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Dissymmetric Calix[4]arenes with C_2 and C_4 Symmetry

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Summary: Chiral calix[4]arenes with C_2 and C_4 symmetry have been prepared and transformed into stable derivatives in the cone conformation. Their structures were established by ^{1}H NMR and mass spectra and by an X-ray structure of a tetraester derivative. The chirality was further confirmed by ^{1}H NMR spectra in the presence of Pirkles reagent.

Due to their easy accessibility and their large variety, calixarenes have attracted increasing interest as synthetic host molecules during the last decade.[1] We have been particularly interested in producing chiral calixarenes suitable for enantioselection. Two general possibilities exist for the production of chiral calixarenes. One is to attach chiral substituents or residues at either the upper or lower rim.[2] A more interesting possibility is to make the calixarene itself inherently chiral.

Since the calix[4]arene molecule is not planar, calix[4]arenes consisting of three (order AABC) or four different para-substituted phenolic units[3] or containing a single meta-substituted unit[4] are chiral as a whole, without having a chiral subunit. However, to obtain stable enantiomers, it is necessary to suppress the ring inversion, which is rapid at room temperature, and to block the calix[4]arene molecule in the cone conformation. This can be done for instance by the introduction of bulky substituents at the phenolic hydroxyl groups.[5] This derivatization, which is well established for symmetrical calix[4]arenes,[1] is more difficult in the case of asymmetrical calix[4]arenes, due to their irregular molecular shape.[6] We therefore tried to synthesize calix[4]arenes that are chiral but not asymmetric, and we report here the first examples with C_4 and C_2 symmetry, respectively.[7]

Selective hydroxymethylation of 3,4-dimethylphenol at the 6-position was possible under carefully controlled conditions (50–60%). Condensation of this monohydroxymethyl derivative **1a** in dioxane in the presence of a stoichiometric amount of $TiCl_4$ yielded in 14–18% the calix[4]arene **2a**, which thus is available in two steps with an overall yield of nearly 10%. The same reaction sequence is possible, starting with 3-methyl-4-isopropylphenol.[8]

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(1) For review articles on calixarenes, see: Gutsche, C. D. *Top. Curr. Chem.* **1984**, *123*, 1. Gutsche, C. D. *Prog. Macrocycl. Chem.* **1987**, *3*, 93. Gutsche, C. D. "Calixarenes", Vol. 1, in *Monographs in Supramolecular Chemistry*; 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, 1990.

(2) Arimura, T.; Edamitsu, S.; Shinkai, S.; Manabe, O.; Muramatsu, T.; Tashiro, M. *Chem. Lett.* **1987**, 2269. Shinkai, S.; Arimura, T.; Satoh, H.; Manabe, O. *J. Chem. Soc., Chem. Commun.* **1987**, 1495. See also: Muthukrishnan, R.; Gutsche, C. D. *J. Org. Chem.* **1979**, *44*, 3962.

(3) Böhmer, V.; Merkel, L.; Kunz, U. *J. Chem. Soc., Chem. Commun.* **1987**, 896. Böhmer, V.; Marschollek, F.; Zetta, L. *J. Org. Chem.* **1987**, *52*, 3200. For the first example, see: No, K. H.; Gutsche, C. D. *J. Org. Chem.* **1982**, *47*, 2713.

(4) Casabianca, H.; Royer, J.; Satrallah, A.; Taty-C, A.; Vicens, J. *Tetrahedron Lett.* **1987**, *28*, 6595.

(5) A further possibility for fixing the cone conformation is to connect two opposite para positions by medium sized bridges: Goldmann, H.; Vogt, W.; Paulus, E.; Böhmer, V. *J. Am. Chem. Soc.* **1988**, *110*, 6811.

(6) Although in principle a *single* residue of sufficient size would be enough to prevent racemization by ring inversion, a complete conversion of all OH groups (as well as the formation of a derivative in the cone conformation) is necessary for asymmetric calix[4]arenes not to end up with an untractable mixture of isomeric or similar compounds.

(7) Concerning the synthesis of a calix[4]aren with four "exo"-methoxy groups, compare: Wu, T.-T.; Speas, J. R. *J. Org. Chem.* **1987**, *52*, 2330.

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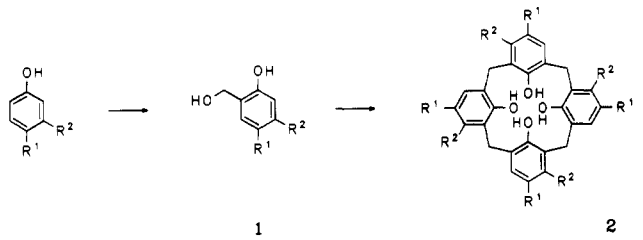


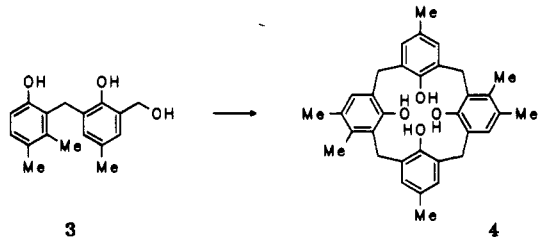
1 2

a $R^1 = R^2 = Me$

b $R^1 = i\text{-}Pr$, $R^2 = Me$

The preparation of chiral calix[4]arenes with C_2 symmetry (e.g. **4**) presents greater difficulties. 3,4-Dimethylphenol was selectively brominated at the 6-position and subsequently bromomethylated at the 2-position. Condensation with excess *p*-cresol, hydroxymethylation of the remaining ortho position, and elimination of the bromine by hydrogenation gave the monohydroxymethylated dimer **3**, which could be cyclized in satisfactory yield (18%); however, the overall yield of the six-step synthesis was only 3%.

The ^1H NMR spectrum of **2a** shows the signal for the OH protons shifted to lower field (10.71 ppm) in comparison with the *p*-methylcalix[4]arene (10.12 ppm). This indicates that the methyl groups in the meta position lead to a more "flattened" cone conformation with stronger intramolecular hydrogen bonds.[9] At lower temperatures the singlet of the methylene protons of **2a** splits into the usual AB system, the doublets of which are less separated (4.04 and 3.84 ppm), however, than those of the *p*-methyl compound (4.15 and 3.42 ppm). Correspondingly, calix[4]arene **4** shows two pairs of doublets (4.16 and 3.39 ppm, respectively, 4.06 and 3.85 ppm) and two signals for the OH protons (10.35 and 10.65 ppm).



3 4

In contrast to asymmetric calixarenes, **2a** can be easily converted by reaction with ethyl bromoacetate to the tetraester derivative **5a** (61% yield) in the cone conformation.[10] This is clearly demonstrated in the ^1H NMR spectrum by a *single* AB system for the $ArCH_2Ar$ protons (4.85 and 3.36 ppm, J = 14.4 Hz), while the AB system of the diastereotopic OCH_2CO protons (4.87 and 4.49 ppm, J = 16.1 Hz) confirms the chirality of the molecule.

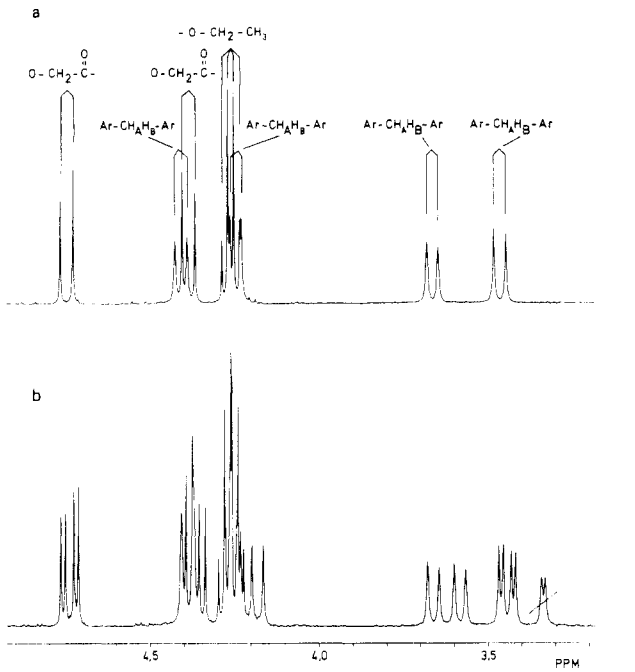
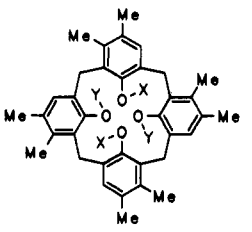


Figure 1. Section of the ^1H NMR spectrum of (a) **5b** (400 MHz, $CDCl_3$; (b) **5b** in the presence of (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol, **6**.



5a X = Y = CH_2–CO–O–Et

5b X = CH_2–CO–O–Et Y = H

Since all four phenolic units of **2a** are identical, only a *single* 1,3-diester derivative (**5b**) is possible (reducing the symmetry from C_4 to C_2), which is also available in excellent yield (86%).[11] The formation of the 1,3-diester derivative follows unambiguously from the ^1H NMR spectrum, showing one singlet for the OH groups (6.95 ppm, no hydrogen bonding), two singlets for ArH (6.87 and 6.49 ppm), two pairs of doublets for $ArCH_2Ar$ (4.40 and 3.46 ppm, J = 14.5 Hz; 4.24 and 3.66 ppm, J = 13.4 Hz), four singlets for ArMe (2.39, 2.22, 1.99, and 1.88 ppm), etc., while a 1,2-diester would have four different aromatic protons, four different $ArCH_2Ar$ groups, and eight different ArMe groups, the signals of which very unlikely will coincide in all cases in the observed manner. All signals of the ^1H NMR spectrum, a section of which is shown in

(8) Satisfactory elemental analyses, ^1H NMR spectra (δ values reported in the text are for $CDCl_3$), and electron impact mass spectra were obtained for all new compounds. The preparation of **2a** is described as an example: To a solution of **1a** (4.57 g, 30 mmol) in 500 mL of dry dioxane was added 5.69 g of $TiCl_4$. The mixture was refluxed under argon for 40 h and the solvent removed under reduced pressure. The dark red residue was dissolved in 200–250 mL of CH_2Cl_2, 50 g of silica gel was added, the solvent was evaporated again, and the dry residue was extracted with CH_2Cl_2 in a Soxhlet apparatus. This procedure to separate oligomeric and polymeric byproducts was repeated once. Finally, a brownish partly crystalline product was obtained, which was further purified by flash chromatography (silica gel, $CHCl_3$, $CHCl_3/CCl_4$ 1:3) to yield colorless crystals of **2a** (570–720 mg, 14–18%); mp > 360 °C.

(9) In contrast, eight methyl groups in the meta positions of a calix[4]arene obviously cause such a strong perturbation of the cone conformation that weakens the intramolecular hydrogen bonds, as indicated by the value of 8.19 ppm for the OH protons, see: Dahan, E.; Biali, S. E. *J. Org. Chem.* **1989**, *54*, 6003.

(10) It is well established that derivatives of this type are conformationally stable.[14] A recent study showed that the ring inversion becomes impossible if residues larger than ethyl are attached at the phenolic oxygen, see: Araki, K.; Iwamoto, K.; Shinkai, S.; Matsuda, T. *Chem. Lett.* **1989**, 1747. The first calix[4]arene derivative having a conformationally rigid cone conformation was described by Gutsche, C. D.; Levine, J. A. *J. Am. Chem. Soc.* **1982**, *104*, 2652.

(11) For the preparation of **5b**, compare: Collins, E. M.; McKervey, M. A.; Harris, S. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 372. Calixarene **2a** (161 mg, 0.3 mmol) was dissolved with warming in 20 mL of dry acetonitrile. K_2CO_3 (41 mg, 0.3 mmol) and 0.1 g (0.067 mL, 0.6 mmol) of ethyl bromoacetate were added, and the mixture was refluxed (under argon) for 3 h. The solvent was evaporated and the residue was dissolved in 50 mL of dilute HCl/50 mL of $CHCl_3$. The organic layer was washed with water, dried ($MgSO_4$), and evaporated again. The solid residue was recrystallized from $CHCl_3$/ethanol (5:1) to yield colorless crystals of **5b** (182 mg, 86%), mp 231–233 °C.

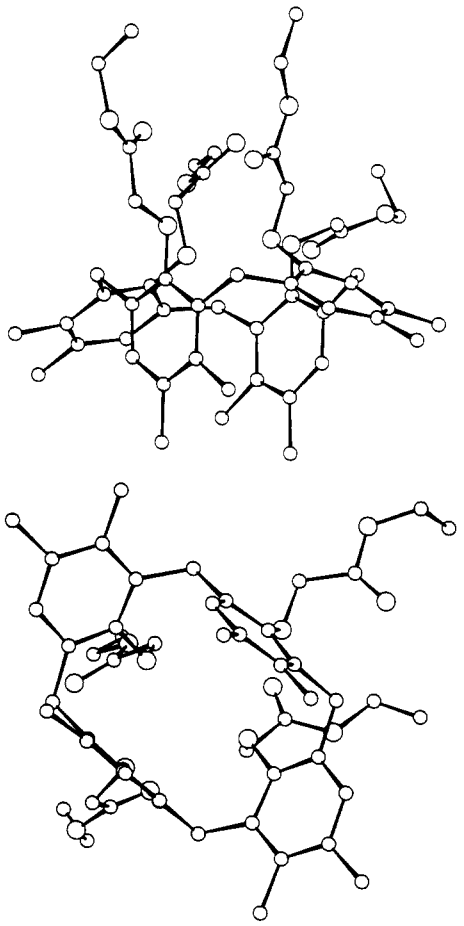


Figure 2. Molecular structure of **5a** seen from two different directions. Two enantiomeric molecules of **5a** are correlated in the crystal lattice via a symmetry center.

Figure 1, are doubled on addition of Pirkles reagent ((*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol, **6**).[12] Surprisingly this doubling is found neither for the tetraester **5a** nor for the calixarene **2a** (at low temperature). Presumably hydroxyl groups not already involved in intramolecular hydrogen bonds are needed for an effective interaction with **6**.

The X-ray analysis of **5a** shows[13] the molecule in a strongly distorted cone conformation (Figure 2). A similar deformation of the calixarene part, obviously due in part to the steric requirements of the residues attached to the phenolic oxygens, was also observed for tetraester or tetraamide derivatives of calix[4]arenes substituted exclusively in the para position.[14] A comparison of the angles formed between the phenyl rings and the plane of the methylene carbons demonstrates that the distortion of **5a** is more pronounced. These angles are 150°, 94°, 147°, and 83° in **5a**, while 139°, 94°, 136°, and 92° were found for the corresponding tetraester derivative of *tert*-butylcalix[4]arene.[14]

The dissymmetric calix[4]arenes described have some important advantages in comparison to asymmetric compounds. As shown for two examples, derivatives in a well-defined conformation, including also mono and 1,2 derivatives,[15] will be easily accessible. Furthermore, it should be possible to obtain similar compounds with different substituents.

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(12) The same set of signals and the analogous doubling on the addition of a chiral reagent would be observed for a nonchiral molecule with C_i symmetry. However, since all 1,3 derivatives prepared up to now by direct derivatization of calix[4]arenes were obtained in the cone conformation, it seems unreasonable to assume a 1,2 alternate conformation for **5b**.

(13) **5a**: triclinic, space group $P\bar{1}$, a = 15.519 (4), b = 12.060 (4), and c = 14.640 (4) Å, α = 109.01 (3), β = 75.24 (3), and γ = 111.31 (3)°, V = 2384 (1) Å^3, Z = 2, ρ_{ber} = 1.227 g·cm^{-3}; Ni-filtered Cu Kα radiation, λ = 1.5418 Å; Siemens AED diffractometer, $\theta/2\theta$ scan; total number of collected reflections 10437 (9057 unique reflections, internal R = 0.02); the structure was solved by direct methods and refined with 6329 reflections (6051 unique reflections, internal R = 0.015) with $I_{hkl} \geq 3\sigma(I_{hkl})$ by a blocked full-matrix least-squares method to R = 0.067 and R_w = 0.076 (weighting formula $W = 2.8132/(\sigma^2(F_o) + 0.001168F_o^2)$).

(14) Arnaud-Neu, F.; Collins, E. M.; Deasy, M.; Ferguson, G.; Harris, S. R.; Kaitner, B.; Lough, A. J.; McKervey, M. A.; Marques, E.; Ruhl, B. H.; Schwing-Weill, M.-J.; Seward, E. M. *J. Am. Chem. Soc.* **1989**, *111*, 388. Arduini, A.; Ghidini, E.; Pochini, A.; Ungaro, R.; Andreetti, G. D.; Calestani, G.; Ugozzoli, F. *J. Incl. Phenom.* **1988**, *6*, 119.

(15) Bottino, F.; Giunta, L.; Pappalardo, S. *J. Org. Chem.* **1989**, *54*, 5407.

Enantioselective Sulfoxidation of a Fatty Acid Analogue by Bakers' Yeast

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Summary: *S*-Benzyl-8-mercaptooctanoic acid methyl ester is converted by bakers' yeast to the corresponding sulfoxide with an enantiomeric excess of ca. 70% as determined by the Kagan chiral shift reagent.

We have shown previously that while sulfur analogues of stearic acid such as **1** are dehydrogenated by the desaturase system of *Saccharomyces cerevisiae* NRC 2335 (bakers' yeast), methyl 9-thiastearate (**2**) is sulfoxidized to give **3**.[1] Due to the pseudosymmetrical nature of **3**, we have been unable to determine the optical purity of this sulfoxide. In light of the current interest in the enantioselective oxidation of sulfides using chemical and mi-

(1) Buist, P. H.; Dallmann, H. G.; Rymerson, R. R.; Seigel, P. M.; Skala, P. *Tetrahedron Lett.* **1988**, *29*, 435.

0022-3263/90/1955-5667$02.50/0