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Stereocontrolled oxidation of a thiacalix[4]arene to the sulfinyl counterpart of a defined S=O configuration

Naoya Morohashi,[a] Nobuhiko Iki,[a,*] Chizuko Kabuto [b] and Sotaro Miyano [a,*]

[a] *Department of Biomolecular Engineering, Graduate School of Engineering, Tohoku University, Aramaki-Aoba 07, Aoba-ku, Sendai 980-8579, Japan*

[b] *Department of Chemistry, Graduate School of Science, Tohoku University, Aramaki-Aoba 07, Aoba-ku, Sendai 980-8578, Japan*

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Abstract

Treatment of *p-tert*-butylthiacalix[4]arene (**1**) with benzyl bromide in THF–DMF using NaH as the base catalyst afforded the tetrabenzyl ether of cone conformation ($\mathbf{4}_C$) as the major product, oxidation of which, with $NaBO_3$ in $CHCl_3$–acetic acid, proceeded readily to give the corresponding sulfinyl compound (**5**) with the four S=O groups disposed on the same side of the plane defined by the macrocyclic ring probably to avoid the steric hindrance imposed by the benzyllic moieties. Cleavage of the ether bonds gave a new stereoisomer of *p-tert*-butylsulfinylcalix[4]arene (**2**(ccc)) with the four S=O groups arranged in a *cis–cis–cis* configuration. © 2000 Elsevier Science Ltd. All rights reserved.

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Since we reported the facile synthesis of *p-tert*-butylthiacalix[4]arene (**1**),[1] we have been engaged in the development of its novel functions and applications which are not attainable by the conventional methylene-bridged calix[4]arenes.[2] One of the most noteworthy features of **1** is its ability to bind various transition metal ions by virtue of the cooperative ligation of the epithio function with that of the phenoxide oxygens as revealed by solvent extraction studies and X-ray crystallography.[3,4]

The well-known ready oxidizability of an epithio function to the sulfinyl and/or sulfonyl group should be another attractive feature of **1**. Thus, we first showed that **1** can be selectively oxidized to either *p-tert*-butylsulfinylcalix[4]arene (**2**) or *p-tert*-butylsulfonylcalix[4]arene (**3**) by controlling the amounts of $NaBO_3$ as the oxidizing agent.[5] Interestingly, the direct oxidation of **1** afforded only one isomer **2**(ttt) exclusively, as evidenced by NMR and X-ray crystallography,[5,6] with the four S=O groups arranged in an up–down–up–down manner to form the *trans–trans–trans*-isomer among the four possible combinations of the S=O configurations (Fig. 1). The stereochemical outcome of the oxidation may be ascribed to the structure of **2**(ttt) which, seemingly, is the least congested and, furthermore, favored by the hydrogen

* Corresponding authors.

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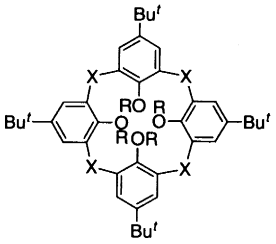
bonding between the OH and S=O groups in the *o*-position and by the least dipole repulsion of the S=O groups.



1 X = S, R = H
2 X = SO, R = H
3 X = SO_2, R = H
4 X = S, R = CH_2Ph
5 X = SO, R = CH_2Ph

Needless to say, it is not only very interesting but also important from the viewpoint of synthetic and molecular recognition chemistry to provide isomeric **2**s of S=O configurations other than the *trans–trans–trans* arrangement. Herein, we report a new synthesis of **2**(ccc) with the four S=O groups residing on the same side of the mean plane defined by the macrocycle to form a *cis–cis–cis* configuration. Our method relied on the initial fixation of the thiacalix[4]arene skeleton to cone conformation by tetra-*O*-benzyllation to give $\mathbf{4}_C$, followed by the stereocontrolled introduction of oxygen atoms onto the sulfur with the aid of the steric bulk imposed by the benzyllic moieties.

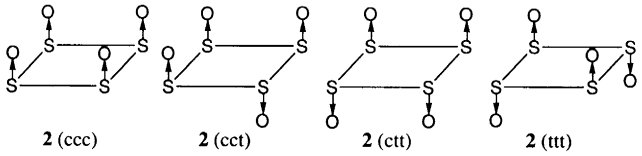


Fig. 1. Schematic representation of four stereoisomers of **2**. Conformational isomers of **2** due to the flip-flop inversion of aryl moieties are omitted for clarity. Herein, we use the term *cis* (c) or *trans* (t) to denote the disposition of sulfoxide oxygen with respect to the mean plane containing four sulfur atoms

As is well-known in calix[4]arene chemistry, *O*-alkylation of **1** may lead to the formation of the four limit conformers including cone, partial cone, 1,2-alternate, and 1,3-alternate according to the relative orientations of the aromatic rings (Fig. 2). Thus, treatment of **1** with benzyl bromide in THF–DMF using NaH as the base catalyst afforded a mixture containing cone-shaped tetra-*O*-benzyl ether ($\mathbf{4}_C$) as the major product (48%) accompanied with two other conformers, i.e., partial cone ($\mathbf{4}_{PC}$) (16%) and 1,3-alternate ($\mathbf{4}_{1,3\text{-}A}$) (4%), which were readily separated by chromatography on silica gel.[7]

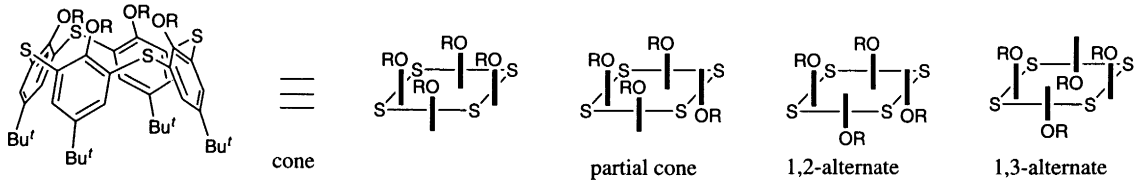


Fig. 2. Schematic representation of four possible isomers of tetra-*O*-alkylated thiacalix[4]arene derivatives

Oxidation of $\mathbf{4}_C$ with 1.1 equiv. of $NaBO_3$ proceeded smoothly in $CHCl_3$–acetic acid to give the corresponding sulfinyl compound **5** in a satisfactory yield (82%), which was found to be comprised of only one of the possible stereoisomers in regard to the configuration of the S=O moieties.[8] Slow diffusion of CH_3CN into a solution of **5** in CH_2Cl_2 at room temperature afforded a single crystal suitable for X-ray

structural analysis (Fig. 3).[9] It can be seen that all four S=O groups direct toward equatorial orientation in a *cis–cis–cis* manner seemingly to avoid the benzyl moieties. The S=O bond length is 1.486(3) Å as is typical for sulfoxides. Apparently, the molecule has a structure of C_4 symmetry including one molecule of CH_3CN in the cavity defined by the four *p-tert*-butylphenyl moieties. On the other hand, the average C–S–O angle is 105.8(2)°, 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.

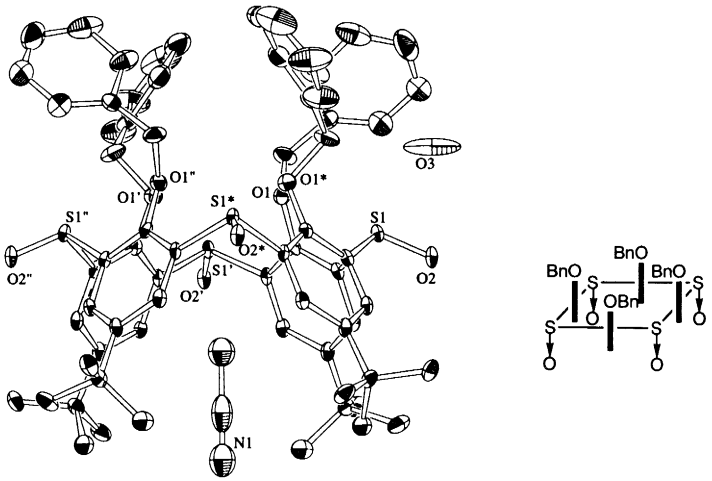


Fig. 3. ORTEP drawing of **5** with thermal ellipsoids drawn at the 30% probability. H atoms are not shown for clarity

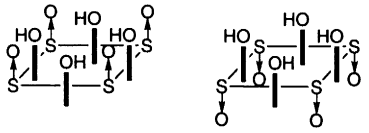
Treatment of **5** with trifluoroacetic acid eliminated the benzyl groups to give the sulfinylcalix[4]arene, which should have the four S=O groups of *cis–cis–cis* relationship and thus be denoted as **2**(ccc).[10] It should be noted here that the removal of the benzyl groups may bring about flip-flop inversion of the *p-tert*-butylphenyl moieties to allow the presence of several conformational isomers for **2**(ccc). The above obtained **2**(ccc) is only sparingly soluble in various solvents examined, which so far has not allowed single crystals to be obtained for X-ray diffraction. However, comparison of the IR and ^{1}H NMR data of **2**(ccc) with those of **2**(ttt), as well as the parent **1** (Table 1), may limit the conformation of **2**(ccc) to be *syn*- or *anti*-**2**(ccc) of cone conformation (Fig. 4). Although **1** and **2**(ttt) have a cone and a 1,3-alternate conformation in crystals, respectively, as evidenced by X-ray analyses,[6,11,12] ^{1}H NMR has revealed that the conformational interconversion of these should be quite fast in solutions at ambient temperature. It is interesting to compare the IR absorptions of ν_{OH} (KBr disk) of **2**(ccc) (3128 cm^{-1}) with that of **1** (3324 cm^{-1}) and **2**(ttt) (3188 cm^{-1}). The substantial shift of the first absorption to lower frequency strongly indicates the presence of greater intramolecular hydrogen bonding in **2**(ccc) than that in **1** and **2**(ttt). The X-ray analysis has shown the presence of hydrogen bonding between the OH and S=O groups in **2**(ttt),[6] whereas there are circular intramolecular hydrogen bonding among four OH groups in **1**.[11,12] On the other hand, **2**(ccc) absorbs $\nu_{S=O}$ at 1028 cm^{-1} falling in between that of **5** (1049 cm^{-1})[8] and that of **2**(ttt) (1001 cm^{-1}) to indicate the presence of some hydrogen bonding between the OH and S=O groups. Therefore, the OH groups of **2**(ccc) seem to form hydrogen bonding not only with adjacent OH but also S=O groups. Furthermore, the ^{1}H NMR spectrum of **2**(ccc) in $CDCl_3$–DMSO-d_6 showed a sharp singlet at 7.69 ppm for the phenyl ring protons indicating that they were equivalent on an NMR time-scale. On the other hand, the ring protons of **2**(ttt) are non-equivalent, showing two broad peaks at 7.37 and 7.76 ppm due to the two adjacent S=O groups in a *trans* relationship. From these discussions,

the conformation of **2**(ccc) may tentatively be assigned as a cone structure with S=O groups in *syn* relationship to the phenolic hydroxy groups as depicted in Fig. 4.

Table 1
The physical properties of **1**, **2**(ttt) and **2**(ccc)

	^{1}H NMR[a] (δ/ppm from TMS)	IR[b] (cm^{-1})	FAB MS[c]
1[d]	1.22(36H, s, Bu^t)[e]	3324(O-H)	720(M$^+$)[f]
	7.64(8H, s, Ar-H)[e]	2946(C-H)	
	9.60(4H, s, OH)[e]		
2(ttt)	1.23(36H, s, Bu^t)	3188(O-H)	785(M+1$^+$)
	7.37(4H, br, Ar-H)	2953(C-H)	
	7.76(4H, br, Ar-H)	1001(S-O)	
2(ccc)	1.24(36H, s, Bu^t)	3128(O-H)	785(M+1$^+$)
	7.69(8H, s, Ar-H)	2959(C-H)	
		1028(S-O)	

a: In $CDCl_3$/DMSO-d_6(1:1) solution. b: In KBr. c: *m*-NBA was used as matrix.
d: Data from lit. 1. e: In $CDCl_3$ solution. f: FD MAS was used.



syn-**2**(ccc) *anti*-**2**(ccc)

Fig. 4. Schematic representation of *syn*- and *anti*-**2**(ccc)

In conclusion, a potential method to obtain sulfinylcalixarenes of a defined S=O configuration has been shown via the oxidation of particularly shaped thiacalixarenes by proper derivatization. The synthesis of chiral sulfinylcalixarenes by use of this protocol is the challenging next step in our study and is currently under investigation.

Acknowledgements

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7. To a suspension of 0.89 g (23 mmol) of NaH (60% oil dispersion washed with two 2 ml portions of hexane) in 15 ml of THF:DMF (9:1) was added 1.0 g (1.4 mmol) of **1** with stirring under an atmosphere of N_2. After 30 min, 2.7 ml (23 mmol) of benzyl bromide was added, and the reaction mixture was refluxed with stirring for 2 h. After cooling, a few drops of MeOH

were added, the solvent was removed on a rotary evaporator, and the residue was poured into 50 ml of water. Extraction into $CHCl_3$ (20 ml×3) followed by washing with water, and the evaporation of the solvent left a crude product as an oil. Trituration with 20 ml of MeOH gave a white powder, which was chromatographed on silica gel (hexane–$CHCl_3$=5) to allow the separation of three conformers of **4** (**4**$_C$, 0.72 g, 48%; **4**$_{PC}$, 0.24 g, 16%; **4**$_{1,3\text{-}A}$, 0.06 g, 4%). Compound **4**$_C$: m.p. 208–209.5°C; FAB MS: 1081 ($M+1^+$); ^{1}H NMR ($CDCl_3$) δ 7.48–7.47 (m, 8, Ar*H*), 7.22 (s, 8, Ar*H*), 7.19–7.15 (m, 12, Ar*H*), 5.24 (s, 8, OCH_2Ph), 1.06 (s, 36, CMe_3). Anal. calcd for $C_{68}H_{72}O_4S_4$: C, 75.51; H, 6.71; S, 11.86. Found: C, 75.73; H, 6.67; S, 11.65. Compound **4**$_{PC}$: m.p. 222.5–224°C; FAB MS: 1081 ($M+1^+$); ^{1}H NMR ($CDCl_3$) δ 7.77–7.76 (m, 2, Ar*H*), 7.68–7.65 (m, 4, Ar*H*), 7.61 (s, 2, Ar*H*), 7.43–7.39 (m, 2, Ar*H*), 7.38 (s, 2, Ar*H*), 7.38 (d, 2, J=2.51 Hz, Ar*H*), 7.36–7.30 (m, 9, Ar*H*), 7.08–7.02 (m, 3, Ar*H*), 6.92 (d, 2, J=2.51 Hz, Ar*H*), 5.11 (d, 2, J=10.1 Hz, OCH_2Ph), 5.08 (s, 2, OCH_2Ph), 4.92 (d, 2, J=10.1 Hz, OCH_2Ph), 4.87 (s, 2, OCH_2Ph), 1.21 (s, 9, CMe_3), 0.85 (s, 18, CMe_3), 0.75 (s, 9, CMe_3). Anal. calcd for $C_{68}H_{72}O_4S_4$: C, 75.51; H, 6.71; S, 11.86. Found: C, 75.62; H, 6.79; S, 11.84. Compound **4**$_{1,3\text{-}A}$: m.p. 278–280°C; FAB MS: 1081 ($M+1^+$); ^{1}H NMR ($CDCl_3$) δ 7.14 (s, 8, Ar*H*), 7.16–7.00 (m, 20, Ar*H*), 5.07 (s, 8, OCH_2Ph), 0.84 (s, 36, CMe_3). Anal. calcd for $C_{68}H_{72}O_4S_4$: C, 75.51; H, 6.71; S, 11.86. Found: C, 75.26; H, 6.70; S, 12.06.

8. To a solution of **4**$_C$ (0.5 g, 0.46 mmol) in chloroform (10 ml) were added acetic acid (12 ml) and $NaBO_3\cdot 4H_2O$ (0.31 g, 2.03 mmol). The mixture was stirred at 50°C for 12 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 recrystallized from CH_2Cl_2–MeOH to give a pure sample of **5** (0.43g, 82%) as white needles. Compound **5**: m.p. 318–319°C; IR (KBr) 2961 (C–H), 1049 (S=O); FAB MS: 1145 ($M+1^+$); ^{1}H NMR ($CDCl_3$) δ 7.63 (s, 8, Ar*H*), 7.37–7.30 (m, 20, Ar*H*), 5.22 (s, 8, OCH_2Ph), 1.12 (s, 36, CMe_3). Anal. 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.
9. X-Ray data for **5**: $C_{68}H_{72}O_8S_4\cdot CH_3CN$, H_2O, M=1204.6, colorless, sizes=0.2×0.2×0.2 mm, tetragonal, a=b=15.8724(6), c=12.5804(3) Å, V=3169.4(3) Å^3, Mo-Kα radiation (λ=0.71069 Å), space group *P4/n* (No. 85), Z=2, D_{calc}=1.262 g/cm^3, T=150 K, μ(Mo-Kα)=2.08 cm^{-1}, data collection using Rigaku/MSC mercury CCD diffractometer, 480 images at 30.0 sec, number of measured reflections=40536 (2θ<54.2°), independent reflections=3604 (R_{int}=0.086), a symmetry-related absorption correction, final R=0.068, R_w=0.072 for 1568 observed reflections (I_O>3.5$_\sigma$(I_O)), *GOF*=1.55. Further details of X-ray analysis are available on request from the Director of the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.
10. To a solution of **5** (0.30 g) in benzene (5 ml) was added trifluoroacetic acid (10 ml). The mixture was refluxed for 3 days. After being cooled, water was added, and the reaction products were extracted into CH_2Cl_2, washed with 6 M HCl and then evaporated to give an oil. Trituration with MeOH and $CHCl_3$ followed by recrystallization from CH_2Cl_2–MeOH gave a pure sample of **2**(ccc) (0.08g, 40%) as a white powder. Compound **2**(ccc): m.p. 316°C (decomp.); IR (KBr) 3128 (O–H), 2959 (C–H), 1028 (S=O); FAB MS: 785 ($M+1^+$); ^{1}H NMR ($CDCl_3$:DMSO-d_6=1:1) δ 7.69 (s, 8, Ar*H*), 1.14 (s, 36, CMe_3). Anal. calcd for $C_{40}H_{48}O_8S_4$: C, 61.19; H, 6.16; S, 16.34. Found: C, 60.98; H, 6.11; S, 16.09. Although it is well known that sulfoxides are highly susceptible to isomerization under strongly acidic conditions, treatment of **2**(ttt) with trifluoroacetic acid under the above conditions did not show any indication of the conformational change of **2**(ttt).
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