Interconversion between *syn* and *anti* Conformations of 1,3-Bis(*O*-cyanomethyl)-*p-tert*-butylthiacalix[4]arene

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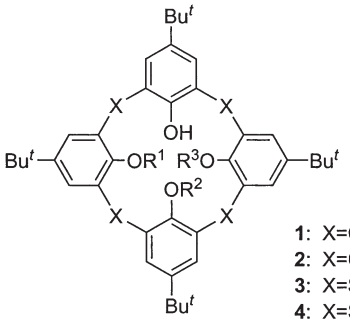
1,3-Bis(*O*-cyanomethyl)-*p-tert*-butylthiacalix[4]arene (**5**) has been found to interconvert between *syn* and *anti* conformations in solution. The equilibrium shifts toward the *anti* form with increasing solvent polarity. In the solid state, it adopts a pinched cone conformation with the *syn* arrangement of the cyanomethyl groups. Reduction of the equilibrium mixture of **5** with $LiAlH_4$ gives only *anti* stereoisomer of 1,3-bis(*O*-aminoethyl)-*p-tert*-butylthiacalix[4]arene.

Calixarenes are an extensively utilized scaffold for the construction of synthetic receptors of metal ions and neutral molecules.[1,2] It has been a common understanding in calixarene chemistry that two propyl[1,2] and even two cyanomethyl[3] groups on the phenoxy oxygens of 1,3-dialkylated calix[4]arenes (e.g. **2**) are bulky enough to prevent the interconversion between their conformational isomers originated from *syn* and *anti* arrangements of the two alkyl groups with respect to the mean plane defined by the macrocycle, via the oxygen-through-the-annulus rotation.[4] It is also well known that the dialkylation of methylene-bridged calix[4]arenes with alkyl halides in the presence of a base preferentially affords 1,3-isomers of *syn* conformation,[5] by virtue of a circular intramolecular hydrogen bonding in the monoalkylated intermediate.[6] Although *p-tert*-butylthiacalix[4]-arene (**3**)[7] has approximately a 10% larger ring radius than the methylene-bridged analog **1**,[8] it has been shown that the dialkylation of **3** with iodopropane also gave *syn*-1,3-diether **4**,[9] indicating that two propyl groups are large enough to prevent the *syn–anti* isomerization even in the case of thiacalix[4]arenes. During the course of the preparation of *syn*-1,3-bis(*O*-aminoethyl)-*p-tert*-butylthiacalix[4]arene (**7**), we have found, however, that 1,3-bis(*O*-cyanomethyl)-*p-tert*-butylthiacalix[4]arene (**5**) is in an equilibrium state between the *syn* and *anti* conformations in solution even at room temperature. This type of behavior is unprecedented so far in calixarene chemistry. Here, we report the conformational behavior of compound **5**.



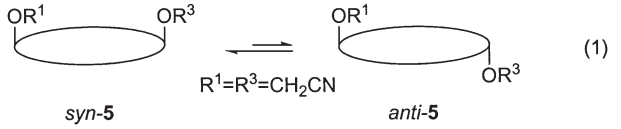
1: X=CH_2, R^1=R^2=R^3=H
2: X=CH_2, R^1=R^3=CH_2CN, R^2=H
3: X=S, R^1=R^2=R^3=H
4: X=S, R^1=R^3=Pr, R^2=H
5: X=S, R^1=R^3=CH_2CN, R^2=H
6: X=S, R^1=R^2=CH_2CN, R^3=H
7: X=S, R^1=R^3=$C_2H_4NH_2$, R^2=H

Chart 1.

The alkylation of thiacalix[4]arene **3** with chloroacetonitrile conducted under the same conditions as used for the conventional calix[4]arene[3] (**3**:$ClCH_2CN$:K_2CO_3:NaI = 1:4:4:4) did not give the desired 1,3-dialkylated product but a complex, hardly isolable mixture. However, the reaction of **3** with 3.5 mol equiv. of chloroacetonitrile in the presence of 1 mol equiv. of Cs_2CO_3 and 3 mol equiv. of NaI in refluxing THF for 7 days gave 1,3- and 1,2-dialkylated products **5** and **6** in 70 and <1% yields, respectively. The compounds showed the molecular ion peak at 798 (M^+) in the FAB mass spectra, indicating that both are doubly cyanomethylated derivatives.

The ^{1}H NMR spectrum of compound **5** revealed that it was in an equilibrium state between two conformational isomers, the ratio being 68:32 in $CDCl_3$. Each conformer showed two singlets (18H each) for the *tert*-butyl protons, one singlet (4H) for the cyanomethyl protons, and two singles (4H each) for the aromatic protons,[10] the magnetic equivalences suggesting C_2-symmetric structures. Thus, one conformer may be assigned to *syn* isomer and the other to *anti*, where the phenol units rapidly interconvert via the oxygen-through-the-annulus rotation (Eq 1).[11] Alternatively, both may be assigned to *syn* isomers which adopt cone and 1,3-alternate conformations, respectively. It is quite interesting to note here that the reduction of **5** with $LiAlH_4$ in THF at 0 °C afforded, though in a poor yield (20%), only *anti*-1,3-bis(*O*-aminoethyl) compound **7**.[12] Considering the fact that *syn*- and *anti*-**7** are stable enough to be isolated,[13] the observation can be interpreted only by the mechanism that compound **5** is in an equilibrium state between *syn* and *anti* isomers and the hydride reagent selectively reacts with the *anti* isomer to give *anti*-**7**. It has been reported that tetrapropyl ether of thiacalixarene **3** gradually isomerizes in refluxing $CHCl_2CHCl_2$.[15] Actually, *syn*-1,3-dipropyl ether **4** was found to isomerize under the same conditions to give, after 48 h, a 16:1 mixture of *syn* and *anti* isomers. On the other hand, compound **5**, bearing smaller substituents than **4**, did not show any change after the same treatment, which may support the *syn–anti* equilibrium at room temperature. In the ^{1}H NMR spectrum, the methylene signal of the minor isomer of **5** appeared at 4.64 ppm in $CDCl_3$, while that of the major at 5.44 ppm.[10] The upfield shift is attributable to the shielding effect by the facing benzene ring, which may tentatively assign the minor isomer to be *anti* form. The ratio of the *syn* and *anti* isomers was found to change from 84:16 in $CDCl_2$-$CDCl_2$, via 68:32 in $CDCl_3$ and 66:34 in THF, to 58:42 in

DMSO-d_6 at room temperature. This means that the equilibrium shifts toward the *anti* isomer with increasing the solvent polarity.[16]



Compound **5**, which is conformationally mobile in solution, however, crystallized out in a pinched cone conformation with the *syn* arrangement of the two cyanomethyl groups, as is clear from the X-ray crystallographic analysis (Figure 1):[10] The two benzene rings (**B** and **D**) bearing the cyanomethyl moiety are almost parallel to each other and the two phenolic rings (**A** and **C**) are tilted so as to place the hydroxy groups inside the macrocycle in such a way that each hydroxy proton (H_A or H_C) forms hydrogen bondings with the same etheral oxygen (O_B) and with one bridging sulfur atom (S_1 or S_2), the bond lengths of H_A–O_B, H_C–O_B, H_A–S_1, and H_C–S_2 being 2.57, 2.28, 2.43, and 2.49 Å, respectively. The former type of asymmetric hydrogen boding between two hydroxy groups and only one ethereal oxygen is quite unique in calixarene chemistry. Interestingly, one of the two methylene moieties is oriented inside the macrocycle, while the other outside. The irregular inward orientation will be attributed to some packing forces.

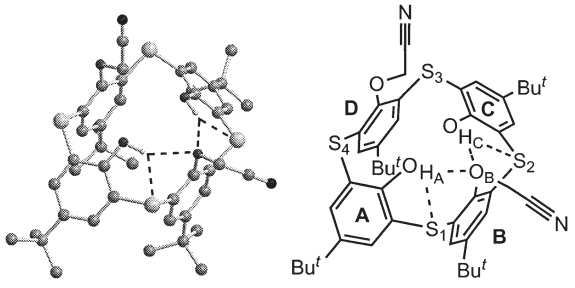


Figure 1. X-ray structure and its schematic view of compound **5**. H atoms except for OH groups are omitted for clarity.

The ^{1}H NMR spectrum of 1,2-bis(*O*-cyanomethyl) counterpart **6** also showed the presence of two conformational isomers in the ratio of 67:33 in $CDCl_3$ at room temperature. Each conformer showed two singlets (18H each) for the *tert*-butyl protons, two doublets (2H each) for the cyanomethyl protons, and four doublets (2H each) for the aromatic protons.[17] Thus, one conformer might be assigned to *syn* isomer and the other to *anti*, if the phenol units rapidly interconvert via the oxygen-through-the-annulus rotation.

In conclusion, we have shown here that 1,3-bis(*O*-cyanomethyl)-*p*-*tert*-butylthiacalix[4]arene (**5**) interconverts between *syn* and *anti* conformations in solution. It was reported that the methylene-bridged analog **2** obtained by a similar etherification of conventional calix[4]arene **1** adopted *syn* form in a cone conformation.[3] It is interesting to note that the enlarged ring size of **5** as compared to **2** critically allows the through-the-annulus rotation of the cyanomethyl group.

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10 Compound **5**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82, 1.26 [18H: s, $C(CH_3)_3 \times 2$ (major); s, $C(CH_3)_3 \times 2$ (minor)], 1.34 [18H, s, $C(CH_3)_3 \times 2$], 4.64, 5.44 [4H: s, $OCH_2 \times 2$ (minor); s, $OCH_2 \times 2$ (major)], 6.98, 7.14 [4H: s, ArH (major); s, ArH (minor)], and 7.46, 7.69 [4H: s, ArH (minor); s, ArH (major)]. Crystal data: $C_{44}H_{50}N_2O_4S_4$, $M_r = 799.13$, monoclinic, $a = 12.976(3)$ Å, $b = 18.603(4)$ Å, $c = 18.335(4)$ Å, $\beta = 105.125(5)^\circ$, $V = 4272(1)$ Å^3, $T = 223$ K, space group $P2_1/n$, $Z = 4$, μ(Mo Kα) = 2.65 cm^{-1}, 33759 reflections measured, 11723 unique ($R_{int} = 0.035$). Final $R_1 = 0.040$, $wR_2 = 0.043$ for 5156 observed reflections data [$I > 3\sigma(I)$]. GOF = 0.71. Data were collected on a Rigaku/MSC Mercury CCD diffractometer with monochromated Mo Kα radiation. The details of the crystal data have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-226829.
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13 The counterpart *syn*-**7** could be obtained by hydrazinolysis of *syn*-1,3-bis(phthalimidoethyl)-*p*-*tert*-butylthiacalix[4]arene, which had been prepared according to the literature procedue,[14] and the stereochemistry was assigned by an X-ray crystallographic analysis.
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17 Compound **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10, 1.24 [18H: s, $C(CH_3)_3 \times 2$ (minor); s, $C(CH_3)_3 \times 2$ (major)], 1.21, 1.29 [18H: s, $C(CH_3)_3 \times 2$ (minor); s, $C(CH_3)_3 \times 2$ (major)], 4.65, 4.79 [2H: d, $J = 16$ Hz, OCH × 2 (minor); d, $J = 15$ Hz, OCH × 2 (major)], 4.89, 5.13 [2H: d, $J = 15$ Hz, OCH × 2 (major); d, $J = 16$ Hz, OCH × 2 (minor)], 7.27, 7.48 [2H: d, $J = 2.4$ Hz, ArH (minor); d, $J = 2.4$ Hz, ArH (major)], 7.42, 7.53 [2H: d, $J = 2.4$ Hz, ArH (minor); d, $J = 2.4$ Hz, ArH (major)], 7.50, 7.57 [2H: d, $J = 2.4$ Hz, ArH (minor); d, $J = 2.5$ Hz, ArH (major)], 7.55, 7.64 [2H: d, $J = 2.4$ Hz, ArH (minor); d, $J = 2.5$ Hz, ArH (major)].

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