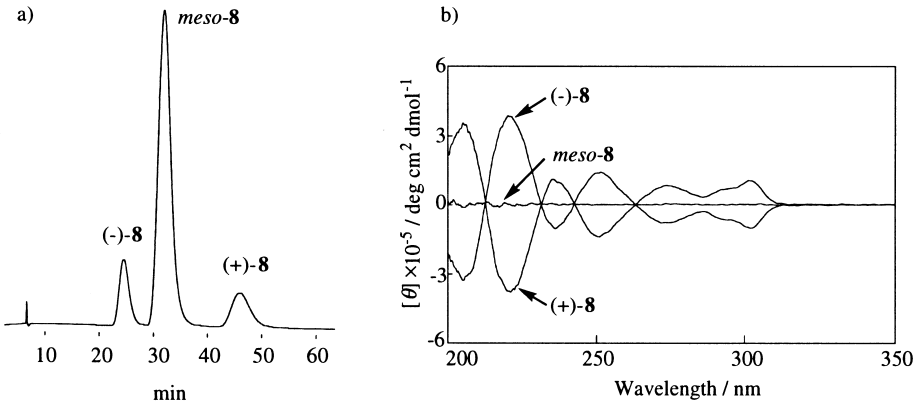


Figure 1. (a) HPLC resolution of stereoisomers of **8**. Column: Chiralpak AD (0.46 cmϕ×25 cm, mobile phase *n*-hexane:2- propanol (98:2) at flow 0.5 ml/min). (b) CD spectra of (+)-**8**, (–)-**8** and *meso*-**8** (1.0×10^{-4} mol dm^{-3}, in EtOH

Vapor diffusion of CH_3CN into a solution of (+)-**8** in CH_2ClCH_2Cl at room temperature afforded a single crystal suitable for X-ray structural analysis. The absolute configuration of (+)-**8** was determined to be (*S*,*S*) adopting 1,3-alternate conformation (Fig. 2).[12] It can be seen that the two adjacent S=O groups disposed in a *trans* relationship, with S=O bond length being 1.457 (3) and 1.481(2) Å as is typical for sulfoxides. On the other hand, the average C–S–O angle is 108.8 (1)°, implying that the sulfur adopts tetrahedral geometry defined by sp^3 hybridization by bonding to two adjacent phenyl carbons and one oxygen with one lone pair electrons on S. The dihedral angles between the opposite phenyl rings are 10.64 and 6.61°, indicating that the phenyl rings are nearly parallel.

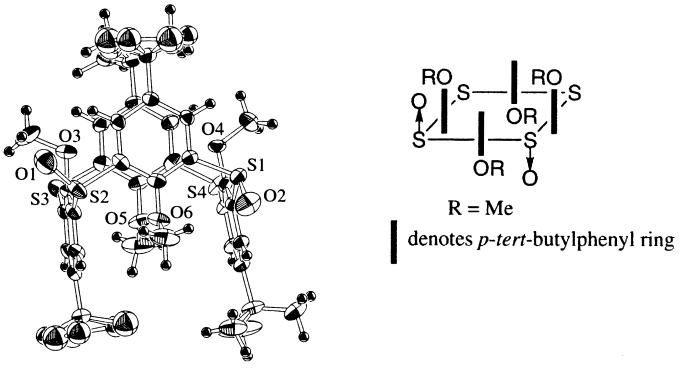


Figure 2. The ORTEP drawing of (*S*,*S*)-(+)-**8** with thermal ellipsoids drawn at the 50% probability

In conclusion, we have demonstrated a new strategy to synthesize chiral thiacalix[4]arene by oxidation of the two proximal epitio groups to chiral sulfinyl groups. Application of the compound **8** as catalysts for asymmetric reaction is under current investigation.

Acknowledgements

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References

1. Gutsche, C. D. *Calixarenes*; Stoddart, J. F., Ed. Monographs in supramolecular chemistry. The Royal Society of Chemistry: Cambridge, 1989; *Calixarenes—A Versatile Class of Macrocyclic Compounds*; Eds. Vicens, J.; Böhmer, V.; Kluwer, Dordrecht, 1991; Gutsche, C. D. *Calixarenes Revisited*; Stoddart, J. F., Ed. Monographs in supramolecular chemistry. The Royal Society of Chemistry: Cambridge, 1998.
2. Kubo, Y.; Maeda, S.; Tokita, S.; Kubo, M. *Nature* **1996**, *382*, 522–524.
3. See for example: Arimura, T.; Kawabata, H.; Matsuda, T.; Muramatsu, T.; Satoh, H.; Fujio, K.; Manabe, O.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 301–306. Marra, A.; Scherrmann, M.-C.; Dondoni, A.; Casnati, A.; Minari, P.; Ungaro, R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2479–2481.
4. See for example: Iwamoto, K.; Shimizu, H.; Araki, K.; Shinkai, S. *J. Am. Chem. Soc.* **1993**, 115, 3997–4006. Caccamese, S.; Notti, A.; Pappalardo, S.; Parisi, M. F.; Principato, G. *Tetrahedron* **1999**, *55*, 5505–5514.
5. Kumagai, H.; Hasegawa, M.; Miyanari, S.; Sugawa, Y.; Sato, Y.; Hori, T.; Ueda, S.; Kamiyama, H.; Miyano, S. *Tetrahedron Lett.* **1997**, *38*, 3971–3972.
6. Iki, N.; Kabuto, C.; Fukushima, T.; Kumagai, H.; Takeya, H.; Miyanari, S.; Miyashi, T.; Miyano, S. *Tetrahedron* **2000**, *56*, 1437–1443.
7. Iki, N.; Kumagai, H.; Morohashi, N.; Ejima, K.; Hasegawa, M.; Miyanari, S.; Miyano, S. *Tetrahedron Lett.* **1998**, *39*, 7559–7562. cf. Mislin, G.; Graf, E.; Hosseini, M. W.; Cian, A. D.; Fischer, J. *Chem. Commun.* **1998**, 1345–1346.
8. Morohashi, N.; Iki, N.; Kabuto, C.; Miyano, S. *Tetrahedron Lett.* **2000**, *41*, 2933–2937.
9. A mixture of **2** (5.0 g, 6.9 mmol), potassium carbonate (19.1 g, 138 mmol) and methyl iodide (8.6 ml, 138 mmol) was stirred under reflux in 100 ml of acetone for 24 h. The reaction mixture was poured into 1 M HCl (200 ml) and extracted with chloroform (100 ml×3). The organic layer was washed with water (100 ml) and evaporated to dryness to give a crude product, which was recrystallized from $CHCl_3$–acetone to give a pure sample of **5** (4.8 g,

90%) as white needles. Compound **5**: mp 314–316°C; FAB MS: 776 (M^+); ^{1}H NMR ($CDCl_3$) δ 7.44(s, 8, Ar*H*), 3.45 (s, 12, OCH_3), 1.24 (s, 36, CMe_3). Calcd for $C_{44}H_{56}O_4S_4$: C, 68.00; H, 7.26; S, 16.50. Found: C, 67.71; H, 7.12; S, 16.75.

10. To a solution of **5** (0.7 g, 0.9 mmol) in chloroform (12 ml) were added acetic acid (15 ml) and $NaBO_3{\cdot}4H_2O$ (0.28 g, 1.8 mmol). The mixture was stirred at 50°C for 2.5 h. After being cooled, the reaction product was extracted with chloroform (20 ml×3) and washed with water (30 ml). The chloroform solution was evaporated to dryness to give a crude product, which was chromatographed on silica gel ($CHCl_3$/hexane = 10) to give **6** (0.19 g, 26%), **7** (0.15 g, 21%), and diastereomeric mixture of **8** (0.19 g, 26%) as a white powder, respectively. The ratio of *meso*-**8** and (±)-**8** was 4:1 as calculated by ^{1}H NMR. The elemental analysis of the diastereomeric mixture of **8** is as follows: calcd for $C_{68}H_{72}O_8S_4$: C, 71.29; H, 6.34; S, 11.20. Found: C, 71.50; H, 6.35; S, 11.26. The HPLC resolution of (±)- and *meso*-**8** was accomplished by Chiralpak AD (size 2 cmϕ×25 cm, column NO. AD00CJ-IG003, *n*-hexane:2-propanol = 97:3). Compound **6**: mp 311–313°C; IR (KBr) 2961 (C-H), 1049 (S-O), 1003 (C-O-C); FAB MS 793 ($M+1^+$); ^{1}H NMR ($CDCl_3$) δ 7.64 (d, 2, J = 2.1 Hz, Ar*H*), 7.57 (d, 2, J = 2.1 Hz, Ar*H*), 7.44 (brs, 4, Ar*H*), 3.79(s, 6, OCH_3), 3.49 (brs, 6H, OCH_3) 1.24 (s, 36, CMe_3). Calcd for $C_{44}H_{56}O_5S_4$: C, 66.63; H, 7.12; S, 16.17. Found: C, 66.63; H, 7.24; S, 16.35. Compound **7**: mp 322–324.5°C; IR (KBr) 2963 (C-H), 1051 (S-O), 1001 (C-O-C); FAB MS 809 ($M+1^+$); ^{1}H NMR ($CDCl_3$) δ 7.65 (brs, 4, Ar*H*), 7.58 (brs, 4, Ar*H*), 3.88 (brs, 6, OCH_3), 3.79 (brs, 6, OCH_3) 1.25 (s, 36, CMe_3). Calcd for $C_{44}H_{56}O_6S_4$: C, 65.31; H, 6.98; S, 15.85. Found: C, 65.05; H, 7.09; S, 15.87. Compound (*S*,*S*)-(+)-**8**: mp 319.5–322°C; IR (KBr) 2963 (C-H), 1057 (S=O), 999 (C-O-C); FAB MS: 809 ($M+1^+$); ^{1}H NMR ($CDCl_3$) δ 7.98 (brs, 1, Ar*H*), 7.72 (br, 3, Ar*H*), 7.61 (brs, 2, Ar*H*), 7.43 (brs, 1, Ar*H*), 7.21 (brs, 1, Ar*H*), 4.08 (s, 3, OCH_3), 3.79 (s, 3, OCH_3), 3.65 (s, 6, OCH_3), 1.31 (s, 18, CMe_3), 1.22 (s, 9, CMe_3), 1,15 (s, 9, CMe_3). $[\alpha]_D^{24}$ +49.3°(*c* 0.51, $CHCl_3$). Compound (*R*,*R*)-(–)-**8**: mp 315–318°C; IR (KBr) 2963 (C-H), 1057 (S=O), 999 (C-O-C); FAB MS: 809 ($M+1^+$); ^{1}H NMR ($CDCl_3$) δ 7.98 (brs, 1, Ar*H*), 7.72 (br, 3, Ar*H*), 7.61 (brs, 2, Ar*H*), 7.43 (brs, 1, Ar*H*), 7.21 (brs, 1, Ar*H*), 4.08 (s, 3, OCH_3), 3.79 (s, 3, OCH_3), 3.65 (s, 6, OCH_3), 1.31 (s, 18, CMe_3), 1.22 (s, 9, CMe_3), 1.15 (s, 9, CMe_3). $[\alpha]_D^{24}$ –49.3° (*c* 0.52, $CHCl_3$). *meso*-**8**: mp 299–301°C; IR (KBr) 2963 (C-H), 1053 (S=O), 1003 (C-O-C); FAB MS: 809 ($M+1^+$); ^{1}H NMR ($CDCl_3$) δ 7.91 (brs, 2, Ar*H*), 7.56 (brs, 2, Ar*H*), 7.79–7.05 (br, 4, Ar*H*), 4.08 (s, 6, OCH_3), 3.66 (s, 3, OCH_3), 3.55 (s, 3, OCH_3), 1.29 (s, 18, CMe_3), 1.16 (s, 18, CMe_3).
11. To a vial tube were added a solution of (+)-**8** in $CHCl_3$ and 2 M HCl. The mixture was shaken at room temperature for 24 h. An aliquot of the organic phase was evaporated to dryness to recover (+)-**8** without epimerization and racemization.
12. X-Ray data for (*S*,*S*)-(+)-**8**: $C_{44}H_{56}O_6S_4$, $M = 809.16$, colorless, sizes = 0.3×0.3×0.45 mm, monoclinic, $a = 10.737(1)$, $b = 18.3262(9)$, $c = 11.5140(6)$ Å, $V = 2224.1(3)$ Å^3, Mo–Kα radiation ($\lambda = 0.71069$ Å), space group $P2_1$ (No. 4), $Z = 2$, $D_{calc} = 1.208$ g/cm^3, $T = 150$ K, μ(Mo–Kα) = 2.08 cm^{-1}, data collection using Rigaku/MSC mercury CCD diffractometer, 900 images at 30.0 sec, number of reflections measured through all reflections of sphere = 21757 ($2\theta < 55°$), independent reflections in which Friedel pairs are not averaged = 9211 ($R_{int} = 0.022$), a symmetry-related absorption correction, final $R = 0.040$, $R_w = 0.043$ for 8511 observed reflections ($I_O > 4.0\sigma(I_O)$), GOF = 1.39. Flack parameters are 0.03(0.03) and 0.97(0.03) for correct and incorrect structures, respectively. Consistency of signs between the Friedel pairs for Fo and Fc are 84 (correct) versus 9 (incorrect) for reflections with larger differences of Fc(+)-Fc(–). A total of three crystals were examined for absolute structure determination, giving the same results. Further details of X-ray analysis are available on request from the Director of the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.