

Conformational Isomerism of Calix[6]arenes: Isolation of Two Conformational Isomers of the 1,2-Bis(*p*-*tert*-butylbenzyl) Ether of *p*-*tert*-Butylcalix[6]arene

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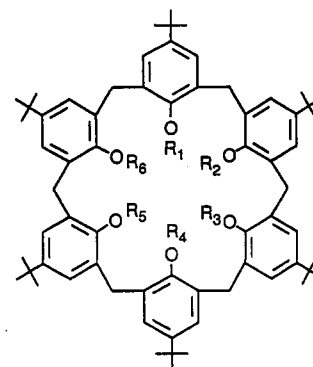
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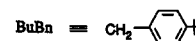
Summary: Two conformational isomers of the 1,2-bis(*p*-*tert*-butylbenzyl) ether of *p*-*tert*-butylcalix[6]arene have been isolated by chromatography, and their conformational features have been inferred from NMR spectral evidence, VT-NMR studies, and MM2 molecular mechanics calculations.

In the last decade calix[4]arenes have aroused considerable interest because they can be elaborated synthetically into selectively substituted, rigid building blocks valuable in the design and construction of new molecular receptors.¹ Perhaps one of the most peculiar features of the chemistry of calix[4]arene derivatives is their conformational isomerism that gives rise to four conformers (i.e., cone, partial-cone, 1,2-alternate, and 1,3-alternate), isolable as discrete chemical entities after appropriate *O*-alkylation of the parent tetrahydroxy compound.^{1,2} In contrast, calix[6]arenes have a comparatively more complex behavior due to their higher degree of conformational flexibility. The introduction at the lower rim of *p*-*tert*-butylcalix[6]arene of substituents of size comparable with or larger than a benzoyl or a *para*-substituted benzyl group usually results in conformational freezing at 25 °C on the NMR time scale.^{3,4} Few examples of more or less conformationally blocked calix[6]arenes and of reversible conformational equilibria have been reported.^{3-5,6} However, in no instance have conformational isomers of calix[6]arenes been described. In the present paper we wish to report the first example of isolation and structural characterization of two conformers, **2** and **2a**, of a partially substituted *p*-*tert*-butylcalix[6]arene.

Treatment of *p*-*tert*-butylcalix[6]arene (**1**) with *p*-*tert*-butylbenzyl bromide and K₂CO₃ in refluxing THF gave a reaction mixture which was separated by column chromatography to afford the 1,2-bis(*p*-*tert*-butylbenzyl) ether **2** (yield 35%), its 1,3-isomer **3** (25%), and the 1,2,3-tris(*p*-*tert*-butylbenzyl) ether **4** (22%). Their structures were established by elemental analysis, ¹H- and ¹³C-NMR spectroscopy, and chemical transformations. In particular, compound **2** was obtained as a white crystalline powder melting with decomposition at 157–159 °C, molecular formula C₈₈H₁₁₂O₆. The ¹H-NMR (CDCl₃) spectrum contains four 18 H signals at 1.12, 1.26, 1.28, and 1.33



Compd	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
1	H	H	H	H	H	H
2	BuBn	BuBn	H	H	H	H
3	BuBn	H	BuBn	H	H	H
4	BuBn	BuBn	BuBn	H	H	H
5	Me	Me	Me	Me	H	H



ppm, respectively, one of them arising from the butyl groups at the para position of the substituents, and the remaining ones from three pairs of equivalent *tert*-butyls of the calixarene skeleton. As evidenced in the COSY spectrum (Figure 1), in the methylene region the oxy-methylene groups give rise to an AB system (4.83 and 5.32 ppm, *J* = 11.2 Hz, 4 H) and the ArCH₂Ar groups to four AB systems (3.41 and 3.94 ppm, *J* = 13.4 Hz; 3.42 and 3.48 ppm, *J* = 11.5 Hz; 3.59 and 3.63 ppm, *J* = 13.3 Hz; 3.61 and 4.88 ppm, *J* = 15.2 Hz) in a 2:1:1:2 intensity ratio. The spectrum also contains two hydroxyl signals at 8.18 and 8.61 ppm. These spectral features revealed the presence of a binary symmetry element and strongly pointed to the 1,2-disubstitution pattern. However, in view of ambiguities due to possible conformational isomerism,⁷ a definitive proof was considered necessary, which was obtained through exhaustive methylation of **2** (NaH/MeI) followed by debenzoylation (Me₃SiBr).⁸ The obtained 1,2,3,4-

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 (1) Gutsche, C. D. *Calixarenes*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1989. *Calixarenes, a Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer: Dordrecht, 1991.

(2) Iwamoto, K.; Araki, K.; Shinkai, S. *Tetrahedron* 1991, 47, 4325.
 (3) (a) Gutsche, C. D.; Bauer, L. *J. Am. Chem. Soc.* 1985, 107, 6059.
 (b) Gutsche, C. D.; Rogers, J. S.; Stewart, D.; Su, K.-A. *Pure Appl. Chem.* 1990, 62, 485.

(4) (a) Rogers, J. S.; Gutsche, C. D. *J. Org. Chem.* 1992, 57, 3152. (b) Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* 1992, 57, 3160.

(5) Casnati, A.; Minari, P.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* 1991, 1413.

(6) (a) Neri, P.; Foti, M.; Ferguson, G.; Gallagher, J. F.; Kaitner, B.; Pons, M.; Molins, M. A.; Giunta, L.; Pappalardo, S. *J. Am. Chem. Soc.* 1992, 114, 7814. (b) Neri, P.; Pappalardo, S. *J. Org. Chem.* 1993, 58, 1048.

(7) See, for instance, the predicted ¹H-NMR spectra for conformational isomers of partially substituted calix[6]arenes reported in the supplementary material of ref 4a.

(8) A similar debenzoylation procedure has been used in the synthesis of calix[4]arene derivatives as a deprotection method: Iwamoto, K.; Shinkai, S. *J. Org. Chem.* 1992, 57, 7066.

(9) Various methoxy-*p*-*tert*-butylcalix[6]arenes, but not **5**, have been recently described: Janssen, R. G.; Verboom, W.; Reinhoudt, D. N.; Casnati, A.; Frerika, M.; Pochini, A.; Ugozzoli, P.; Ungaro, R.; Nieto, P. M.; Carramolino, M.; Cuevas, F.; Prados, P.; de Mendoza, J. *Synthesis* 1993, 380.

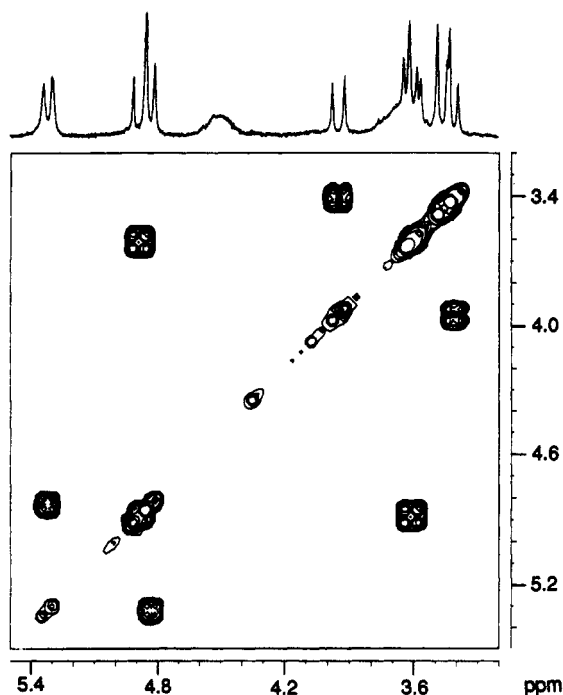


Figure 1. Methylene region of the $^1\text{H-NMR}$ and COSY spectrum of **2** (250 MHz, CDCl_3 , 295 K).

tetramethoxy ether **5**⁹ is conformationally mobile and therefore unambiguously identified by its $^1\text{H-NMR}$ spectrum.¹⁰

The structures of compound **3**, $\text{C}_{88}\text{H}_{112}\text{O}_6$, and **4**, $\text{C}_{99}\text{H}_{126}\text{O}_6$, were similarly inferred mainly from their $^1\text{H-NMR}$ spectra.¹¹

In the course of D-NMR studies to elucidate their preferred conformations, we observed that, upon heating, each of the compounds **2** and **3** originated new conformers, as indicated by the appearance of additional signals in their $^1\text{H-NMR}$ spectra. This behavior was not temperature reversible, and upon cooling the spectra remained unchanged appearing as the superimposition of those of various species, including the parent one. The presence of newly-generated spots in thin layer chromatograms suggested that the heat-produced conformers could be isolated by chromatography. Attempts toward this end were successful with **2**, and its conformational isomer **2a** was indeed isolated,¹² whereas in the case of **3** only equilibrium mixtures were obtained.

The $^1\text{H-NMR}$ spectrum of **2a** (CDCl_3) is different from that of the parent **2**, but yet completely compatible with the 1,2-disubstitution pattern. It contains four 18 H resonances at 0.97, 1.22, 1.27, and 1.29 ppm for the *tert*-butyl groups and an OCH_2 AB system (4.59 and 4.95 ppm, $J = 11.3$ Hz, 4 H). Four ArCH_2Ar signals appear as two

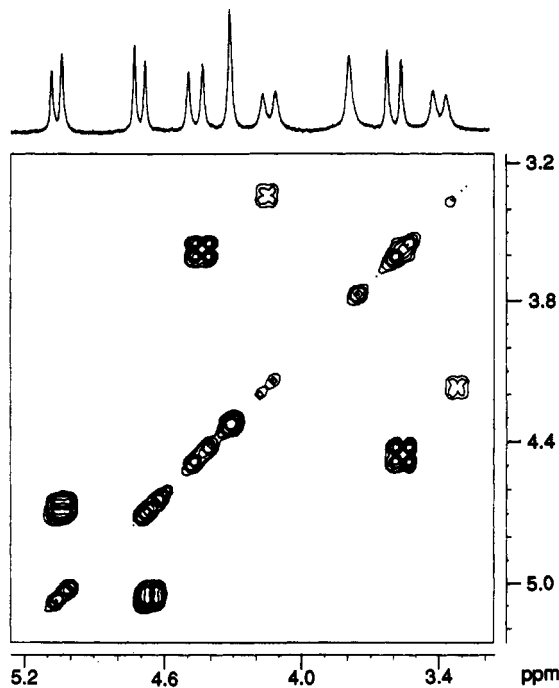


Figure 2. Methylene region of the $^1\text{H-NMR}$ and COSY spectrum of the conformational isomer **2a** (250 MHz, CDCl_3 , 295 K).

AB systems (3.27 and 4.05 ppm, $J = 13.8$ Hz, 4 H; 3.49 and 4.36 ppm, $J = 15.3$ Hz, 4 H) and two broad singlets (3.68 and 4.22 ppm, 2 H each) (Figure 2). Conclusive proof of the substitution pattern was obtained *via* methylation-debenzylation as described above for **2**, which afforded the same 1,2,3,4-tetramethoxy ether **5**.

The conformational interconversion between **2** and **2a** takes place at temperatures above 45 °C and can be easily monitored by chromatography or $^1\text{H-NMR}$ analysis.¹³ Dynamic NMR studies in various solvents indicate that in the NMR time scale this interconversion remains in the slow exchange regime, with no coalescence up to 380 K. By NMR kinetic measurements at 320 K, using the equilibration rate treatment for slow exchanging systems,¹⁴ the free energy barrier for the conversion of **2** to **2a** and that of **2a** to **2** were calculated to be 26.7 and 26.3 kcal/mol, respectively. From the relative intensity of signals the free energy difference between the two conformers was estimated around 0.4 kcal/mol at 320 K, with **2** as the more stable species.

The most relevant spectral differences between the two conformers are (i) the presence in the $^1\text{H-NMR}$ spectrum of **2a** of two singlets for the two nonsymmetry-related methylenes that replace two AB systems in the spectrum of **2** and (ii) the shift in the $^{13}\text{C-NMR}$ spectrum of **2a** of one of the ArCH_2Ar carbons from the "normal" value (29–33 ppm) to 39.1 ppm.¹⁵ According to previous observations on 1,2,4,5-tetrasubstituted calix[6]arenes,^{6a} these spectral

(10) Relevant $^1\text{H-NMR}$ data of **5**: (CDCl_3) δ 1.05, 1.15, 1.26 [s, $\text{C}(\text{CH}_3)_3$, 18 H each], 3.16, 3.70 (s, OCH_3 , 6 H each), 3.61, 3.80, 4.02 and 4.03 (s, ArCH_2Ar , 2 H, 4 H, 2 H, 4 H, respectively).

(11) Relevant $^1\text{H-NMR}$ data of **3**: (250 MHz, C_6D_6 , 295 K) δ 1.02, 1.26, 1.28, 1.31, 1.35 [s, $\text{C}(\text{CH}_3)_3$, 18 H, 18 H, 18 H, 9 H, 9 H, respectively], 3.55, 4.62 (AB, $J = 16.2$ Hz, ArCH_2Ar , 4 H), 3.59, 4.49 (AB, $J = 14.7$ Hz, ArCH_2Ar , 4 H), 3.65 (s, ArCH_2Ar , 4 H) and 5.02 (s, OCH_2 , 4 H). Relevant $^1\text{H-NMR}$ data of **4**: (250 MHz, CDCl_3 , 343 K) δ 1.04, 1.22, 1.24, 1.25, 1.27, 1.28 [s, $\text{C}(\text{CH}_3)_3$, 18 H, 9 H, 18 H, 9 H, 18 H, 9 H, respectively], 3.33, 4.31 (AB, $J = 15.0$ Hz, ArCH_2Ar , 4 H), 3.45, 3.54 (AB, $J = 14.2$ Hz, ArCH_2Ar , 4 H), 3.48, 4.90 (AB, $J = 15.0$ Hz, ArCH_2Ar , 4 H), 4.23 (s, OCH_2 , 2 H), 4.81 and 5.00 (AB, $J = 11.3$ Hz, OCH_2 , 4 H).

(12) A similar behavior has been observed for a tetraethoxy-*p-tert*-butylcalix[4]arene: Araki, K.; Iwamoto, K.; Shinkai, S.; Matsuda, T. *Chem. Lett.* 1989, 1747.

(13) Conformational isomers **2** and **2a** can be conveniently stored at -20 °C for at least 2 months without any interconversion.

(14) Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: London, 1982; pp. 143–146. See also: Günther, H. *NMR Spectroscopy*; John Wiley & Sons: Chichester, 1980; pp. 245–247.

(15) For the determination of calix[4]arene conformation a single rule, based on the chemical shift of the pertinent ArCH_2Ar carbon (29–33 ppm, *syn*-orientation and 38–40 ppm *anti*-orientation of the adjacent aromatic rings), has been proposed: Jaime, C.; de Mendoza, J.; Prados, P.; Nieto, P. M.; Sanchez, C. *J. Org. Chem.* 1991, 56, 3372. This rule appears to be to some extent also valid for calix[6]arenes (see ref 6a).

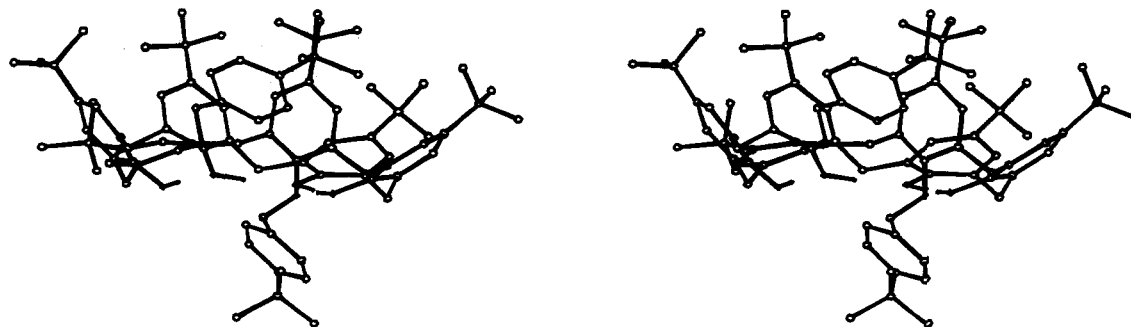


Figure 3. Stereoview of the calculated MM2 lowest energy structure of conformational isomer 2a.

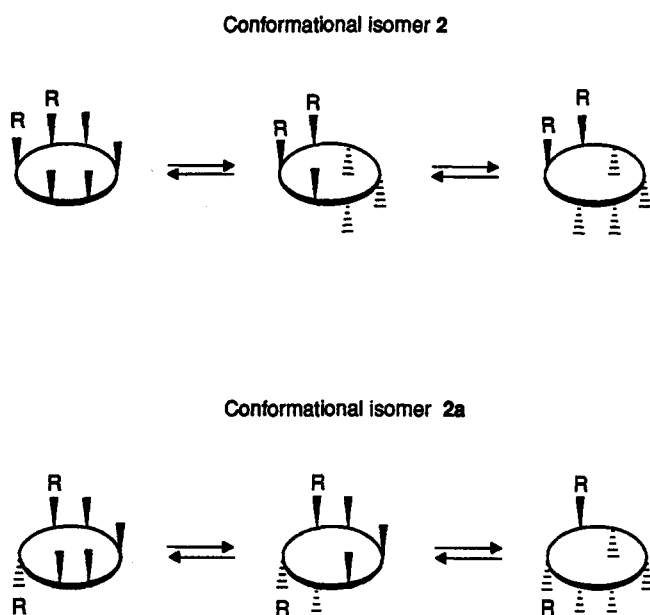


Figure 4. Schematic representation of the proposed conformational equilibria for the isomers 2 and 2a. Filled and dashed triangles denote "up" or "down" relative orientation of the phenolic rings. R indicates an arylmethylated phenolic moiety. The structures included in each equilibrium were found to be within ca. 1 kcal/mol from the lowest energy value of each class.

differences indicate the presence of two contiguous phenolic moieties in *anti* disposition. On the whole, the NMR spectral properties of both 2 and 2a reveal the presence of a binary symmetry element passing through the CH₂ group connecting the benzylated phenolic groups, and this imposes some restrictions to the possible conformational state in solution. In fact, either a single, rigid symmetric conformer exists or a mixture of various conformations is in fast exchange regime giving rise to time-averaged symmetrical spectra. That the latter is the case was proved by VT-¹H-NMR studies in CDCl₃ which evidenced the freezing out of two or more conformers at temperatures below 230 K for both 2 and 2a.

To gain deeper insight into the two conformations 2 and 2a we undertook a molecular mechanics (MM2) study¹⁶ on the 21 possible structures with different "up-down" relative orientations of the phenolic rings.⁷ These can be grouped into two main classes in which the adjacent (*p*-*tert*-butylbenzyl)oxy moieties, are respectively, *syn* or *anti* to one another. On the basis of the spectral evidence 2a should belong to the *anti* class, whereas 2 is to be ascribed

to the *syn* class. As could be anticipated intuitively, MM2 calculations evidenced that within each class the lower energy conformers have the maximum number of OH...O hydrogen bonds with additional stabilization through CH- π or π - π interactions.¹⁷

The calculated lowest energy conformer of the *anti* class (Figure 3) is cone-shaped, with an inverted (benzyloxy)-aryl moiety which points into the cone cavity forming a sort of self-inclusion complex. In the *syn* class two almost degenerate conformers (cone and 1,2,3-alternate) were found to be the most stable.

In summary, two isomers of the 1,2-bis(*p*-*tert*-butylbenzyl) ether of *p*-*tert*-butylcalix[6]arene have been isolated by column chromatography of the mixture obtained by heating a tetrachloroethylene solution of 2. Each isomer in solution at room temperature is a mixture of various conformers of the same class (*syn* or *anti*, respectively) in a fast exchange regime (Figure 4), thus giving rise to symmetrical NMR spectra.

Work in progress indicates that other 1,2-(*para*-substituted)benzyl ethers of *p*-*tert*-butylcalix[6]arene (1) behave similarly,¹⁸ giving conformational isomers stable enough to be isolated when bulky *para*-substituents are present in the arylmethyl moieties of the molecule. Consequently, it can be reasonably expected that the introduction of an adequate number of suitably substituted benzyl groups at the lower rim of *p*-*tert*-butylcalix[6]arene would result in the complete blockage of the conformational interconversion to give atropisomers, as it is observed for calix[4]arenes. This would pave the way for new applications in host-guest chemistry of calix[6]arenes.

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Supplementary Material Available: Experimental procedures, ¹H-, ¹³C-, and COSY NMR spectra, VT-NMR spectra, and selected kinetic NMR measurements for the conversion of 2 to 2a and *vice versa* (24 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(17) For the importance of the stabilizing effect of these interactions in similar compounds see: Kobayashi, K.; Asakawa, Y.; Kikuchi, Y.; Toi, H.; Aoyama, Y. *J. Am. Chem. Soc.* 1993, 115, 2648.

(18) The 1,2-picoyl *p*-*tert*-butylcalix[6]arene reported in ref 6b, as judged by its ¹H-NMR spectrum (see Figure 2 in ref 6b), gives rise also to two conformational isomers in rapid equilibrium and not separable by chromatography.

(16) The program used was MacroModel V2.5 by Still, W. C. *et al.* Department of Chemistry, Columbia University, New York, 1989.