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Synthesis and Optical Resolution of a Chiral Calix[4]arene Asymmetrically-Substituted on the Lower Rim

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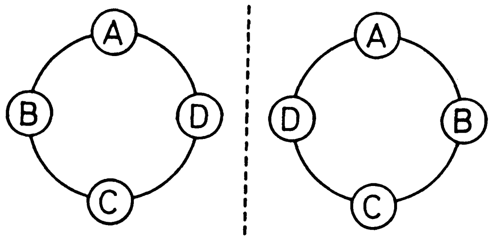
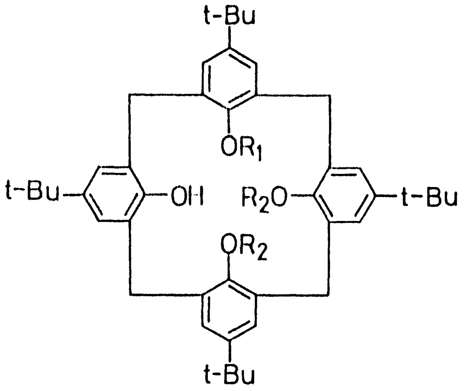
A cone-shaped, asymmetrically-substituted calix[4]arene has been synthesized by a stepwise O-alkylation method and optically-resolved by an HPLC method. This is the first example for successful optical resolution of a calix[4]arene with ring-originating chirality.

Calix[4]arenes are cyclic tetramers having four OH groups on the lower rim. Hence, calix[4]arenes with four (or at least three) different substituents may result in racemates as illustrated below. Previously, Böhmer1) and Vicens2) synthesized calix[4]arenes presenting no plane of symmetry, but they could not find any evidence for asymmetry in calix[4]arenes. It is known that in dynamic ^{1}H NMR, the ArCH$_2$Ar methylene protons in calix[4]arenes give a pair of doublets at low temperature and a sharp singlet at high temperature.3,4) This indicates that in conventional calix[4]arenes, ring inversion takes place in a speed comparable with that of the NMR time-scale.5) Hence, their failure may be ascribed to racemization through rapid ring inversion. The situation suggests an idea that O-alkylation with bulky substituents inhibits the oxygen-through-the-annulus rotation and results in racemates.6,7) In fact, however, O-alkylation with bulky alkyl halogens and NaH affords a mixture of several conformational isomers known for calix[4]arenes (e.g., cone, partial cone, etc.).6,7) Thus, one has to develope a new O-alkylation method which affords only one conformational isomer. After trial-and-error experiments, we finally found that when Ba(OH)$_2$ is used as base, the O-alkylation reaction affords only a "cone" isomer. With the aid of this breakthrough, we could synthesize a conformationally-fixed, asymmetrically-substituted, cone-shaped calix[4]arene (**1**) from p-t-butylcalix[4]arene and optically resolve the racemates by an HPLC method.



Racemates possible for asymmetrically-substituted calix[4]arenes



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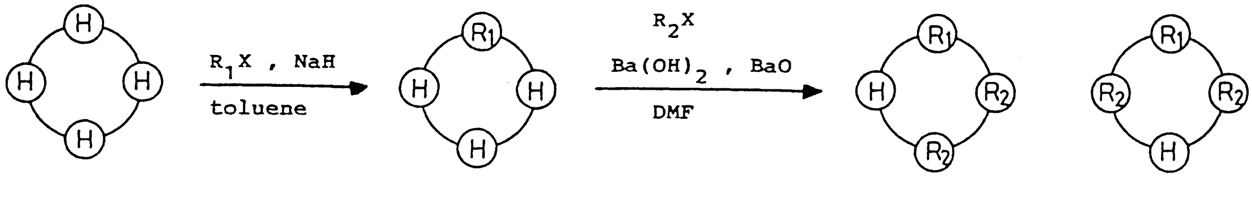
We designed the following reaction scheme in which H and R denote the unsubstituted OH group and the ether group alkylated with R, respectively. The key step is the reaction with R_2X because the conformation of calix[4]arenes is determined when the third R comes in.[7,8] Here, $Ba(OH)_2$ was used: the reaction with R_2X afforded only a "cone" isomer. When NaH was used as base for the reaction with R_2X, we detected (at least) six conformational isomers in the TLC separation. If two R_2 substituents are introduced into the distal position, the product (**1'**) has a plane of symmetry. To avoid this, we first introduced a bulky R_1 (= 2-pyridylmethyl) group followed by the reaction with less bulky R_2 (= propyl) groups.[9]



p-t-butylcalix[4]arene **2** **1** **1'**

2 was synthesized by the reaction of 2-chloromethylpyridine (R_1X) hydrochloride and p-t-butylcalix[4]arene in toluene in the presence of NaH at 70 °C for 20 h: yield 59%, mp 275-276 °C. The product was identified by elemental analysis.[10] **1** was synthesized by the reaction of propyl bromide and **2** in DMF in the presence of $Ba(OH)_2 \cdot 8H_2O$ and BaO at 70 °C. The product was identified by elemental analysis.[11] In ^1H NMR ($CDCl_3$, 30 °C), the $ArCH_2Ar$ protons in **1** gave four pairs of doublets.[12] The result indicates that **1** is fixed to a cone-shape and R_1 and R_2 are asymmetrically introduced. In **1'** the $ArCH_2Ar$ protons should give two pairs of doublets.

In order to confirm that **1** is a pair of ring-originating racemates, we measured the ^1H NMR spectra in the presence of a chiral shift reagent (Pirkle's reagent, (S)-2,2,2-trifluoromethyl-1-(9-anthryl)ethanol). As shown in Fig. 1, most peaks were duplicated.

Racemic 1 was optically resolved by a HPLC method using a chiral packing column (Sumipax OA-2000; mobile phase hexane:2-propanol=98:2 v/v). The peak separation was complete. We separated the eluent into three fractions and recovered 50 mg of (+)-1 from the first fraction and 20 mg of (-)-1 from the third fraction from 120 mg of racemic 1. Re-examination of these fractions using HPLC and ^{1}H NMR in the presence of Pirkle's reagent established that (+)-1 and (-)-1 are 100 %e.e. and 99.8 %e.e., respectively: $[\alpha]_D$ for (+)-1 (c 0.004, hexane, 25 °C)=+12.5. The circular dichroism (Fig. 2) showed symmetrical spectra, indicating that these compounds are optical isomers: λ_{max} for (+)-1, 254 nm (θ -4100) and 286 nm (θ 6720).

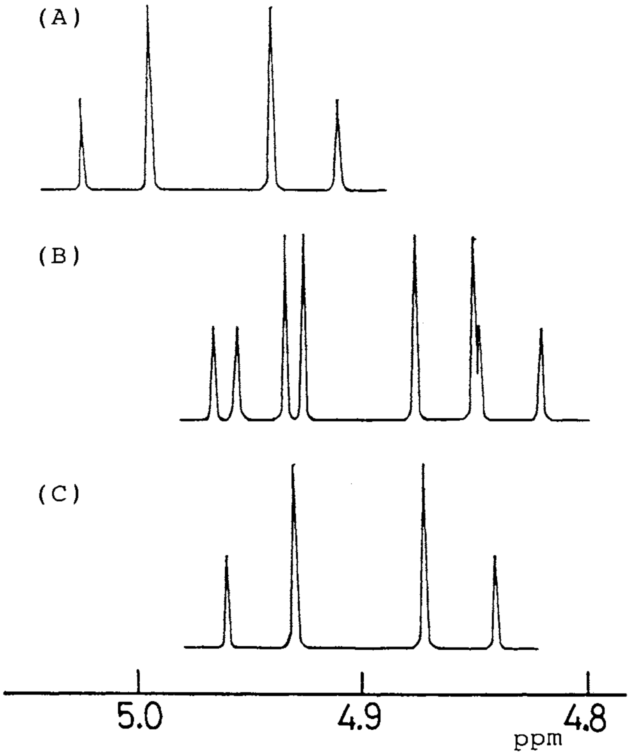


Fig. 1. Partial ^{1}H NMR spectra for the $PyCH_2$ protons in 1 ($CDCl_3$, 30 °C, [1]=1.22 x 10^{-2} M): (A) racemic 1, (B) racemic 1 + Perkle's reagent (1.2 times of [1]), (C) (+)-1 + Perkle's reagent (1.2 times of [1]).

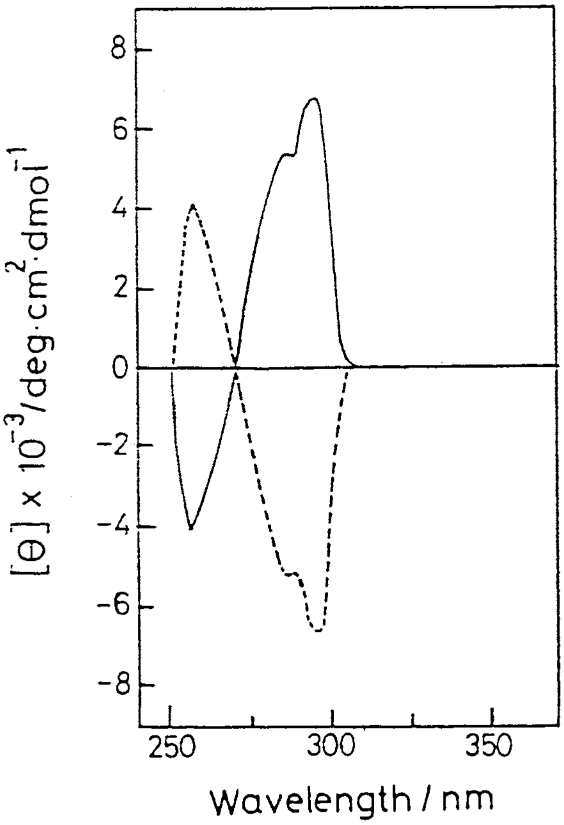


Fig. 2. CD spectra of (+)- and (-)-1 (solid and dotted lines, respectively: 25 °C, hexane).

In conclusion, this paper demonstrated the first successful synthesis and optical resolution of an asymmetrically-substituted calix[4]arene.

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References

1) V. Böhmer, F. Marschollek, and L. Zetta, J. Org. Chem., 52, 3200(1987).

2) H. Casabianca, J. Royer, A. Satrallah, A. Taty-C, and J. Vicens, Tetrahedron Lett., 28, 6595(1987).

3) C. D. Gutsche, Acc. Chem. Res., 16, 161(1983).

4) C. D. Gutsche and L. J. Bauer, J. Am. Chem. Soc., 107, 6052(1985).

5) K. Araki, S. Shinkai, and T. Matsuda, Chem. Lett., 1989, 581.

6) C. D. Gutsche, B. Dhawan, J. A. Levine, K. Hyun, and L. J. Bauer, Tetrahedron, 39, 409(1983).

7) K. Araki, K. Iwamoto, S. Shinkai, and T. Matsuda, Chem. Lett., 1989, 1747. The oxygen-through-the-annulus rotation can be inhibited by R greater than Et.

8) K. Iwamoto and S. Shinkai, to be submitted.

9) **2** can be synthesized by using either NaH or $Ba(OH)_2$ as base. NaH affords not only **2** but a considerable amount of di-R_1-substituted products whereas $Ba(OH)_2$ affords **2** selectively. When a propyl group is first introduced followed by the reaction with 2-chloromethylpyridine, we obtained both **1**-type and **1'**-type compounds.

10) Found: C, 80.41; H, 8.29; N, 1.80%. Calcd for $C_{50}H_{61}NO_4$: C, 81.15; H, 8.31; N, 1.89%.

11) Found: C, 81.72; H, 8.41; N, 1.67%. Calcd for $C_{56}H_{69}NO_4$: C, 82.01; H, 8.48; N, 1.71%.

12) δ_H($CDCl_3$, 30 °C): for H_{exo} 3,16, 3,20, 3,23, and 3,28 ppm; for H_{endo} 4.28, 4.34, 4.43, and 4.47 ppm. It has been established on the basis of ^1H NMR and X-ray crystallographic studies that the $ArCH_2Ar$ methylene protons flanked by two syn Ar groups provide H_{exo} which appears at higher magnetic field and H_{endo} which appears at lower magnetic field, the difference in the chemical shifts being more than 1 ppm, whereas those flanked by two anti Ar groups show the similar chemical shifts: see references 3-7 and Grootenhuis et al., J. Am. Chem. Soc., 112, 4165(1990). Thus, the present ^1H NMR data for H_{exo} and H_{endo} indicate the isolation of a cone conformer.

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