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A Conformationally Flexible Tetrahydroxycalix[4]arene Adopting the Unusual 1,3-Alternate Conformation

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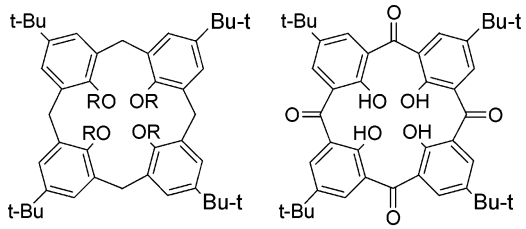
Abstract: The use of a chiral solvating agent enabled the determination of the NMR-silent ring-inversion process of the ketocalixarene **3**. Spectroscopic and crystal data indicate that **3** adopts the unusual 1,3-alternate conformation.

The conformation of *p-tert*-butylcalix[4]arene (**1**) is usually discussed in terms of four basic conformations: cone, partial cone, 1,2-alternate, and 1,3-alternate (Figure 1).[1] Replacement of the hydroxyl protons by bulky groups (e.g., propyls) sterically hinders the rotation through the annulus of the rings, and the four forms are available as stable atropisomers on the laboratory time scale.[2] The parent tetrahydroxy derivative is conformationally flexible and adopts a cone conformation that is stabilized by a circular array of hydrogen bonds involving the four OH groups. Indeed, most tetrahydroxycalixarenes (i.e., with nonderivatized OH groups), which have been synthesized and conformationally characterized, prefer the cone conformation irrespective of the nature of the para or meta substituents.[3,4]



1 R = H
2 R = $COCH_3$

3

An exception to this conformational rule is present when the substituent at the bridges can successfully disrupt the cyclic array of hydrogen bonds. According to X-ray crystallography, some oxidized derivatives of thiacalix[4]arenes adopt an 1,3-alternate conformation stabilized by intramolecular hydrogen bonds between the OH and the bridging SO (or SO_2) groups.[5] In this paper, we report the determination of the conformation and

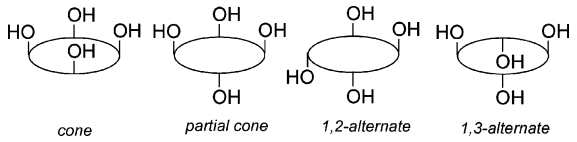


FIGURE 1. Schematic representation of the four ideal conformations of a tetrahydroxycalix[4]arene.

rotational barrier of the tetrahydroxycalixarene derivative **3**[6] (where the bridging methylene groups of **1** are replaced by carbonyl groups, i.e., a "ketocalixarene").[7] This compound is of synthetic interest since, as shown by Görmar and co-workers, the carbonyl groups of **3** can be further modified (i.e., by $NaBH_4$ reduction),[6a] and therefore, **3** could serve as an intermediate for the preparation of calixarenes functionalized at the methylene groups.[8,9] In contrast to **1**, ketocalixarene **3** lacks methylene protons, and due to the high symmetry of the preferred conformation (see below), neither the preferred conformation nor the rotation through the annulus process can be directly determined by temperature-dependent NMR in the usual achiral media.

p-tert-Butylcalix[4]arene tetraacetate **2** was prepared according to the literature procedure.[6a,10] NMR analysis of the product indicated a mixture of forms, the two major ones (in a nearly 1:1 ratio) corresponding to the partial cone and 1,3-alternate forms.[11] Ketocalixarene **3** was prepared from **2** by the procedure of Görmar and co-

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(1) (a) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713. (b) Gutsche, C. D. *Aldrichim. Acta* **1995**, *28*, 1. (c) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1998.

(2) See, for example: (a) Iwamoto, K.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4955. (b) Verboom, W.; Datta, S.; Asfari, Z.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1992**, *57*, 5394.

(3) To avoid the steric interaction between *m*-methyl groups, an octamethyl tetrahydroxycalix[4]arene derivative adopts a flattened cone conformation ("pinched cone" or "boat"). See: Dahan, E.; Biali, S. E. *J. Org. Chem.* **1991**, *56*, 7269. A similar distortion of the cone conformation is observed in calix[4]arene derivatives bridged at two para positions at nonvicinal rings. See: Goldmann, H.; Vogt, W.; Paulus, E.; Böhmer, V. *J. Am. Chem. Soc.* **1988**, *110*, 6811.

(4) *p*-Hexanoylcalix[4]arene undergoes upon heating a solid-phase transition. On the basis of solid-state ^{13}C NMR and FTIR data, it has been concluded that in the two phases the calixarene molecules adopt different conformations (cone and partial cone). See: Shinkai, S.; Nagasaki, T.; Iwamoto, K.; Ikeda, A.; He, G.-X.; Matsuda, T.; Iwamoto, M. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 381.

(5) Mislin, G.; Graf, E.; Hosseini, M. W.; De Cian, A.; Fischer, J. *Tetrahedron Lett.* **1999**, *40*, 1129. Mislin, G.; Graf, E.; Hosseini, M. W.; De Cian, A.; Fischer, J. *Chem. Commun.* **1998**, 1345.

(6) (a) Görmar, G.; Seiffarth, K.; Schultz, M.; Zimmerman, J.; Flämig, G. *Macromol. Chem.* **1990**, *191*, 81. See also: (b) Ninagawa, A.; Cho, K.; Matsuda, H. *Makromol. Chem.* **1985**, *186*, 1379. (c) Ito, K.; Izawa, S.; Ohba, T.; Ohba, Y.; Sone, T. *Tetrahedron Lett.* **1996**, *37*, 5959.

(7) Following Gutsche (ref 1c, page 130), we use the term "ketocalixarenes" to designate calixarene analogues possessing phenol rings connected by carbonyl groups.

(8) For additional examples of the methylene functionalization of calixarenes, see: (a) Klenke, B.; Näther, C.; Friedrichsen, W. *Tetrahedron Lett.* **1998**, *39*, 8967. (b) Middel, O.; Greff, Z.; Taylor, N. J.; Verboom, W.; Reinhoudt, D. N.; Snieckus, V. *J. Org. Chem.* **2000**, *65*, 667. (c) Scully, P. A.; Hamilton, T. M.; Bennett, J. L. *Org. Lett.* **2001**, *3*, 2741. (d) Agbaria, K.; Biali, S. E. *J. Am. Chem. Soc.* **2001**, *123*, 12495. (e) Simaan, S.; Agbaria, K.; Biali, S. E. *J. Org. Chem.* **2002**, *67*, 6136. (f) Simaan, S.; Biali, S. E. *J. Org. Chem.* **2003**, *68*, 3634.

(9) An alternative route for the preparation of methylene-functionalized calixarenes involves the fragment condensation method. See, for example: (a) Tabatai, M.; Vogt, W.; Böhmer, V. *Tetrahedron Lett.* **1990**, *31*, 3295. (b) Sartori, G.; Maggi, R.; Bigi, F.; Arduini, A.; Pastorio, A.; Porta, C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1657. For a review on the synthesis of calixarenes via the stepwise and fragment condensation methods see: Böhmer, V. *Liebigs Ann./Recueil* **1997**, 2019.

(10) Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron* **1983**, *39*, 403.

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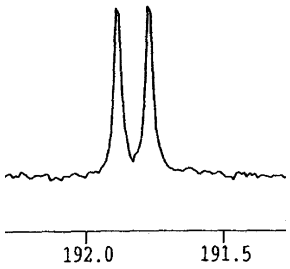
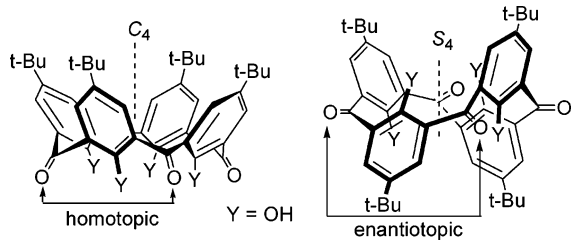


FIGURE 2. ^{13}C NMR spectrum of **3** at 220 K (carbonyl region) after addition of the CSA.

SCHEME 1



workers.[6a] The ^{13}C NMR spectrum of the product was identical to the one reported in the literature. However, in the ^{1}H NMR spectrum the observed chemical shifts of the aromatic and OH protons in $CDCl_3$ (7.95 and 5.98 ppm) were substantially different from those reported in the literature (7.23 and 10.33 ppm). The chemical shift of the OH groups of **3** is shifted upfield relative to the chemical shift of the OH groups of **1** in the same solvent (10.2 ppm). In the IR spectrum of **3** the OH stretching frequency appears at a higher wavenumber (3492 cm^{-1}, KBr) than the one of **1** (3177 cm^{-1}) and is relatively sharp. Both the NMR and IR data suggest that most likely no circular array of hydrogen bonds is present in **3**.

Cooling a $CDCl_3$ solution of **3** down to 220 K did not result in any apparent change in the ^{1}H NMR spectrum. Assuming that under these conditions the rotations around the Ar−CO bonds are slow on the NMR time scale (see below), and precluding accidental isochrony, the observed NMR pattern is only consistent with a cone or an 1,3-alternate conformation. On the basis of the spectroscopic data, which indicate a highly symmetric conformation lacking the circular array of hydrogen bonds characteristic of a cone conformation, the solution conformation of **3** is ascribed to the 1,3-alternate form. This conformational assignment was corroborated by ^{13}C NMR spectroscopy. In the cone conformation the four carbonyl groups are homotopic (they are symmetry related by a C_4 axis, Scheme 1). These carbonyl groups are expected to be isochronous, in both achiral and chiral environments. On the other hand, for an 1,3-alternate conformation, pairs of carbonyl groups attached to a given ring are enantiotopic (they are related by both the S_4 axis and the mirror plane bisecting the ring) and should be rendered diastereotopic in a chiral nonracemic media. The ^{13}C NMR spectrum of **3** ($CDCl_3$, 220 K) in the presence of the chiral solvating agent (CSA) *R*-(−)-α-(trifluoromethyl)benzyl alcohol displayed two carbonyl signals, in agreement with the presence of the 1,3-alternate conformation (Figure 2). MM3 calculations[12] support the stability reversal between the cone and 1,3-alternate conformation. Whereas according to MM3 calculations in **1** the 1,3-alternate form is 11.2 kcal mol^{-1} less stable than the cone form,[13] in **3** the 1,3-alternate conformation is 0.7 kcal mol^{-1} more stable than the cone form.

In the 1,3-alternate conformation of **3**, under slow exchange conditions, pairs of aromatic protons on a given ring are enantiotopic (they are related by the mirror plane perpendicular to the ring). A 1,3-alternate-to-1,3-alternate inversion process will result in the mutual exchange of enantiotopic sites (Figure 3). Although in the ^{1}H NMR spectrum this inversion process is silent in achiral media (due to the isochrony of the enantiotopic protons), addition of a CSA renders pairs of the enan-

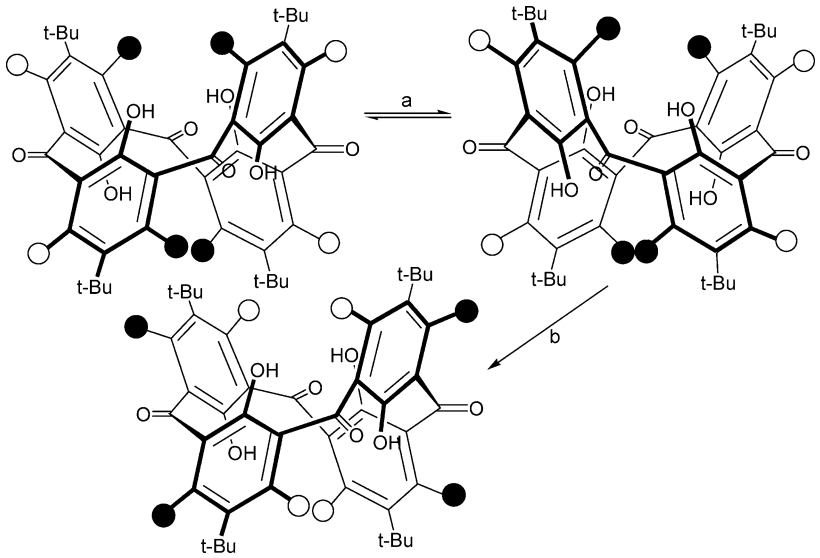


FIGURE 3. Topomerization of the ketocalixarene **3**. The filled and empty circles represent enantiotopic aromatic protons. A 1,3-alternate-to-1,3-alternate inversion process ("a") mutually exchanges pairs of enantiotopic protons. This can be visualized by reorienting the molecule by a rigid 180° rotation ("b") after the inversion process. As readily seen by comparing the structures of the top and bottom left, the filled and empty circles had exchanged places.

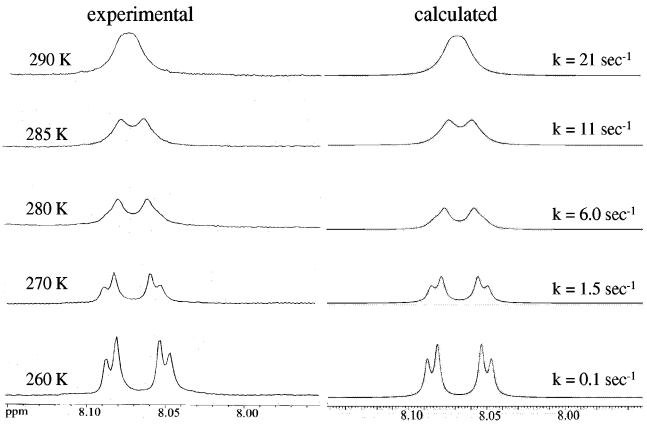


FIGURE 4. Experimental (left) and calculated (right) ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **3** in the presence of a CSA at different temperatures.

tiotopic protons anisochronous, thus enabling monitoring their mutual exchange by dynamic NMR.[14]

To achieve a 0.033 ppm separation of the signals, a large excess of the CSA was necessary.[15] The ^{1}H NMR spectrum at 260 K (400 MHz, $CDCl_3$) in the presence of the CSA displayed a pair of doublets (J = 2.6 Hz) for the aromatic protons, their mutual coupling indicating that the signals correspond to a pair of aromatic protons on the same ring. Upon raising the temperature, the aromatic signals broadened and coalesced (Figure 4). The exchange rates at different temperatures were obtained by simulation of the experimental spectra with the gNMR program.[16] From the simulation, a barrier of 15.2 kcal mol^{-1} was determined for the inversion process (at 290 K), a value fortuitously similar to the one determined for **1** in $CDCl_3$ (15.7 kcal mol^{-1}).[17]

A single crystal of **3** was grown from the $CDCl_3$ NMR solution in the presence of the CSA. The crystals of **3** were very sensitive to the X-ray radiation and the intensities of the reflections decreased dramatically in a very short time. Although the crystal structure was solved and refined, the quality of the geometric data is poor (R = 0.16).[18] Nevertheless the overall conformation of the macrocycle is unequivocally the 1,3-alternate

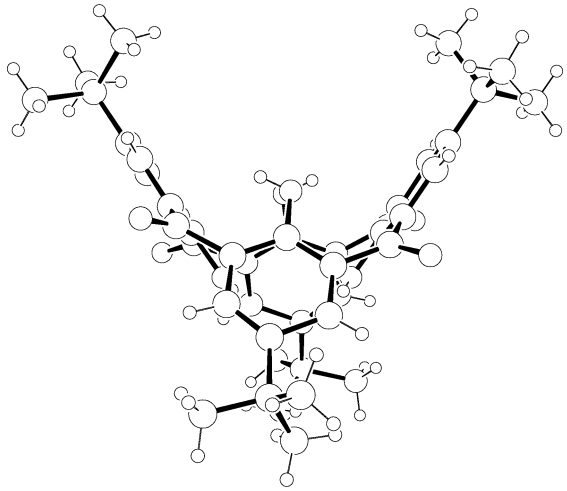


FIGURE 5. Side view of the crystal structure of **3**. The CSA molecule which cocrystallized was omitted for clarity.

(Figure 5). The conformation is somewhat more "flat" than the 1,3-alternate form calculated by the MM3 program for either **1**[13,19] or **3**, with the carbonyl groups oriented in a nearly mutual coplanar arrangement.

In conclusion, the solution conformation of the tetrahydroxy ketocalixarene **3** and the barrier of its "NMR silent" inversion process were determined by means of a chiral solvating agent. In principle, the use of a chiral solvating agent should enable the determination of the solution conformation and rotational barrier of other calixarenes derivatives lacking bridging methylene protons (e.g., thiacalixarenes).[20] Although the carbonyl groups are not involved in intramolecular hydrogen bonds, the preferred conformation is the 1,3-alternate. It seems likely that repulsive dipole/dipole interactions in the cone form as well a larger Ar−CO conjugation in the 1,3-alternate form are responsible in part for the reversal in the usual stability order.

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Supporting Information Available: Final calculated coordinates of the cone and 1,3-alternate conformations of **3**, crystal packing of **3**, and crystallographic data for **3** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The crystal structure of the partial cone form of **2** has been reported. See: Rizzoli, C.; Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Mol. Struct.* **1982**, *82*, 133.

(12) Alchemy 2000. Tripos Inc., St. Louis, MO 63144.

(13) Thondorf, I.; Brenn, J. *THEOCHEM* **1997**, *398*−*399*, 307.

(14) For a recent example of the use of a CSA for following the exchange of enantiotopic groups, see: Grilli, S.; Lunazzi, L.; Mazzanti, A.; Casarini, D.; Femoni, C. *J. Org. Chem.* **2001**, *66*, 488. (b) For an example of the use of a chiral auxiliary for the determination of the rotational barrier of a calixarene adopting the 1,3-alternate conformation, see: Parzuchowski, P.; Böhmer, V.; Biali, S. E.; Thondorf, I. *Tetrahedron: Asymmetry* **2000**, *11*, 2393.

(15) The NMR sample was prepared by dissolving 190 mg of the CSA and 1.5 mg **3** (a 507:1 molar equivalent ratio) in ca. 0.5 mL of solvent.

(16) gNMR v4.1.0. Cherwell Scientific Publishing: Oxford, UK.

(17) Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 6052.

(18) Crystal data: tetragonal, space group $I4_1$, $a = b$ = 20.437(4), c = 16.810(3) Å, Z = 4. The solvent molecules were disordered and were refined using a rigid group treatment.

(19) For a review on calculations of the conformation of calixarenes see: Thondorf, I. In *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, 2001; p 280.

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