Chiral Calix[4]arene[a]

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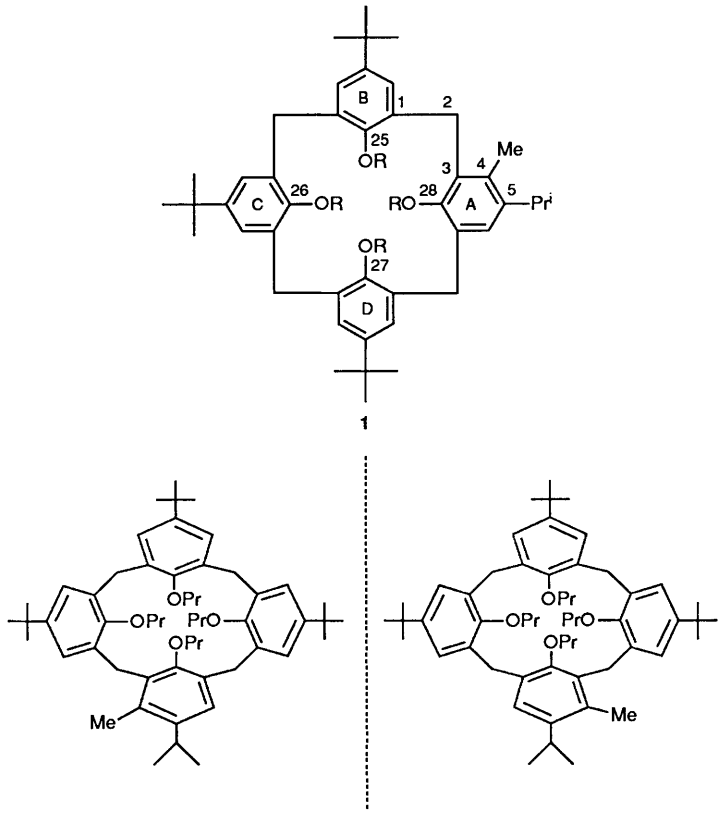
A cone-shaped, asymmetrically substituted *p-tert*-butylcalix[4]arene has been synthesized and optically resolved. The oxygen-through-the-annulus rotation which causes racemization of these ring-originating optical isomers is suppressed by four *O*-propyl substituents. In the synthesis the use of $Ba(OH)_2$ as the base for the *O*-propylation is a key point: it affords only a cone-shaped, conformationally immobile tri-*O*-propylated *p-tert*-butylcalix[4]arene. After *O*-substitution with the fourth propyl group, the racemic product can be optically resolved by HPLC. This is the first example of a successful optical resolution of an asymmetrically substituted calix[4]arene.

Calix[4]arenes are cyclic tetramers made up of phenol and formaldehyde building blocks.[1,2] Recently, Böhmer[3] and Vicens[4] synthesized calix[4]arenes which have no plane of symmetry. Their research aimed to provide evidence for the existence of the optical isomers expected for this class of asymmetrically substituted calix[4]arenes. For example, calix[4]arenes with four different substituents should result in racemates. However, they did not report the optical resolution of these racemates. In their dynamic ^1H NMR spectra, the $ArCH_2Ar$ methylene protons in calix[4]arenes appear as a pair of doublets at low temperature and as a sharp singlet at high temperature.[1,2,5–7] This indicates that, in conventional calix[4]arenes, ring inversion takes place at a speed comparable with that of the NMR time-scale.[6,7] This suggests that the optical resolution would be effected only when ring inversion is sufficiently suppressed. It is known that ring inversion can be readily inhibited by introducing bulky substituents (*e.g.*, Pr groups) onto the OH groups (*i.e.*, etherification).[1,2,6,8–13] However, *O*-substitution results in a mixture of many conformational isomers of calix[4]arenes (*e.g.*, 'cone', 'partial cone', *etc.*).† Therefore one has to isolate, prior to optical resolution, a pair of enantiomers from many other isomers. This strategy seems to be practically hopeless because tetra-*O*-substitution results in a number of conformational isomers.† This situation suggests an alternative idea, to find a new *O*-substitution method which selectively affords only one conformational isomer which would allow successful optical resolution. After much trial and error we finally found that when $Ba(OH)_2$ is used as the base *O*-substitution results in only a 'cone' isomer. This breakthrough enabled us to synthesize conformationally fixed, cone-shaped calixarene **1** and to resolve optically the racemates by HPLC. This is the first example of a successful optical resolution of an asymmetrically substituted calix[4]arene.



Scheme 1 Racemates possible for cone-shaped **1**

Experimental

11,17,23-*Tri*-tert-*butyl*-5-*isopropyl*-4-*methylcalix*[4]*arene* **2**.—Compound **2** was prepared by the high-dilution method. In a 1 dm^3 three-necked flask with a mechanical stirrer was placed a dioxane solution of $TiCl_4$ (10.0 cm^3, 91.0 mmol in 600 cm^3), and solutions of 2,6-bis(bromomethyl)-4-isopropyl-3-methylphenol (3.28 g, 9.76 mmol) in dioxane (120 cm^3) from one dropping funnel and 2,6-bis-(5-*tert*-butyl-2-hydroxybenzyl)-4-*tert*-butylphenol (4.63 g, 9.76 mmol) in dioxane (120 cm^3) from another dropping funnel were added simultaneously dropwise. The additions took 34 h. The reaction mixture was then concentrated to dryness and the residue was dissolved in dichloromethane. The solution was washed with water and dried over Na_2SO_4. After filtration, the filtrate was concentrated in the presence of silica gel (30 g). The product was extracted from this silica gel by using a Soxhlet extractor (solvent, dichloromethane). The solution was evaporated to dryness and residue was subjected to preparative TLC (PLC) separation [silica gel; benzene–hexane (1:1 v/v)]. Finally, the *product* was recrystallized from toluene, m.p. 265–266 °C; yield 9%; ν_{max}(Nujol)/cm^{-1} 3160 (OH) and 1200 (C–O); *m/z* 648; $\delta_H(CDCl_3; -40\ °C)$ 1.12 and 1.15 (each 3 H, each d, $CHMe_2$), 1.19, 1.20 and 1.23 (each 9 H, each s, Bu^t), 2.45 (3 H, s, 4-Me),

[a] Preliminary communication: ref. 17.

† *e.g.*, When compound **2** was directly tetra-*O*-propylated with PrBr in the presence of NaH (this is the most typical method for *O*-alkylation) we obtained a mixture of conformational isomers (at least 6 spots were detected by TLC). Isolation of a pair of enantiomers from this mixture in reasonable yield would be almost impossible.

2.97 (1 H, m, C*H*Me$_2$), 3.92 and 4.12 (each 1 H, each d, ArC*H*$_2$Ar near 4-Me), 3.53, 3.54 and 4.26 (2, 1 and 3 H resp., d, d, and m, resp.), other ArCH$_2$Ar), 7.02–7.33 (8 H, m, ArH) and 10.25 (4 H, s, OH) [Found: C, 82.3; H, 8.5 (recrystallized from toluene). $C_{44}H_{56}O_4$·C_7H_8 (toluene) requires C, 82.66; H, 8.70%]. In the ^{1}H NMR spectrum the Me protons of the concomitant toluene of crystallization appeared at δ_H 2.30.

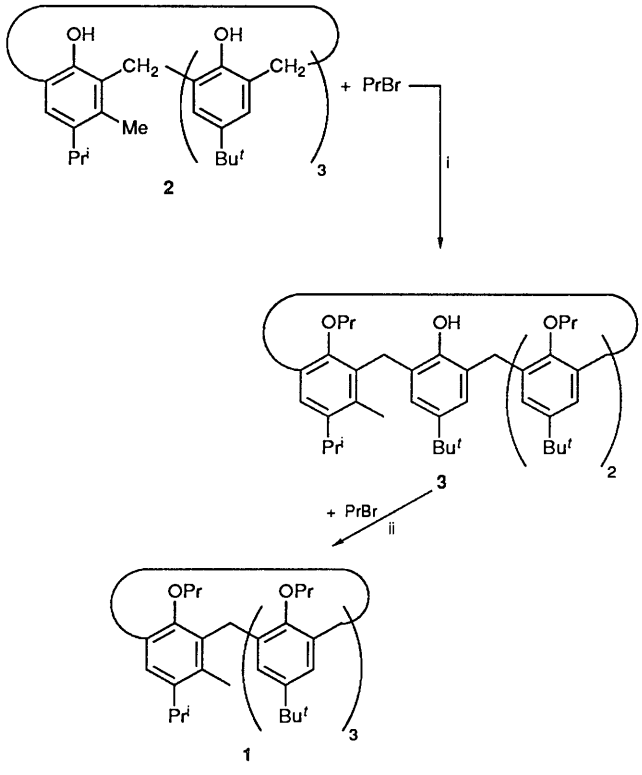
11,17,23-*Tri*-tert-*butyl*-25-*hydroxy*-5-*isopropyl*-4-*methyl*-26,27,28-*tripropoxycalix*[4]*arene* **3**.—Compound **2** (0.35 g, 0.539 mmol), Ba(OH)$_2$·8H$_2$O (0.60 g, 1.90 mmol), and BaO (0.56 g, 3.29 mmol) were added to dimethylformamide (DMF) (10 cm^3). To this mixture was added 1-bromopropane (2.91 cm^3, 32.3 mmol) dropwise and the mixture was stirred for 19 h at room temperature. The solution was diluted with water (10 cm^3) and the precipitate was extracted with chloroform. The extract was separated, washed with water, and dried over MgSO$_4$. After filtration, the filtrate was concentrated to dryness. The residue was subjected to TLC separation [silica gel; benzene–hexane (1:2)]. Thus, we recovered two compounds, with R_f 0.65 (45% yield and 0.59 (11% yield). The *compound* with R_f 0.65 had m.p. 251–253 °C; ν_{max}(Nujol)/cm^{-1} 3450 (OH) and 1120 and 1210 (C–O); *m/z* 774; δ_H(CDCl$_3$; 30 °C) 0.61, 1.33 and 1.37 (each 9 H, each s, Bu^t), 0.83 and 0.94 (each 3 H, each d, CH*Me*$_2$), 0.92, 1.07 and 1.11 (each 3 H, each t, *Me*CH$_2$CH$_2$O), 1.79–2.03 and 2.39–2.45 (6 H, m, MeC*H*$_2$CH$_2$O), 1.87 (3 H, s, 4-Me), 2.62 (1 H, m, C*H*Me$_2$), 3.15, 3.16, 3.19 and 3.37 (each 1 H, each d, H$_{exo}$ in ArC*H*$_2$Ar), 4.27, 4.29, 4.41 and 4.46 (each 1 H, each d, H$_{endo}$ in ArC*H*$_2$Ar), 3.64–3.92 (6 H, m, OCH$_2$), 5.82 (1 H, s, OH) and 6.20, 6.57, 7.07, 7.08, 7.14 and 7.20 (2, 1, 1, 1, 1 and 1 H resp., s, s, d, d, d and d, resp., ArH) (Found: C, 82.0; H, 9.6. $C_{53}H_{74}O_4$ requires C, 82.12; H, 9.62%). The *compound* with R_f 0.59 had m.p. 203–204 °C; ν_{max}(Nujol)/cm^{-1} 3450 (OH) 1130 and 1215 (C–O); *m/z* 774; δ_H(CDCl$_3$; 30 °C) 0.74, 0.87 and 1.34 (each 9 H, each s, Bu^t), 1.18 and 1.27 (each 3 H, each d, CH*Me*$_2$), 0.94, 1.08 and 1.10 (each 3 H, each t, *Me*CH$_2$CH$_2$O), 1.81–2.04 and 2.23–2.47 (7 H, m, MeC*H*$_2$–CH$_2$O and C*H*Me$_2$), 2.44 (3 H, s, 4-Me), 3.16, 3.17, 3.23 and 3.64 (each 1 H, each d, H$_{exo}$ in ArC*H*$_2$Ar), 4.24, 4.27, 4.35 and 4.39 (each 1 H, each d, H$_{endo}$ in ArC*H*$_2$Ar), 3.68–3.89 (6 H, m, OCH$_2$), 5.46 (1 H, s, OH) and 6.29, 6.42, 6.55, 6.58, 6.91 and 7.13 (1, 1, 1, 1, 1 and 2 H resp., d, d, d, d, s and s, resp., ArH) (Found: C, 81.8; H, 9.6. $C_{53}H_{74}O_4$ requires C, 82.12; H, 9.62%). In the ArH proton NMR region four protons appear as doublets and 6-H and two other protons appear as singlets. These four protons are assigned to the aromatic protons in phenol B and phenol D proximal to the asymmetric phenol A, because these protons are strongly influenced by the asymmetric phenol A and therefore become non-equivalent. In contrast, the two other protons, which are less affected by the asymmetric phenol A, are assigned to the aromatic protons in phenol C distal to the asymmetric phenol A. Now, aromatic protons in compound **2** appear at δ_H 7.02–7.33. In the compound with R_f 0.65 these two protons appear at δ 6.20 whereas in the compound with R_f 0.59 they appear at δ 7.13. The difference in the chemical shift indicates that, in the former compound, phenol C is propylated whereas in the latter compound phenol C is not propylated. As described above, the major product is the compound with R_f 0.65. This indicates that the OH group proximal to asymmetrically substituted phenol A tends to remain unalkylated. This OH group is probably more sterically crowded.

11,17,23-*Tri*-tert-*butyl*-5-*isopropyl*-4-*methyl*-25,26,27,28-*tetrapropoxycalix*[4]*arene* **1**.—Compound **3** (275 mg, 0.355 mmol) was dissolved in a mixed solvent of tetrahydrofuran (THF) (13 cm^3) and DMF (1.3 cm^3). After the addition of oil-dispersed NaH (85 mg, 2.13 mmol) the mixture was refluxed for 3 h. After the mixture had cooled, bromopropane (0.48 cm^3, 5.28 mmol) was added and the mixture was refluxed for 15 h. The reaction was stopped by the addition of a small amount of methanol. The solution was diluted with aq. 7% HCl (20 cm^3) and extracted with chloroform. The extract was separated, washed with water, and dried over Na$_2$SO$_4$. After filtration the filtrate was concentrated to dryness. The residue was crystallized from propan-2-ol, m.p. 163–164 °C; yield 72%; ν_{max}(Nujol)/cm^{-1} 1130 and 1220 (C–O), no ν_{OH}; δ_H(CDCl$_3$; 30 °C) 0.95–1.04 (15 H, m, *Me*CH$_2$CH$_2$O and CH*Me*$_2$Me), 1.01, 1.05 and 1.06 (each 9 H, each s, Bu^t), 1.12 (3 H, d, CHMe*Me*), 1.89–2.06 (8 H, m, MeC*H*$_2$CH$_2$O), 2.12 (3 H, s, 4-Me), 2.90 (1 H, m, C*H*Me$_2$), 3.10, 3.11, 3.12 and 3.37 (each 1 H, each d, H$_{exo}$ in ArC*H*$_2$Ar), 4.40, 4.41, 4.42 and 4.43 (each 1 H, each d, H$_{endo}$ in ArC*H*$_2$Ar), 3.69–4.03 (8 H, m, OCH$_2$) and 6.62, 6.68, 6.69, 6.73, 6.74 and 7.26 (7 H, br, ArH) (Found: C, 82.3; H, 9.9. $C_{56}H_{80}O_4$ requires C, 82.30; H, 9.87%).

Optical Resolution.—Racemic compound **1** was optically resolved by an LC method using a chiral packing column [Daicel Chiralpak OP(+)], 0.46 × 25 cm. The mobile phase was hexane–propan-2-ol–methanol (1:3:16). The flow rate was 0.4 cm^3 min^{-1}. The typical chromatogram is shown in Fig. 6 (see later).

Results and Discussion

Ba(OH)$_2$ has previously been used for the synthesis of tri-*O*-alkylcalix[4]arenes.[8] In the reaction of *p-tert*-butylcalix[4]-arene and PrBr we unexpectedly found that when Ba(OH)$_2$ was used as base only the cone-shaped tri-*O*-propyl-*p-tert*-butylcalix[4]arene resulted.[14] The conformation of calix[4]arenes is determined when the third Pr group enters, and it remains unaltered when the fourth Pr group enters.[12,15] We therefore postulated the following reaction scheme (Scheme 1) for the synthesis of asymmetrically substituted, cone-shaped calixarene **1**.



Scheme 2 *Reagents:* i, BaO, Ba(OH)$_2$·8H$_2$O, DMF; ii, NaH, THF–DMF

Synthesis and Characterization of Compound **2**.—Compound **2** was synthesized from 2,6-bis(bromomethyl)-4-isopropyl-3-methylphenol and 2,6-bis-(5-*tert*-butyl-2-hydroxybenzyl)-4-*tert*-butylphenol under high-dilution conditions ($TiCl_4$, reflux in dioxane). To obtain insight into the conformation of compound **2** in solution we conducted a nuclear Overhauser effect (NOE) experiment on the compound (400 MHz; $CDCl_3$; −40 °C). Fig. 1 shows the NOE peak intensities measured with respect to the 4-methyl group. The results establish that (i) the space around the 4-methyl group is considerably crowded, (ii) nevertheless, two phenol units constitute parts of a 'cone'-shaped cavity and (iii) the rotation of the 5-isopropyl group is partially restricted. Result (ii) is also supported by the fact that each $ArCH_2Ar$ methylene proton appears as a pair of doublets.[1,2,5] Result (iii) is also supported by the facts that the two methyl groups in the *para*-isopropyl group show different chemical shifts and that the peak shape changes with change in temperature.

We then investigated how compound **2** behaves as a function of temperature when in solution. ^1H NMR spectra of compound **2** were measured in [$^2H_8$]toluene with a 400 MHz NMR apparatus (Fig. 2, A). At −20 °C the $ArCH_2Ar$ protons appeared as four pairs of doublets in 1:1:1:1 integral intensity proportions. The chemical shifts for H_{exo} are δ 3.23, 3.25, 3.26 and 3.63 whereas those for H_{endo} are δ 4.14, 4.24, 4.25 and 4.27. The NOE study established that a pair of doublets (δ 3.63 and 4.14; integral intensity 2 H) isolated from other peaks is assigned to the methylene protons near the 4-methyl group. According to Gutsche,[2] Δδ between H_{exo} and H_{endo} is generally *ca.* 0.9 ± 0.2 ppm for a system in the cone conformation and zero for a system in the 1,3-alternate conformation. In compound **2**, therefore, the asymmetrically substituted phenol unit (Δδ 0.51 ppm, is considerably 'flattened' because of the steric crowding, whereas the three other phenols (Δδ 1.01 ± 0.03 ppm) are similar to those in the true cone conformation. The result is in line with the fact that the asymmetrically substituted phenol tends to remain unalkylated. These results indicate that compound **2** features symmetry lower than that of conventional cone-shaped calix[4]arenes (with C_{4v} symmetry) but still maintains a 'cone'-like conformation.

Upon raising of the temperature the peaks gradually broadened and finally coalesced into two peaks (Fig. 2, A: integral intensity ratio 1:3, coalescence temperature T_c 50 °C). The temperature-dependent spectral change was simulated by assuming a lifetime (τ) for a mirror-image conformer by a complete lineshape-analysis method[7,16] (Fig. 2, B). Excellent agreement is seen between the observed and the simulated spectra. An Arrhenius plot of log k (rate constant for ring inversion, $k = \tau^{-1}$) *vs.* T^{-1} afforded an excellent linear relationship ($r > 0.999$). By least-squares computation we obtained the following activation parameters: A 4.01 × 10^{12} s^{-1}, E_a 15.5 kcal mol^{-1} * $\Delta H^{\ddagger}$ 14.9 kcal mol^{-1}, $\Delta S^{\ddagger}$ 2.0 e.u. The

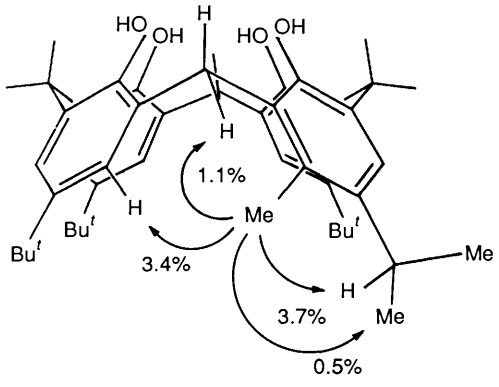


Fig. 1 NOE peak intensities with respect to the 4-methyl group in compound **2** ($CDCl_3$; −40 °C)

* 1 cal = 4.184 J.

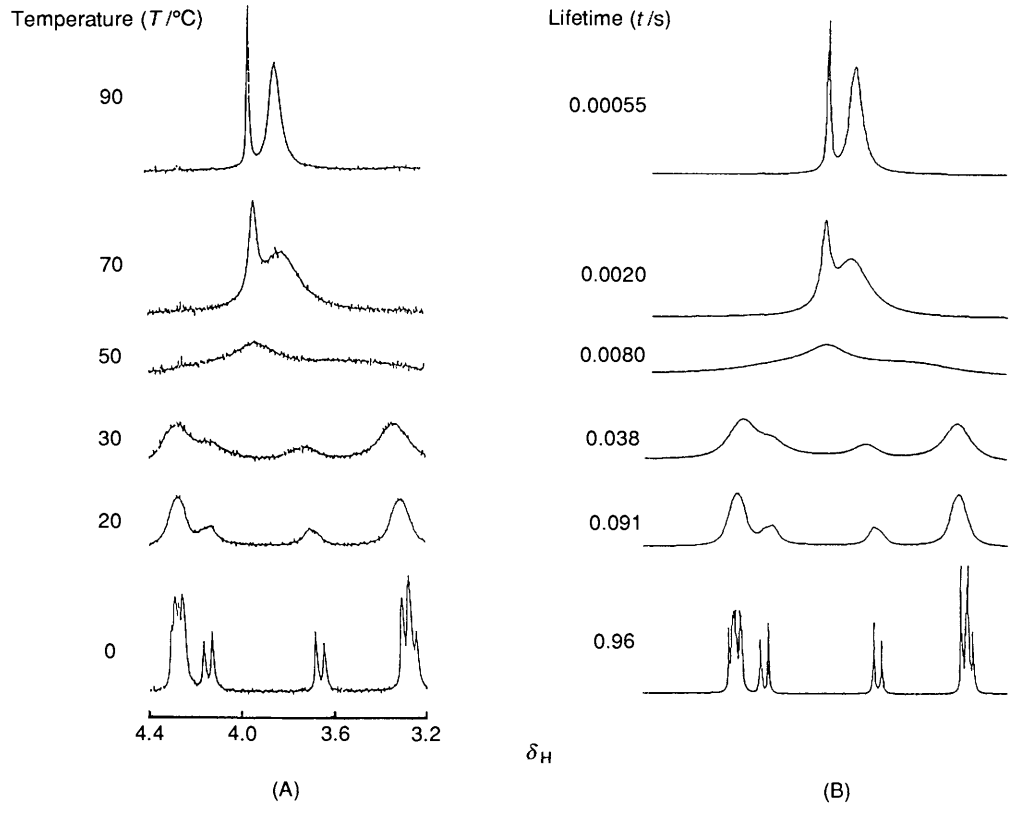


Fig. 2 Partial ^1H NMR spectra for the $ArCH_2Ar$ protons in compound **2** ([$^2H_8$]toluene): (A) observed spectra, (B) simulated spectra assuming a (given) lifetime for the spin exchange

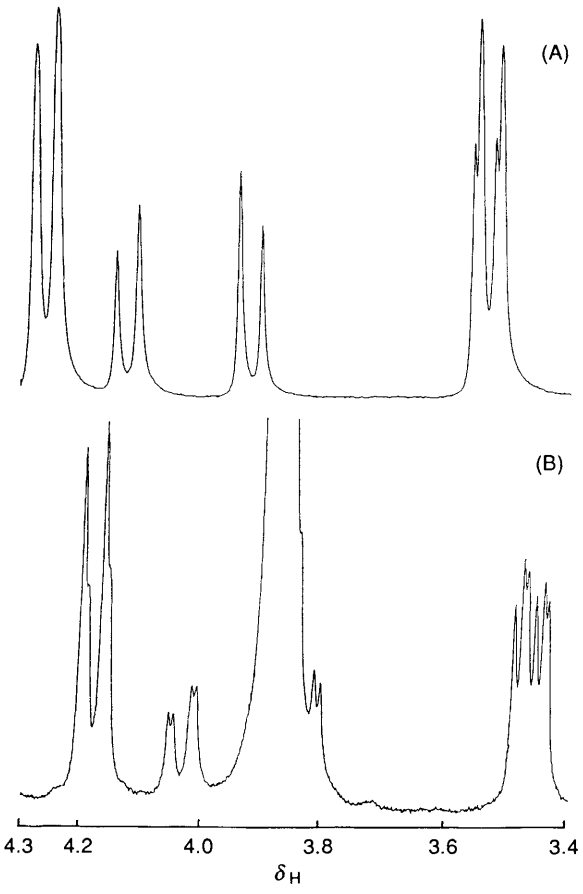


Fig. 3 Split patterns of the ^1H NMR spectra in the absence (A) and the presence (B) of Pirkle's reagent **4**: solvent $CDCl_3$; −40 °C; [**2**] 1.28×10^{-2} mol dm^{-3}, [**4**] 2.56×10^{-1} mol dm^{-3}

$\Delta H^{\ddagger}$-value, which is known to act as a main energy barrier for ring inversion,[7] is somewhat smaller than those observed for conventional calix[4]arenes (15.7–16.4 kcal mol^{-1}).[7] Presumably, the difference is caused by destabilization of the initial state of sterically crowded compound **2**. The facts that (i) conformers other than the cone, which may appear in the course of cone–cone ring inversion, cannot be detected by ^1H NMR spectroscopy, (ii) the spectra could be simulated with a single parameter (τ) and (iii) the Arrhenius plot is linear support the view that the ring inversion is an A ⟶ B-type reaction.

The foregoing results indicate that the ring of compound **2** is inverted with a speed comparable with the NMR time-scale and racemization can take place through ring inversion. Is it, then, difficult to find evidence for the presence of optical isomers under these conditions? We noticed that one can discriminate racemates by chiral shift reagents in the temperature region where the rate of ring inversion is slower than the NMR time-scale. We therefore measured the ^1H NMR spectrum of compound **2** in the presence of several chiral shift reagents (−40 °C; $CDCl_3$).* We found that most peaks change into split pairs in the presence of Pirkle's reagent **4** [(*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol] (Fig. 3). The results clearly indicate that compound **2** actually exists as ring-originating racemates and that racemization occurs through ring inversion.[8]

* Chiral shift reagents tested herein are (*S*)-(−)-1,1′-bi-2-naphthol, (+)-tris-[3-(heptafluoropropylhydroxymethylene)camphorato]-praseodymium(III) and Pirkle's reagent. Among these, only Pirkle's reagent was effective.

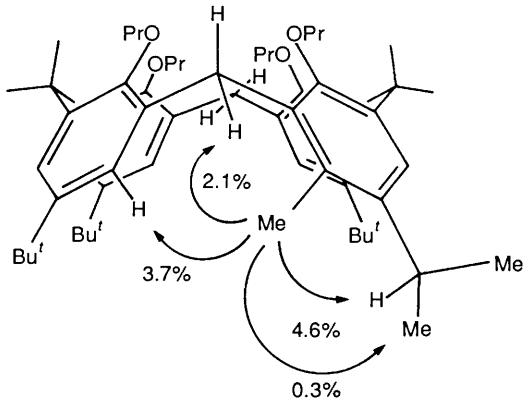
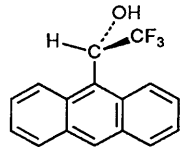
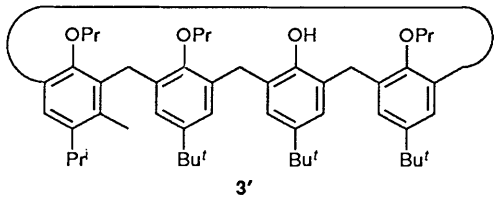


Fig. 4 NOE peak intensities with respect to the 4-methyl group in compound **1** ($CDCl_3$; 30 °C)



4

Synthesis of Compound **1** *and its Optical Resolution.*—Compound **2** was tri-*O*-propylated with PrBr in the presence of $Ba(OH)_2 \cdot 8H_2O$ and BaO in DMF. Upon TLC separation [silica gel; chloroform–methanol (1:2)] we observed two spots, at R_f 0.65 and 0.59. These two compounds are shown to be compound **3** (45% yield) and 11,17,23-tri-*tert*-butyl-26-hydroxy-5-isopropyl-4-methyl-25,27,28-tripropoxycalix[4]-arene **3′** (11% yield), respectively, by ^1H NMR spectroscopy. The structure of these compounds was further identified by IR and mass spectroscopy, and by elemental analysis (see Experimental section). The conformations were assigned as 'cone' by the ^1H NMR spectra because the signals for the ArCH_2 Ar protons appeared as four pairs of doublets (see Experimental section). In particular, the fact that the $\Delta\delta$-values between H_{exo} and H_{endo} are greater than 0.90 ppm supports the cone conformation.[2] Finally, the remaining, fourth OH group in compound **3** was propylated with PrBr in the presence of NaH in the mixed solvent DMF–THF. The product was identified as compound **1** by IR and ^1H NMR spectroscopy and elemental analysis. The conformation was 'cone' (determined by the ^1H NMR spectrum, $\Delta\delta > 1.03$ ppm: see Experimental section), indicating that the conformational change does not take place in this step.



3′

The structure of compound **1** was further investigated by the NOE method. The NOE peak intensities with respect to the 4-methyl group (Fig. 4) are similar to those for compound **2** (Fig. 1). The sole significant difference between the NOE results of compounds **2** and **1** is the increase in the peak intensity for H_{exo} in the ArCH_2Ar linkage near the asymmetrically substituted phenol unit (1.1% in **2** and 2.1% in **1**). The lower rim of the calix[4]arene cavity is probably forced to open by the introduction of four propyl groups. As a result the distance between

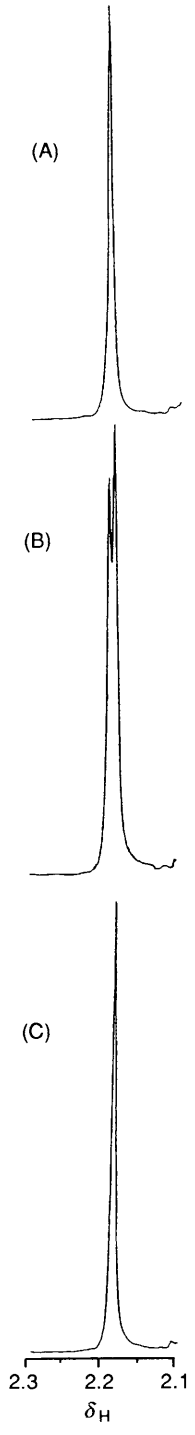


Fig. 5 Partial ^1H NMR spectra for the 4-methyl protons in compound **1** ($CDCl_3$; 50 °C): (A) racemic **1**, (B) racemic **1** + **4** (1:20 mol/mol), (C) (+)-**1** + **4** (1:20 mol/mol). In (B), the peak at higher magnetic field is assigned to (+)-**1**.

H_{exo} and 4-Me is shortened. This conjecture is compatible with the chemical shifts of H_{exo} and H_{endo}. As mentioned above, the $\Delta\delta$-value for compound **2** is 0.47 ppm, indicating that the asymmetrically substituted phenol unit is considerably flattened. In compound **1**, on the other hand, the $\Delta\delta$-value is 1.03 ppm (δ 3.37 for H_{exo} and 4.40 for H_{endo}). This means that in compound **1** the asymmetrically substituted phenol unit is not flattened any more but the conformation is close to that of a true cone.

In order to confirm that compound **1** is a pair of ring-originating racemates we measured the ^1H NMR spectrum in the presence of Pirkle's reagent **4**. Most signals changed into split pairs with a 1:1 intensity ratio even at 25 °C (a typical peak is shown in Fig. 5). The result, together with the NOE data, indicates that compound **1** is immobilized to a cone conformation by its four *O*-propyl groups.

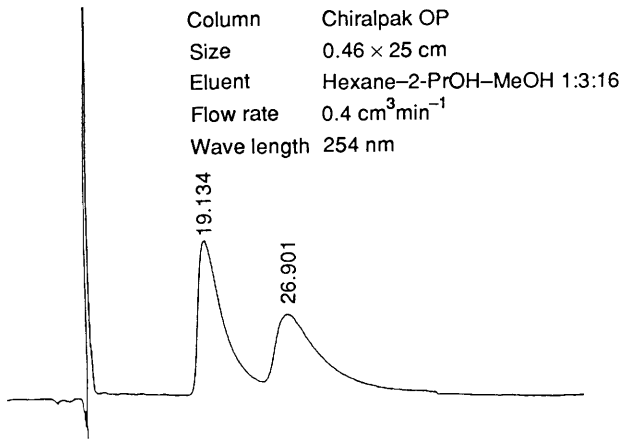


Fig. 6 Chromatogram for optical resolution of compound **1**: for separation conditions see the data in the Fig. Numbers recorded on the peaks are the retention times (t/min).

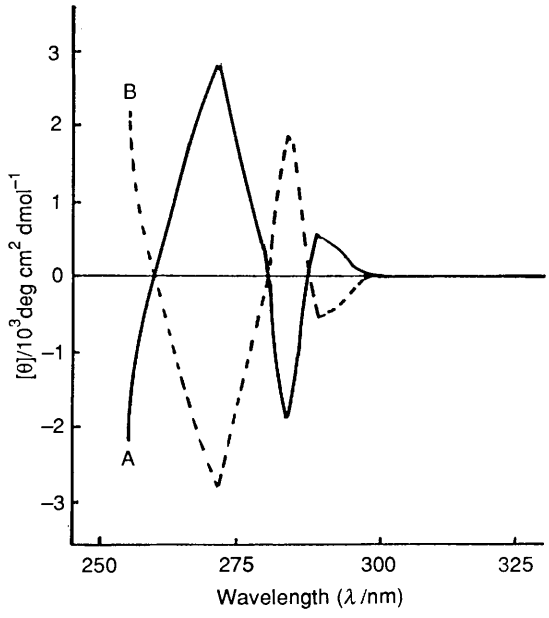


Fig. 7 CD spectra of compound **1** ($CHCl_3$; 25 °C): A, (+)-**1**; B, (−)-**1**

Racemic **1** was optically resolved by HPLC on a chiral packing column [Daicel Chiralpak OP(+)]. The mobile phase was hexane–propan-2-ol–methanol (1:3:16). Peak separation was nearly complete (Fig. 6). We separated the eluent into three fractions and obtained compound (+)-**1** (~35 mg) from the first fraction and compound (−)-**1** (25 mg) from the third fraction, from racemic **1** (100 mg). The ^1H NMR spectrum in the presence of Pirkle's reagent **4** and the HPLC analysis on the chiral packing column showed that the optical purity of isomer (+)-**1** was 100% (Fig. 5), whereas that of isomer (−)-**1** was somewhat inferior because of 'tailing' of (+)-**1** (95% optical purity): $[\alpha]_D$ for (+)-**1** (*c* 0.08, solvent $CHCl_3$) +225°. The CD spectra are shown in Fig. 7: λ_{max} 271 nm (θ +2830) and 284 nm (θ −1890) for isomer (+)-**1**. The symmetrical spectra indicate that these two compounds are optical isomers. Compound (+)-**1** was heated in 1,1,2,2-tetrachloroethane at 100 °C for 24 h, but thermal isomerization did not take place. This indicates that racemization through

ring inversion is completely suppressed by four *O*-propyl groups.*

Conclusions.—This paper demonstrates the first successful optical resolution of a cone-shaped, asymmetrically-substituted calix[4]arene. Applications to chiral recognition, asymmetric syntheses, *etc.* are now currently being investigated in this laboratory.

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* This result provides an important implication with regard to ring inversion of calix[4]arenes. In conventional calix[4]arenes the occurrence of cone–cone ring inversion cannot be detected by an NMR method if the rate is slower than the NMR time-scale. The discrimination is possible only by monitoring of the racemization of chiral calix[4]arenes such as compound **1**.

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