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Atropisomerism in 1,5-Bridged Calix[8]arenes†

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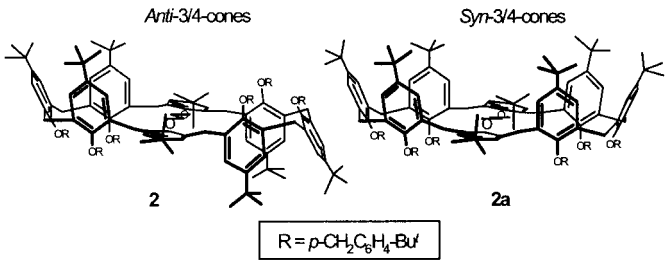
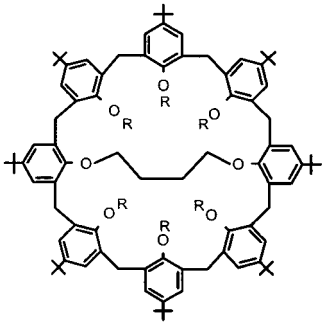
ABSTRACT



The first example of two discrete calix[8]arene conformational isomers, 2 and 2a, has been obtained by exhaustive benzylation of 1,5-tetramethylene-bridged calix[8]arene 1. It is demonstrated, with the aid of X-ray crystallography, that these atropisomers have two 3/4-cone halves oriented *syn* or *anti* with respect to the bridge/bridgeheads moiety. VT NMR studies indicate that the *tert*-butyl-through-the-annulus inversion is inhibited in 1, while groups larger than *n*-hexyl or benzyl are required for curtailing the O-through-the-annulus route.

One peculiar feature of calixarene macrocycles is their conformational isomerism that allows the tailoring of variously shaped cavities valuable in ion or molecular recognition.[1] This atropisomerism is due to the presence of sufficiently bulky groups at both rims of the cavity, which prevents conformational interconversion by curtailing their "through-the-annulus" passage. To this end, the minimal bulkiness requirements have been determined and discrete conformers (e.g., cone, partial-cone, 1,2-alternate, 1,3-alternate, 1,2,3-alternate) have been isolated for calixarene tetramers,[2] pentamers,[3] and hexamers.[4] In contrast, no example of isolated atropisomers are currently known for the higher homologues, probably because the larger dimension of their annulus requires uncommon bulkier groups. In the present paper we wish to report the first example of isolation and structural characterization of two calix[8]arene atropisomers.



1	R = H
2,**2a**	R = *p*-$CH_2C_6H_4Bu^t$
3	R = CH_3
4	R = *n*-$CH_2CH_2CH_3$
5	R = *n*-$CH_2(CH_2)_2CH_3$
6	R = *n*-$CH_2(CH_2)_3CH_3$
7	R = *n*-$CH_2(CH_2)_4CH_3$

† Dedicated to the memory of Professor Guido Sodano (Università di Salerno).

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(1) For comprehensive reviews on calixarenes see: Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713. Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1998. *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens J., Eds.; Kluwer: Dordrecht, 2001.

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On the basis of previous works on calix[8]arenes,[5] we have focused our interest on easily accessible intrabridged derivatives having a reduced space for the through-the-annulus passages. Thus, in conformationally mobile 1,5-tetramethylene-bridged calix[8]arene **1**,[6] the original 32-membered ring of the parent *p-tert*-butylcalix[8]arene is scaled down to two 23-membered rings of intermediate size between those of calix[5]- and -[6]arenes (20- and 24-membered, respectively). This would allow conformational isomerism if bulky-enough groups are appended at the OH functions. Therefore, we subjected **1** to overnight alkylation with *p-tert*-butylbenzylbromide (32 equiv) in DMF (80 °C) in the presence of NaH (32 equiv). After usual workup, column chromatography of the reaction mixture afforded, in the elution order, hexabenzyl derivatives **2** and **2a** in 14% and 16% yield, respectively. A higher stereoselectivity was obtained at room temperature, affording **2** and **2a** in 15% and 40% yield, respectively.[7]

From elemental analyses and MALDI-TOF(+) MS spectra, the stereoisomeric nature of **2** and **2a** was readily apparent. This was confirmed by their very similar ^{1}H NMR spectra, which both contain five 1:2:1:2:1 singlets for the *tert*-butyl groups of calix[8]arene skeleton and *tert*-butylbenzyl substituents.[8] In the methylene region both **2** and **2a** display (Figure 1) one AX and one AB system for the $ArCH_2$-Ar groups. As expected, the ^{13}C NMR spectra were also very similar, showing inter alia two $ArCH_2Ar$ signals (DEPT) at 29−32 ppm (**2**, 29.6 and 31.1 ppm; **2a**, 30.0 and 30.7 ppm).

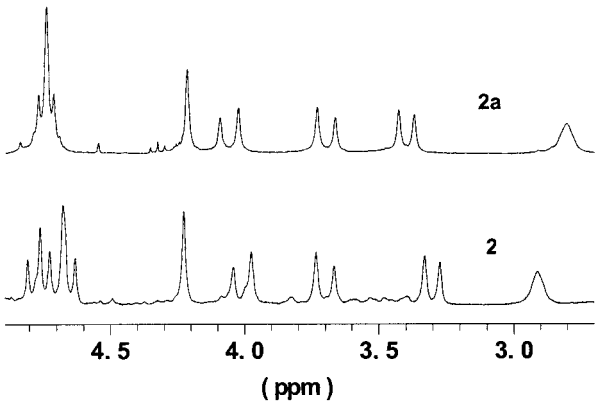
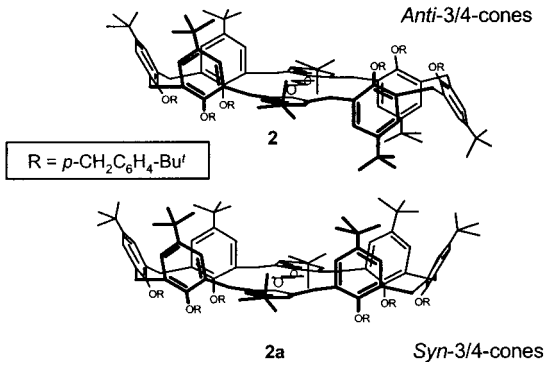


Figure 1. Methylene region of the ^{1}H NMR spectra (250 MHz, $CDCl_3$, 295 K) of 1,5-tetramethylene-bridged hexabenzyl calix[8]arene derivatives **2** (bottom) and **2a** (top).

The above spectral features clearly point to a very similar stereochemical environment for benzylated calixarene rings of **2** and **2a**, whose structures possess two orthogonal binary symmetry elements. In particular, the chemical shift separation of AX (**2**, $\Delta\delta = 1.40$; **2a**, $\Delta\delta = 1.34$) and AB (**2**, $\Delta\delta = 0.31$; **2a**, $\Delta\delta = 0.45$) systems of $ArCH_2Ar$ groups indicate a "cone" and an "out", respectively, local orientation of pertinent couples of calixarene aryl rings.[9] Assignment of all ^{1}H and ^{13}C NMR resonances, with the aid of 2D ^{1}H−^{13}C long-range HETCOR experiments, allowed us to attribute the *cone* relationship to the contiguous triads of benzylated rings (at positions 2−4 and 6−8), which therefore adopt a 3/4-cone geometry.

Obviously, the *out* orientation is assumed by the bridgehead aryls. Consequently, the stereoisomerism of **2** and **2a** has to be attributed to the relative *syn* or *anti* relationship of the two 3/4-cone halves with respect to the 1,5-tetramethylene-bridge/bridgeheads moiety.[10]



Because of the structural symmetry, NOESY and ROESY data did not allow a confident assignment of *syn*- or *anti*-3/4-cones conformation to **2** and **2a**. However, the observa-

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(6) (a) Consoli, G. M. L.; Cunsolo, F.; Geraci, C.; Neri, P. *Org. Lett.* **2001**, *3*, 1605. (b) Geraci, C.; Garuzzo, E.; Neri, P. *Tetrahedron Lett.* **2002**, *43*, 1209.

(7) **General Procedure for Preparation of Compounds 2−7.** To a suspension of 0.15 mmol of compound **1** and 4.8 mmol of NaH in DMF (15 mL) was added 4.8 mmol of appropriate alkylating agent. The mixture was stirred overnight at room temperature and then dried under vacuum. The residue was triturated with 1 N HCl (20 mL), collected by filtration, washed with MeOH, and dried. Compounds **2** and **2a** were isolated by flash chromatography on silica gel (gradient CH_2Cl_2/petroleum ether), whereas compounds **3**−**7** were purified by crystallization (CH_2Cl_2/MeOH).

(8) Satisfactory microanalytical and spectral data were obtained for all new compounds. Compound **2**: ^{1}H NMR (250 MHz, $CDCl_3$, 295 K), δ 0.89 (bs, OCH_2CH_2, 4 H), 1.01, 1.16, 1.27, 1.28, 1.29 [s, $(CH_3)_3$, 18 H, 36 H, 36 H, 18 H, 18 H], 2.93 (bs, OCH_2CH_2, 4 H), 3.32 and 4.72 (AX, J = 13.0 Hz, $ArCH_2Ar$, 8 H), 3.72 and 4.03 (AB, J = 16.8 Hz, $ArCH_2Ar$, 8 H), 4.25 (s, OCH_2Ar, 4 H), 4.67 and 4.80 (AB, J = 11.4 Hz, OCH_2Ar, 8 H), 6.68 and 6.99 (AB, J = 2.2 Hz, ArH, 8 H), 6.97 (s, ArH, 4 H), 7.21 (s, ArH, 4 H), 7.26 and 7.41 (AB, J = 8.2 Hz, ArH, 8 H), 7.28 (d, J = 8.3 Hz, ArH, 16 H). Compound **2a**: ^{1}H NMR (250 MHz, $CDCl_3$, 295 K), δ 0.58 (bs, OCH_2CH_2, 4 H), 0.92, 1.18, 1.26, 1.27, 1.31 (s, $(CH_3)_3$, 36 H, 18 H, 18 H, 36 H, 18 H), 2.80 (bs, OCH_2CH_2, 4 H), 3.40 and 4.74 (AX, J = 13.9 Hz, $ArCH_2Ar$, 8 H), 3.70 and 4.15 (AB, J = 17.0 Hz, $ArCH_2Ar$, 8 H), 4.21, 4.73 (s, OCH_2Ar, 4 H, 8 H), 6.61 and 6.91 (AX, J = 2.2 Hz, ArH, 8 H), 6.96 (s, ArH, 4 H), 7.14 and 7.35 (AB, J = 8.2, ArH, 8 H), 7.21 (s, ArH, 4 H), 7.22−7.28 (overlapped, ArH, 16 H).

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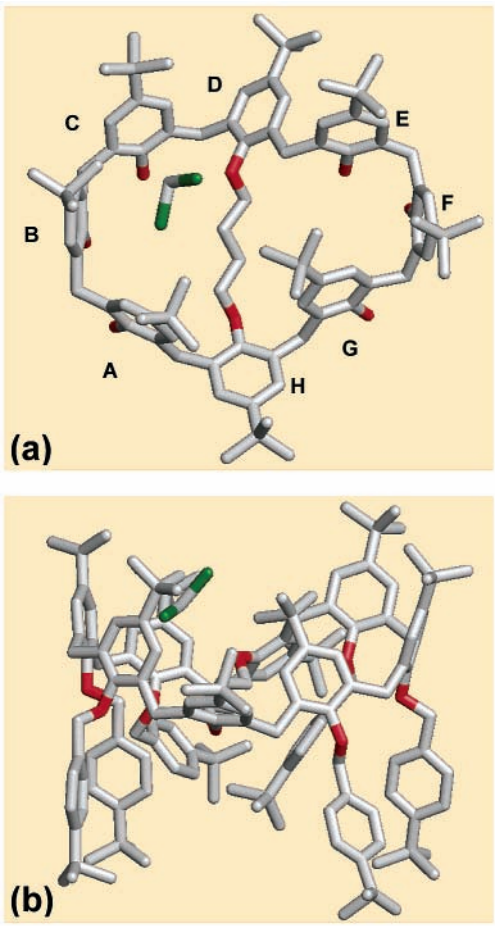

Figure 2. X-ray crystal structure of **2a** (H atoms and H_2O molecule omitted): (a) top view (*p*-*tert*-butylbenzyl groups omitted); (b) side view.

tion of an easy crystallization of **2a** from CH_2Cl_2/MeOH solutions prompted us to solve the problem by means of X-ray crystallography.

The crystal structure of **2a** (Figure 2)[11] shows an elongated calix[8]arene skeleton with an extended tetramethylene chain lying almost coplanar to the mean molecular plane. The benzylated ABC rings (Figure 2a) form one well defined 3/4-cone cleft, while the triad of EFG rings originates a very distorted 3/4-cone geometry due to the inward inclination of G aryl self-filling the cavity. Both 3/4-cone cavities are oriented above the mean molecular plane, while the six benzyl substituents are below it, to give an overall *syn*-3/4-cones conformation for **2a** (Figure 2b). A more accurate description is obtained by using the ϕ and χ torsion angles values leading to the sequence + −, + −, + −, − +, + −, + −, − −, + − according to the Ugozzoli−Andreetti convention.[13]

In the ABC cleft the "cone" pitch appears to be less smooth than that observed in a cesium complex of **1**[6b] as indicated by the canting angle of each ring [A 87.1(3)°, B 60.7(3)°, C 46.2(3)°]. The canting angles of the triad EFG are E 39.7(3)°, F 76.0(4)°, G 137.5(3)°, this latter testifying the inward folding of ring G. The opposite bridgeheads rings D and H have an interplanar angle of 41.0(3)° and form angles of −47.9(2)° and 34.7(3)°, respectively, with the mean plane of the eight $ArCH_2Ar$ carbons. One CH_2Cl_2 solvent molecule is found within the ABC cleft, probably stabilizing the 3/4-cone geometry. One water molecule is present outside the **2a** structure and forms an H-bond with the centrosymmetric related molecule. The packing of the host molecules is mainly governed by van der Waals interactions.

At this point, obviously, the *anti*-3/4-cones conformation has to be assigned to **2**, thus also justifying its lower chromatographic polarity. Then, it is worthy to pin down some ^{1}H NMR spectral differences between **2** and **2a**, which could be useful for stereochemical assignment of close analogues. In particular, a significant upfield shift of tetramethylene resonances is observed for both **2** and **2a** with respect to the parent compound **1**, probably as a consequence of the strongly reduced mobility. This shielding appears to be more effective for the *syn*-3/4-cones conformer **2a** ($\Delta\delta$ = 1.80 and 1.92 for OCH_2 and OCH_2CH_2, respectively) with respect to the *anti* isomer **2** ($\Delta\delta$ = 1.75 and 1.61 for OCH_2 and OCH_2CH_2, respectively) (Figure 1). In addition, the oxymethylene resonance of benzyls appended at the equivalent 2, 4, 6, 8 rings appears as singlet or AB system for **2a** or **2**, respectively, indicating a more pronounced diastereotopical difference for the latter (Figure 1).

The easy isolation of conformational isomers **2** and **2a** implies a high energy barrier for their conformational interconversion. In fact, no hint of coalescence is observed in their VT ^{1}H NMR spectra upon heating to 400 K. This conformational stability was confirmed by prolonged heating in refluxing toluene (up to 4 days), which showed no trace

(10) Similar geometrical considerations were reported for 1,5-*p*-xylenyl-bridged calix[8]arene derivatives, but no conformational isomers were detected; see: Cunsolo, F.; Piattelli, M.; Neri, P. *J. Chem. Soc., Chem. Commun.* **1994**, 1917. These structures are reminescent of the two atropisomers of some multiply bridged calix[6]arenes; see: Grynszpan, F.; Aleksiuk, O.; Biali, S. E. *J. Chem. Soc., Chem. Commun.* **1993**, 13. Blanda, M. T.; Farmer, D. B.; Brodbelt, J. S.; Goolsby, B. J. *J. Am. Chem. Soc.* **2000**, *122*, 1486.

(11) Crystal data for **2a**: $C_{158}H_{202}O_8 \cdot CH_2Cl_2 \cdot H_2O$, M = 2332.3, triclinic, space group *P*-1 (No. 2), a = 18.310(4), b = 26.681(6), c = 16.809(2) Å, α = 101.45(1)°, β = 110.20(1)°, γ = 72.86(2)°, U = 7321(3) Å^3, Z = 2, D_c = 1.06 g cm^{-3}, μ(Cu Kα) = 0.819 cm^{-1}, F(000) = 2532. Prismatic crystals were grown by slow evaporation from a dichloromethane/methanol solution. A crystal (0.18 × 0.15 × 0.12 mm^3) was sealed with its mother liquid in a Lindemann capillary and used for data collection on a Rigaku AFC5R diffractometer at room temperature. Data were collected till $2\theta_{max}$ = 124°, LP corrected, 23090 considered unique. The structure was solved and refined with the SIR97 program.[12] The final isotropic refinement was based on 10813 reflections with $F_o > 8.0\sigma(F_o)$ and 725 variable parameters (ratio 14.9): R = 0.163, R_w = 0.216, $\Delta\rho_{max}$ = 0.91 and $\Delta\rho_{min}$ = −1.05 e Å^{-3}. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-185520. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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(13) Ugozzoli, F.; Andreetti, G. D. *J. Inclusion Phenom.* **1992**, *15*, 337. The actual ϕ and χ torsion angles values (deg, esd 1.0−2.0°), which define the solid state conformation of **2a**, are (joined rings, ϕ, χ) A−B, 59.8, −86.6; B−C, 61.5, −76.1; C−D, 31.9, −100.8; D−E, −19.3, 99.2; E−F, 99.8, −66.6; F−G, 83.8, −17.0; G−H, −18.9, −85.2; H−A, 80.6, −9.8.

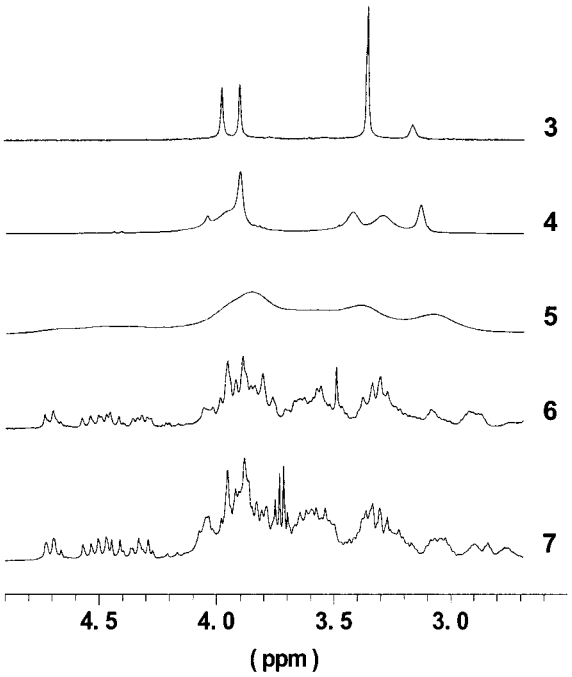

Figure 3. Comparison of the methylene regions of the ^{1}H NMR spectra (400 MHz, $CDCl_3$, 295 K) of **3**−**7**.

of mutual interconversion (TLC and ^{1}H NMR). Therefore, it can be concluded that **2** and **2a** are permanently blocked conformational isomers (i.e., atropisomers). This result proves that the *tert*-butyl-through-the-annulus passage is inhibited in 1,5-tetramethylene-bridged calix[8]arenes as a result of the small dimension of the 23-membered ring, and that *p-tert*-butylbenzyl substituent is bulky enough to prevent the oxygen-through-the-annulus route.[14]

In this regard it is of interest to assess the minimal substituent bulkiness required. Therefore, we prepared hexa-*O*-substituted derivatives **3**−**7** (75−90% yield) by treatment of **1** with the proper alkyl halide (32 equiv) under conditions identical to those described above for **2**.[7]

Hexamethoxy derivative **3** shows two sharp singlets for $ArCH_2Ar$ groups in its room temperature ^{1}H NMR spectrum (Figure 3). Increasingly broader signals are observed for hexapropoxy and hexabutoxy derivatives **4** and **5** (Figure 3), which require heating above 340 or 400 K (sealed tube), respectively, to sharpen. VT NMR (400 MHz) studies indicated that the coalescence temperature of $ArCH_2Ar$ signals of **3** falls slightly below the threshold of measurability in acetone-d_6 ($T_c \leq 175$ K), while those of **4** and **5** occurred at 245 or 320 K in $CDCl_3$, respectively. These data indicate a high conformational mobility for hexamethoxy calix[8]-arene **3**, which is increasingly reduced in hexapropoxy and hexabutoxy derivatives **4** and **5**.

(14) An analogous conclusion was drawn for other 1,5-monobridged calix[8]arene derivatives (see ref 5).

A different behavior was observed for hexa-*n*-pentyl and hexa-*n*-hexyl ethers **6** and **7** that show a complex pattern of sharp-enough signals in the methylene region (Figure 3). Interestingly, the coalescence temperature of $ArCH_2Ar$ signals of **6** falls slightly above the threshold of measurability in toluene-d_8 ($T_c \geq 400$ K), whereas only a slight broadening of them was observed for hexa-*n*-hexyl ether **7** under identical conditions ($T_c \gg 400$ K). These data clearly indicate that **6** and **7** are less conformationally mobile and that they exist as possible mixture of conformers, blocked on the NMR time scale but nonseparable by chromatography. This implies $\Delta G^{\ddagger}$ values of 18−22 kcal/mol for their conformational interconversion.[15] Consequently, groups bulkier than *n*-hexyl are required to obtain discrete conformational isomers from 1,5-bridged calix[8]arene **1**.

From the above results it can be concluded that the 23-membered sub-rings in 1,5-tetramethylene-bridged calix[8]-arenes are directly comparable to the 20-membered calix-[5]arene annulus. In fact, Gutsche and co-workers similarly reported that the upper-rim-through-the-annulus inversion is inoperative in *p-tert*-butylcalix[5]arenes and that benzyl group suffices to give pentaethers in a stable *cone* conformation.[3] On the other hand, the 24-membered calix[6]arene annulus appears sufficiently more accessible because the *tert*-butyl-through-the-annulus inversion is allowed ($\Delta G^{\ddagger} \cong 21$ kcal/mol) and only slowly interconverting conformational isomers of *p-tert*-butylcalix[6]arene derivatives can be isolated.[16]

In conclusion we report on the first example of isolation of two calix[8]arene conformational isomers. 1,5-Bridging of calix[8]arene skeleton allows an effective inhibition of the *tert*-butyl-through-the-annulus passage, while groups larger than *n*-hexyl or benzyl are required for curtailing the O-through-the-annulus route. These results represent a further step in understanding the conformational features of calix-[8]arenes and can be considered a "fine-tuning" of the properties of this macrocycle. These data are of interest for a better design of calix[8]arene-based artificial receptors or supramolecular systems.

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