Isolation of Two Conformationally Frozen Isomers of a Bridged Calix[6]arene

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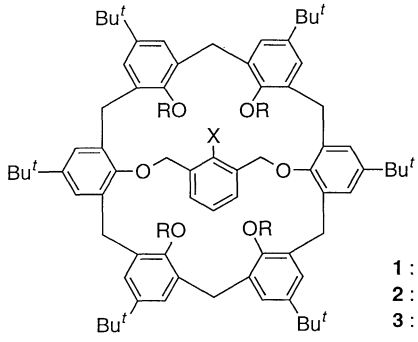
Two conformationally frozen isomers of a 1,4-bridged calix[6]arene, one of which is a cone conformer while the other adopts a 1,2,3-alternate conformation, have been isolated by silica-gel chromatography. The interconversion between them was not observed even after heating either of them at 120 °C.

In contrast to calix[4]arenes where four different conformationally immobilized isomers (cone, partial-cone, 1,2-alternate, and 1,3-alternate) have been obtained by simple derivatization at the lower rim and utilized as versatile molecular platforms,[1,2] the use of calix[6]arenes has been hampered by their large conformational flexibility. Recently, Neri et al. reported the isolation of two conformational isomers of the 1,2-bis(*p*-*t*-butylbenzyl)ether of *p*-*t*-butylcalix[6]arene by chromatography.[3] However, in those isomers, only two of six phenol units are fixed and each of them in solution at room temperature is a mixture of various conformers in a fast exchange regime. Furthermore, the conformational interconversion between the two isomers was observed above 45 °C. For the construction of more defined structures, the intramolecular bridging or capping toward calix[6]arene seems to be the most promising approach[4] as demonstrated, for example, by the optical resolution of inherently chiral calix[6]arenes bearing a 1,3-xylenyl-bridged framework reported very recently by Shinkai et al.[5]

We have been investigating the design of a novel type of reaction field based on 1,4-*m*-xylenyl-bridged calix[6]arenes[6] and recently reported the structures of compounds **1** and **2** bearing a bromide functionality.[6c] Although the conformational flexibility of **2** was found to be considerably reduced by bridging, **2** still undergoes flipping of the four non-bridged phenyl rings with the OMe groups passing through the annulus at high temperatures above 120 °C. The introduction of bulkier substituents, such as benzyl groups, instead of methyl groups into the lower rim is expected to suppress the conformational interconversion more effectively. In this communication, we report the isolation of two conformationally frozen isomers of calix[6]arene, one of which is a cone conformer while the other adopts a 1,2,3-alternate conformation.

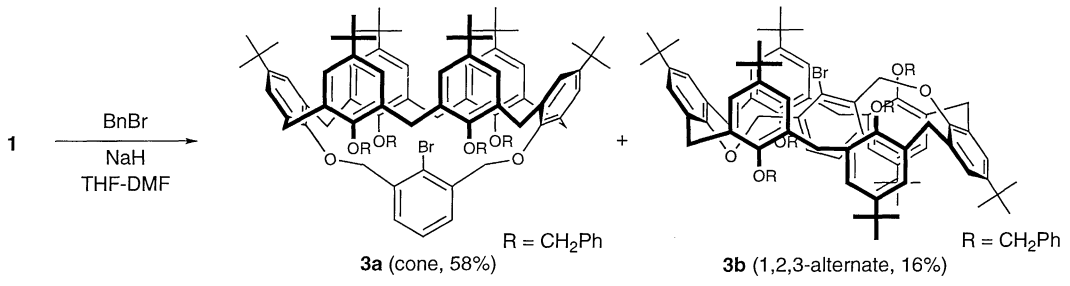


1 : X = Br, R = H
2 : X = Br, R = Me
3 : X = Br, R = CH_2Ph

Benzylation of the bridged calix[6]arene **1** with NaH and benzyl bromide in THF-DMF (10:1) under reflux conditions afforded two kinds of tetrabenzylated products **3a** and **3b**, which were isolated as pure compounds by silica gel chromatography in the yields of 58 and 16%, respectively. The elemental analysis and high resolution mass spectra confirmed that both **3a** and **3b** have a formula $C_{102}H_{113}BrO_6$, indicating that they are conformational isomers to each other.

X-ray crystallographic analysis revealed that **3a** takes a cone conformation as shown in Figure 1.[7] It was found that two molecules of **3a** are solvated by one solvent molecule (*p*-xylene) in the outside of the cavity. The spectral features of **3a** indicate that this molecule takes a cone conformation also in solution.[8] The ^{1}H NMR spectrum of **3a** at room temperature showed two singlets (ratio 2:1) for the *t*-butyl groups, two pairs of doublets (ratio 1:2) for the $ArCH_2Ar$ methylenes, one pair of doublets for the OCH_2Ph methylenes, and a singlet for the $ArOCH_2Ar$ methylenes of the bridging unit. The large differences in the chemical shifts of the pairs of doublets belonging to the $ArCH_2Ar$ methylenes ($\Delta\delta$ = 1.17 and 1.19) are consistent with the conformation where all the phenyl rings of the calixarene macrocycle are oriented *syn*.[9]

On the other hand, the spectral characterization of **3b** indicated the 1,2,3-alternate conformation of the molecule. The ^{1}H NMR spectra of **3b** at room temperature[8] showed three singlets (ratio 1:1:1) for the *t*-butyl groups, three pairs of doublets (ratio 1:1:1) for the $ArCH_2Ar$ methylenes, two pairs of



Scheme 1. Synthesis of conformational isomers of bridged calix[6]arenes **3a**,**b**.

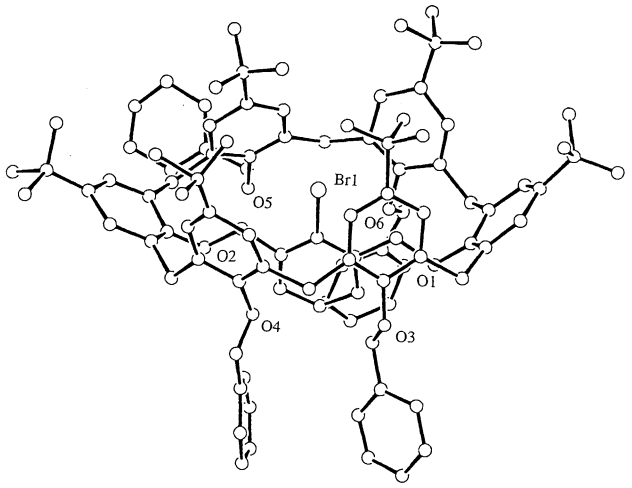


Figure 1. X-ray crystal structure of **3a**. A solvent molecule is omitted for clarify.

doublets for the OCH_2Ph methylenes, and two singlets for the $ArOCH_2Ar$ methylenes of the bridging unit. The $\Delta\delta$ separations of the $ArCH_2Ar$ methylenes are 0.78 and 1.11 for those attached to the bridgehead phenyl rings and 0.05 for those between the non-bridged phenyl rings, indicating that the bridgehead ring and the non-bridged rings adjacent to it are oriented *syn* while two non-bridged rings adjacent to each other are *anti*.[9]

The spectral patterns of **3a** and **3b**, which are completely consistent with the cone and 1,2,3-alternate conformations, respectively, scarcely changed up to 130 °C. Furthermore, the interconversion between them or their conversion to other isomers was not observed even after heating either of them at 120 °C for 24 h. Such remarkable conformational stability of **3a** and **3b** clearly indicates that, in these tetrabenzyl ethers of the bridged calix[6]arene, the oxygen-through-the-annulus rotation of the four non-bridged phenyl rings is entirely suppressed by the *O*-benzyl groups on the "laboratory" time-scale and excludes the possibility that they exist as a mixture of various conformers which undergo the rapid conformational interconversion to give the averaged signals showing C_{2v} and C_s symmetry, respectively. Thus, it is reasonably concluded that **3a** and **3b** are conformationally immobilized on the "laboratory" time-scale and separated as single conformers, a cone and a 1,2,3-alternate conformer, respectively

Further investigations on the application of these rigid calix[6]arene frameworks as a molecular platform are currently in progress.

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7 Crystallographic data for **3a**·0.5C_8H_{10}: $C_{106}H_{118}BrO_6$, M = 1568.00, crystal system triclinic, space group $P\bar{1}$, unit cell dimensions a = 17.062(7) Å, b = 22.29(1) Å, c = 12.666(6) Å, α = 104.49(4) °, β = 101.94(4) °, γ = 76.67(4) °, V = 4481(4) Å^3, Z = 2, D_{calc} = 1.123 g cm^{-3}. The intensity data were collected at 296 K on a Rigaku AFC7R diffractometer with MoKα radiation. Of the 16370 reflections which were collected, 15792 were independent. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement was based on 3581 observed reflections [$I > 3.00\sigma(I)$]. R = 0.099, R_w = 0.102 for 1018 parameters.

8 **3a**: colorless crystals; mp 272-275 °C (dec); ^{1}H NMR (500 MHz, $CDCl_3$, 26 °C) δ 1.03 (s, 36H), 1.44 (s, 18H), 3.24 (d, ^2J = 14.6 Hz, 2H), 3.34 (d, ^2J = 15.0 Hz, 4H), 3.91 (s, 4H), 4.407 (d, ^2J = 11.9 Hz, 4H), 4.409 (d, ^2J = 14.6 Hz, 2H), 4.46 (d, ^2J = 11.9 Hz, 4H), 4.53 (d, ^2J = 15.0 Hz, 4H), 6.68 (t, ^3J = 7.6 Hz, 1H), 6.816-6.820 (m, 4H), 7.04-7.05 (m, 8H), 7.09 (d, ^3J = 7.6 Hz, 2H), 7.11-7.20 (m, 16H), 7.31 (s, 4H). HRMS (FAB) *m/z* observed 1514.7732 (M^+), calcd for $C_{102}H_{113}{}^{81}BrO_6$ 1514.7736. Anal. Found: C, 80.16; H, 7.49; Br, 5.54%. Calcd for $C_{102}H_{113}BrO_6{\cdot}H_2O$: C, 79.92; H, 7.56; Br, 5.21%.
3b: colorless crystals; mp > 300 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 0.93 (s, 18H), 0.94 (s, 18H), 1.28 (s, 9H), 1.30 (s, 9H), 3.32 (d, ^2J = 15.9 Hz, 2H), 3.40 (d, ^2J = 15.7 Hz, 2H), 3.54-3.56 (m, 1H), 3.76 (d, ^2J = 12.5 Hz, 2H), 3.81 (d, ^2J = 12.5 Hz, 2H), 3.97 (s, 2H), 4.09 (s, 2H), 4.10 (d, ^2J = 15.9 Hz, 2H), 4.51 (d, ^2J= 15.7 Hz, 2H), 4.77 (d, ^2J = 10.7 Hz, 2H), 4.78 (d, ^2J = 10.7 Hz, 2H), 4.87 (d, ^2J = 10.7 Hz, 2H), 4.94 (d, ^2J = 10.7 Hz, 2H), 6.09-6.12 (m, 1H), 6.57-6.69 (m, 4H), 6.82-6.83 (m, 1H), 6.98-7.10 (m, 8H), 7.34-7.64 (m, 20H). HRMS (FAB) *m/z* observed 1514.7753 (M^+), calcd for $C_{102}H_{113}{}^{81}BrO_6$ 1514.7736. Anal. Found: C, 81.08; H, 7.53; Br, 5.26%. Calcd for $C_{102}H_{113}BrO_6$: C, 80.87; H, 7.52; Br, 5.27%.
The structures of **3a** and **3b** were further supported by the ^{13}C NMR, HH-COSY, CH-COSY, and NOE experiments.

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