

Acid-Promoted Rearrangement of Carbonate Functionality Anchored to the Lower Rim of a Calix[4]arene Skeleton: A New Class of Chiral Calix[4]arene and Its Chiroptical Properties

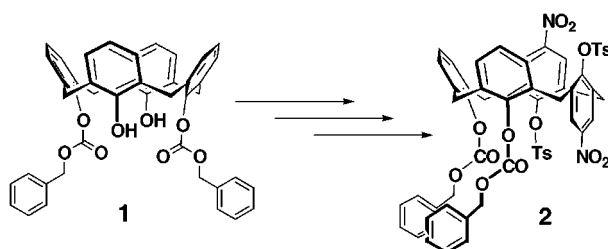
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ABSTRACT



A unique calix[4]arene lower-rim intramolecular rearrangement, resulting in molecular asymmetry arising from the upper- and lower-rim substitution pattern, produces a new class of inherently chiral calix[4]arenes in a partial cone conformation. This was aided by molecular rigidification arising from π - π and C-H $\cdots\pi$ interactions between bulky lower-rim substituents, with the corresponding circular dichroism spectra exhibiting the most intense bisignate Cotton effects yet observed for calix[4]arenes not bearing a chiral center.

As a part of our ongoing work on calix[4]arene derived compounds, we are developing hosts that are able to carry out chiral recognition processes during complexation and which allow energy/electron transfer and we are further investigating the effects of weak intramolecular interactions¹ on the conformation of calix[4]arenes. To achieve the synthesis of chiral calix[4]arenes without attaching asymmetric groups to the calixarene moiety, the lower rim must be derivatized with at least three different substituents (including the OH group) if the molecule adopts a *cone*

conformation.² Modification of the upper rim can simplify this situation; then only two different substituents are required on the lower rim, although a controlled preparation of the required asymmetrically derivatized lower rim is still not a simple task to achieve. However, the preparation can be facilitated by rigidifying the calixarene conformation, which is accomplished here by restricting the rotation of the phenyl units in the calix[4]arene core, by the introduction of selected bulky substituents at the top and/or bottom of the rim.

A particularly straightforward, but elegant, example of such an idea was achieved here when the diametrically

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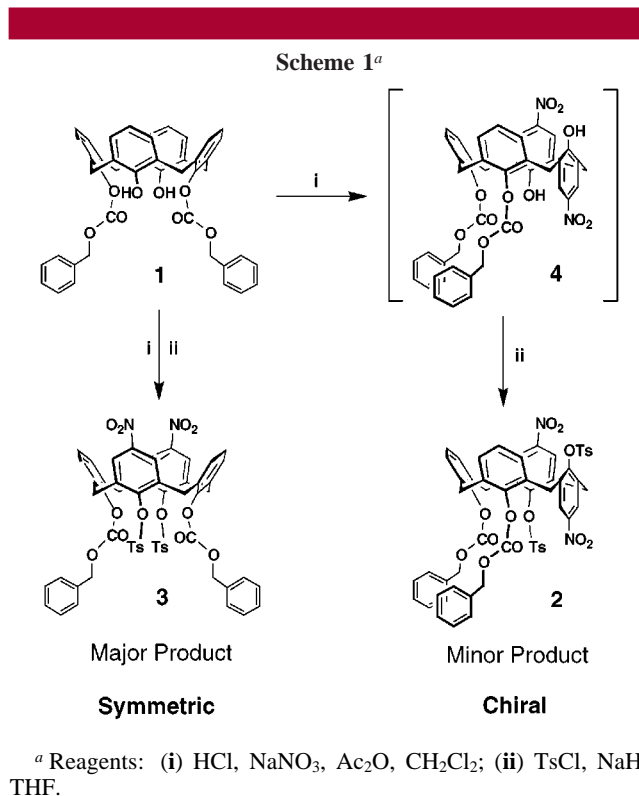
(2) Iwamoto, K.; Shimizu, H.; Araki, K.; Shinkai, S. *J. Am. Chem. Soc.* **1993**, 115, 3997–4006.

substituted calix[4]arene **1** (synthesis described below)³ was initially nitrated using an AcONO₂/CH₂Cl₂ solution (generated in situ from HCl, NaNO₃ and a catalytic amount of Ac₂O in CH₂Cl₂). Under the reaction conditions employed, the nitration leads to two products, one major and one minor, **4**. The benzyloxycarbonyl protecting group anchored to the calix[4]arene moiety at the bottom of the rim was chosen specifically for its resistance to oxidation in the presence of nitric acid and its stability in acidic media.

Under optimized reaction conditions, the combined yield of these two products could be obtained in a moderate 77%. Subsequent tosylation in order to allow full characterization afforded **2** and **3** in a ratio of 15:85 (Scheme 1),⁴ although

(3) **Experimental Procedure for 1**: A mixture of calix[4]arene (4.2 g, 10 mmol) and NaH (80% in oil, 0.7 g, 23 mmol) in anhydrous THF (100 mL) was stirred at room temperature for 1 h. Chlorobenzyl carbonate (3.2 mL) was then added, and the mixture was stirred for 6 h. The progress of the reaction was followed by monitoring the disappearance of calix[4]arene on TLC (SiO₂, toluene/hexane/acetonitrile, 7:2:1 v/v). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.55–7.35 (m, 10H, ArH), 7.08 (d, *J* = 7.3 Hz, 4H, ArH), 6.90–6.7 (m, 8H, ArH), 5.30 (s, 4H, OCH₂Ar), 4.00 and 3.51 (ABq, 8H, *J* = 14.3 Hz, ArCH₂Ar). ¹³C NMR (CDCl₃) δ 188.3 (s, C=O), 155.0 and 152.7 (s, Ar 25, 26, 27, 28-C), 145.8 (s, Ar-C), 135.0 (s, Ar-C), 132.2 (s, Ar-C), 129.0 (d, Ar-C), 128.7 (d, Ar-C), 128.6 (d, Ar-C), 128.5 (d, Ar-C), 127.9 (d, Ar-C), 126.8 (d, Ar-C), 119.9 (d, Ar-C), 70.7 (t, OCH₂Ar), 32.2 (t, ArCH₂Ar). MS *m/z* 692 (*M* + 1, 100). Anal. Calcd for C₄₄H₃₆O₈ (692.77): C, 76.29; H, 5.24. Found: C, 76.20; H, 5.18.

(4) **Experimental Procedure for 2 and 3**: To a solution of **1** (0.69 g, 1 mmol) dissolved in a CH₂Cl₂ (10 mL)–diethyl ether (17 mL) solvent mixture were added NaNO₃ (0.45 g, 5 mmol), concentrated HCl (1.5 mL, 18 mmol), and a catalytic amount of acetic anhydride. The mixture was allowed to stir at room temperature for 1 h. The organic solvents were removed under diminished pressure. Water (10 mL) was added to the yellow residue, and the solid material formed was filtered off. The product was dissolved in CH₂Cl₂ and washed with water, and the solvent was evaporated to dryness. The material formed was solidified by addition of methanol and filtered off. The crude product was recrystallized from toluene in the presence of charcoal to give a 0.6 g (77%) yield containing two products, one major and one minor (85:15). The mixture was introduced into the next reaction step without further purification. The mixture of major and minor products (0.78 g, 1 mmol) and NaH (80% in oil, 0.12 g, 4 mmol) in THF (20 mL) was stirred at room temperature for 10 min. Toluene-4-sulfonyl chloride (0.5 g, 2.6 mmol) was added, and the reaction mixture was allowed to stir for 12 h. The progress of the reaction was followed by monitoring the disappearance of the major product on thin-layer chromatography (SiO₂, benzene/CH₂Cl₂, 7:3 v/v). The reaction was quenched with water (20 mL), and the sample was reduced to dryness. The excess toluene-4-sulfonyl chloride was removed by heating the residue with *n*-hexane, producing a yellow solid which was purified by recrystallization from toluene/hexane to give 0.75 g (68%) yield. Analytical samples of **2** and **3** were further purified by column chromatography on silica gel, eluting with benzene/CH₂Cl₂, 7:3 v/v. **2**: ¹H NMR (400 NMR, CD₂Cl₂) δ (ppm) 8.41 (d, *J* = 2.7 Hz, 1H), 8.22 (d, *J* = 2.8 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 2H, ArH-Tos), 7.87 (d, *J* = 2.7 Hz, 1H), 7.45 (m, 22H), 6.51 (m, 3H), 5.40 (d, *J* = 11.8 Hz, 1H, OCH₂), 5.26 (d, *J* = 11.8 Hz, 1H, OCH₂), 4.93 (d, *J* = 12.7 Hz, 1H, OCH₂), 4.57 (d, *J* = 12.7 Hz, 1H, OCH₂), 4.08 (d, *J* = 14.5 Hz, 2H, CH₂), 3.78 (d, *J* = 13.5 Hz, 1H, CH₂), 3.61 (d, *J* = 14.0 Hz, 1H, CH₂), 3.42 (d, *J* = 13.5 Hz, 1H, CH₂), 3.20 (dd, *J* = 14.1 Hz, 2H, CH₂), 2.60 (d, *J* = 14.4 Hz, 1H, CH₂), 2.53 (s, 3H, CH₃), 2.43 (s, 3H, CH₃). ¹³C NMR (CD₂Cl₂) δ (ppm) 153.5 (s), 153.1 (s), 151.6 (s), 149.9 (s), 148.1 (s), 147.3 (s), 146.6 (s), 145.2 (s), 145.0 (s), 136.6 (s), 136.4 (s), 135.9 (s), 135.8 (s), 134.6 (s), 134.4 (s), 133.7 (s), 133.4 (s), 132.6 (s), 132.4 (s), 130.8 (d), 130.6 (d), 129.9 (d), 129.8 (d), 129.7 (d), 129.3 (d), 129.1 (d), 129.0 (d), 128.9 (d), 128.6 (d), 128.5 (d), 128.4 (d), 128.2 (d), 127.1 (d), 126.8 (d), 126.7 (d), 125.1 (d), 125.0 (d), 124.6 (d), 71.0 (t), 70.9 (t), 35.9 (t), 35.6 (t), 30.7 (t), 30.4 (t), 21.9 (q), 21.6 (q). MS *m/z* 1091 (*M* + 1, 100). Anal. Calcd for C₅₈H₄₆O₁₆S₂N₂ (1091.31): C, 63.84; H, 4.25; N, 2.57. Found: C, 63.52; H, 4.25; N 2.63. **3**: ¹H NMR (400 MHz, CDCl₃)



optimization of the reaction conditions to maximize the yield of **2** was not performed.

This approach led to the synthesis of a new class of inherently chiral calix[4]arene **2**, whose asymmetry derives from the substitution pattern of the upper and lower rims.

The formation of precursor **4** is likely to occur via a proton-assisted intramolecular rearrangement of the BnO-(CO) group. The intramolecular nature of this rearrangement is supported by the absence of the mono- and tris- benzyloxycarbonyl substituted products that would occur from an intermolecular rearrangement process. The distance found from the crystal structure of **1** between the unprotected hydroxyl group and the carbonyl of the carbonate group is 4.53 Å (Figure 1),⁵ which could be reduced by molecular

δ (ppm) 7.82 (d, *J* = 7.3 Hz, 4H, ArH), 7.54 (d, 4H, ArH), 7.56 (s, 4H, ArH, ortho to NO₂), 7.50 (m, 10H, ArH), 7.32 (d, *J* = 7.6 Hz, 4H, ArH), 7.16 (dd, 2H, ArH), 5.62 (s, 4H, OCH₂Ar), 4.02 and 3.00 (ABq, *J* = 13.9 Hz, 8H, ArCH₂Ar), 2.43 (s, 6H, CH₃). ¹³C NMR (CDCl₃) δ (ppm) 188.0 (s, C=O), 154.4 (s, Ar-C), 148.1 (s, Ar-C), 145.2 (s, Ar-C), 136.7 (s, Ar-C), 134.1 (s, Ar-C), 131.7 (s, Ar-C), 130.0 (d, Ar-C), 129.2 (d, Ar-C), 128.8 (d, Ar-C), 128.7 (d, Ar-C), 128.6 (d, Ar-C), 128.3 (d, Ar-C), 127.2 (d, Ar-C), 124.0 (d, Ar-C), 71.1 (t, OCH₂Ar), 31.1 (t, ArCH₂Ar), 21.7 (q, CH₃). MS *m/z* 1091 (*M* + 1, 100). Anal. Calcd for C₅₈H₄₆N₂O₁₆S₂ (1091.31): C, 63.84; H, 4.25; N, 2.57. Found: C, 63.72; H, 4.20; N, 2.55.

(5) (a) Crystal data for **1**: C₄₄H₃₅O₈; FW = 691.72, monoclinic, space group *P*2₁/*a*, *Z* = 4, *a* = 12.302(12), *b* = 20.42(3), and *c* = 14.135(17) Å, β = 105.90(1)°, *V* = 3414 Å³, *D*_{calc} = 1.346 g/cm³. Crystal data for **2**: C₅₈H₄₆N₂O₁₆S₂; FW = 1091.09, orthorhombic, space group *F*dd2, *Z* = 16, *a* = 37.289(5), *b* = 54.376(13), and *c* = 10.517(6) Å, *V* = 21325 Å³, *D*_{calc} = 1.359 g/cm³. Both sets of data were taken using Mo Kα radiation at 293 K. For **1** 6081 independent reflections were measured on a Marresearch Image Plate system and for **2** 3994 reflections were measured on a Rigaku AFC7R circle diffractometer using the ω-scan technique. Both structures were determined by direct methods using Shelx86.^{3b} All non-hydrogen atoms were refined anisotropically; hydrogen atoms were included in calculated positions. Both structures were refined on F² to convergence using Shelxl.^{3c}

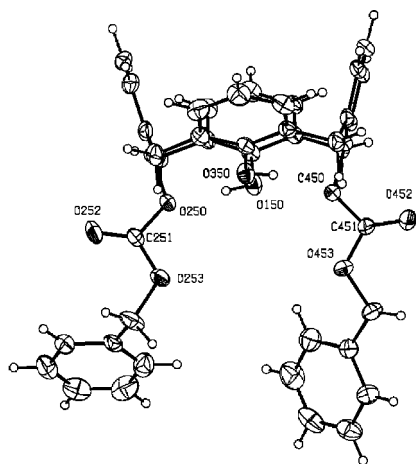


Figure 1. X-ray structure of **1** (50% probability).

motions in solution, showing that this order of distance may be suitable for the intramolecular rearrangement to occur.

This is the first time that such a chirogenic rearrangement process between the lower-rim phenoxy groups (and after-sylation) has been observed, although nonchiral rearrangements between lower-rim phenoxy substituents and the methylene position have been reported.⁶ The conformational stability of these highly preorganized macrocycles allows us to separate racemic **2** into its pure enantiomers by chiral stationary phase HPLC on a CHIRALCEL OJ-R column eluting with a (7:3) acetonitrile/water solvent and thus investigate the chiroptical properties of these newly synthesized calix[4]arene derivatives (see Figure 2).

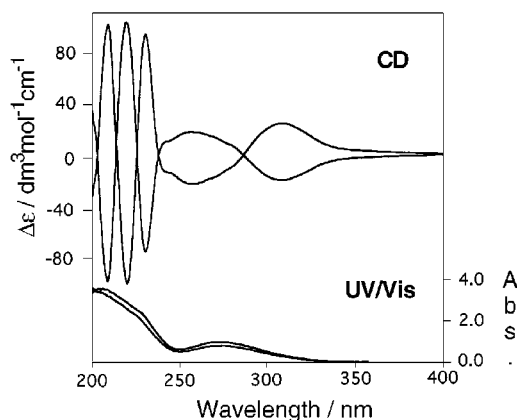


Figure 2. CD and UV/vis spectra of **2** in CH₃CN.

Although circular dichroism (CD) spectra have been reported for calixarenes in which the chirality arises from

Final R1 and wR2 values for observed data ($> 2\sigma(I)$) were 0.0804, 0.1710 and 0.0396, 0.0714, respectively. Crystallographic details have been deposited at the Cambridge Crystallographic Data Centre. (b) Sheldrick, G. M. (Shelx86), *Acta Crystallogr.* **1990**, A46, 467. (c) Sheldrick, G. M. Shelxl program for structure refinement, University of Göttingen, Germany, 1993.

rim substitution and not from chiral centers,⁷ the CD spectra of the enantiomers of **2** show multiple bisignate Cotton effects which are particularly intense in the region between 250 and 200 nm, a feature which has not been reported previously in calixarene chemistry. These interactions observed by the CD spectroscopy are attributed to exciton coupling between the aromatic chromophores, which are in a *partial cone* conformation.⁸

The assignments of the 1D proton resonances were made on the basis of DIFNOE and 2D NMR (COSY, ROESY) experiments, revealing typical splitting patterns of AB quartets (ca. $J = 13$ Hz) arising from the Ar-CH₂-Ar linking groups, possessing C_{2v} symmetry in **1** and **3**. A complicated splitting pattern of Ar-CH₂-Ar resonances and a set of through-space interactions arising from the neighboring aromatic rings in **2** indicated that these moieties possess C_1 symmetry (Figure 3). ¹H NMR spectra shows a large

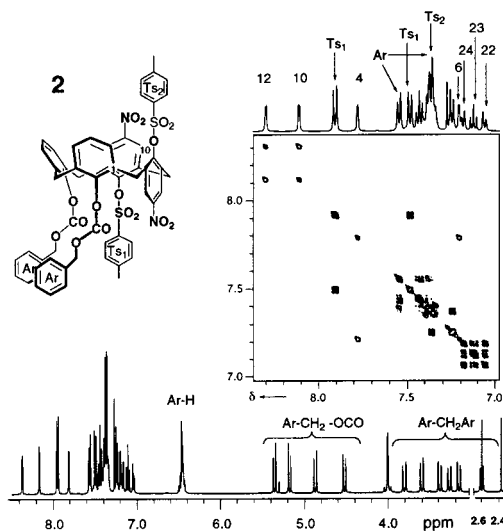


Figure 3. 1D and 2D COSY ¹H NMR spectra of **2** in CDCl₃.

difference in the resonance frequencies of the AB quartets of the two methylene groups in ArCH₂OCO, indicating that the magnetic environments experienced by these two groups are not identical.

The conformation of the derivatives synthesized in this work were further analyzed by means of VT ¹H NMR measurements of **2**, which when carried out in the temperature range of -100 to 25 °C in acetone-*d*₆ revealed no shifts in the signal positions, while between 25 and 100 °C in DMSO-*d*₆ shifts were observed (Figure 4), but they are small in comparison to those expected for major conformational rearrangements,⁹ i.e., the increase in temperature does not significantly affect the conformation, implying that the structure of the molecule is particularly rigid.

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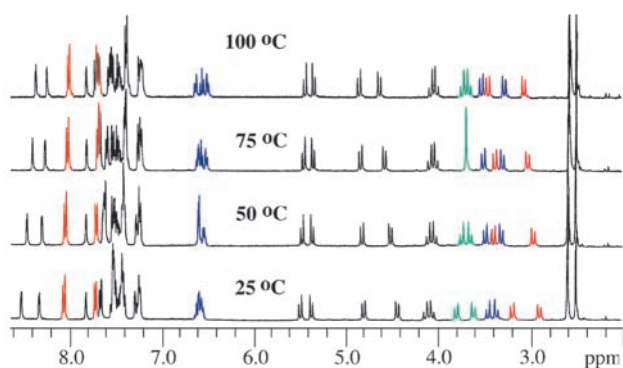


Figure 4. ^1H VT NMR spectra of **2** in $\text{DMSO}-d_6$.

X-ray crystallographic studies were subsequently carried out in order to examine the structural characteristics of **2** and to understand the reasons for this structural rigidity. The structure of **2** (Figure 5)⁵ shows the four aromatic rings on the substituents augmenting the four aromatic rings of the calixarene in the *partial cone* conformation to form a rigid, crowded, cylindrically shaped molecule.

There are several close π – π and $\text{C}-\text{H}\cdots\pi$ contacts between the substituents which contribute to the stability of the *partial cone* conformation, with distances in the range of 2.42–2.67 Å, although no interactions are found between atoms significantly less than the sum of van der Waals radii.¹ Preliminary molecular dynamics calculations confirm the rigidity of this molecular conformation. The detailed elucidation of the reaction mechanism and intramolecular rearrangement are currently under investigation.

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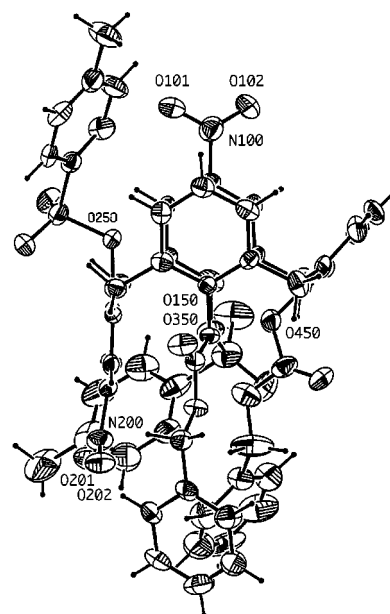


Figure 5. X-ray structure of **2** (50% probability).

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Supporting Information Available: Additional ^1H and ^{13}C NMR spectra for **1**, **2**, **3** and the **major intermediate**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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