Synthesis and optical resolution of a fluorescent chiral calix[4]arene with two pyrene moieties forming an intramolecular excimer

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An inherently fluorescent chiral calix[4]arene 2 with two pyrene moieties forming an intramolecular pyrene excimer has been synthesized and optically resolved by an HPLC method using a chiral-packed column.

Calixarenes are unique host molecules which have complexing abilities toward ions and/or organic molecules.[1] Recent interest in the synthesis of calixarenes has focused on chiral species, since such a chiral host has potential as an enantioselective artificial receptor of chiral or racemic ligands.[2] Chiral calix[4]arenes have been produced by the addition of chiral residues to calix[4]arene skeletons,[3] or by the introduction of asymmetric substituent patterns into the lower rim[4] or the phenolic rings.[5] Although more than twenty studies of the synthesis of chiral calix[4]arenes have been reported, there are only a few examples of fluorescent chiral calix[4]arenes.[4b,5g] Fluorescent-detectable chiral calixarenes have a great advantage in their high sensitivity as enantioselective sensors of biologically important organic molecules. Herein we describe a simple method for the synthesis of a tri-*O*-alkyated fluorescent chiral calix[4]arene (ABBH-type) that has two pyrene moieties *via* a two-step alkylation of the parent calix[4]arene.

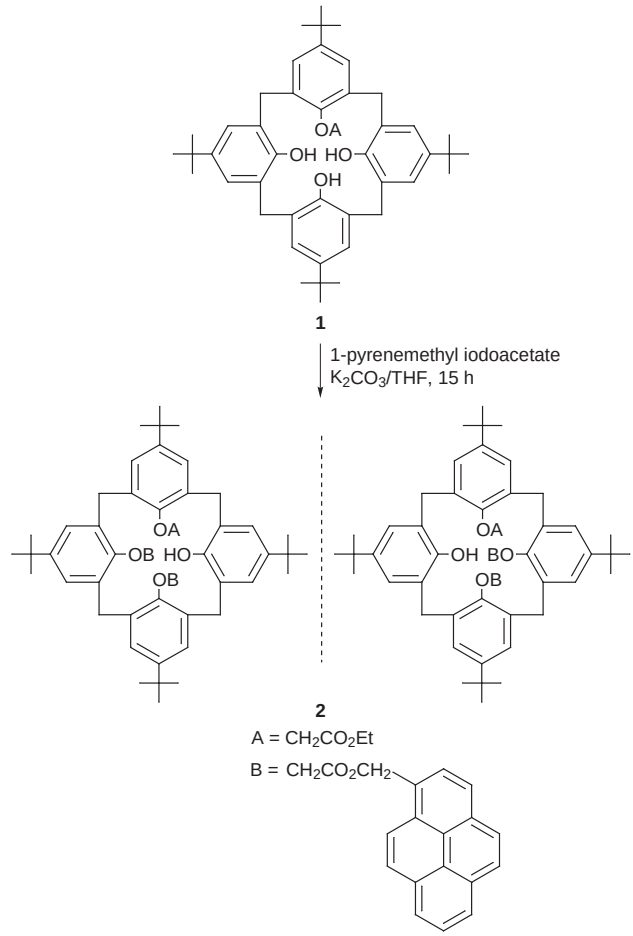
The fluorescent calix[4]arene **2** was synthesised by the reaction of **1**‡ (92 mg) with 2 equiv. (100 mg) of pyren-1-ylmethyl iodoacetate (Molecular Prob. Inc.) in the presence of K_2CO_3 (103 mg) in anhydrous THF (Scheme 1). Racemic compound **2** was obtained as a white powder (55% yield) after a simple chromatographic purification. The structure of **2** was identified by ^{1}H NMR and FD mass spectroscopy.§

The ^{1}H NMR spectrum of **2** showed four singlets for the *tert*-butyl groups and four pairs of doublets from the bridging CH_2 groups, suggesting that the pyrene moieties were introduced to the proximal positions of the lower rim and that **2** adopted a cone conformation. Considering the intensity of the pyrene protons in the NMR spectrum and the results of the FD mass spectrum, calix[4]arene **2** should have an ABBH configuration with two pyrene moieties. To clarify the substituted pattern, a ^{1}H NMR spectrum of **2** in the presence of a chiral shift reagent was measured. The addition of Pirkle's reagent [(S)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol] to a $CDCl_3$-solution of **2** caused doubling of the methylene signals of the OCH_2CO groups (δ 4.56 and 4.69). This result confirmed that the substituted pattern of calix[4]arene **2** was of the ABBH type, not the ABHB type.

Optical resolution of **2** was performed *via* an HPLC method using a chiral-packed column (Chiracel OD, Daicel, 0.46 × 25 cm). Fig. 1(*a*) shows an HPLC chromatogram for the optical resolution of **2**. Up to 1 mg of **2** per injection could be separated completely in two fractions. To check the enantiomeric resolution, the first and second fractions were subjected to circular dichroism (CD) measurements. The CD spectra [Fig 1(*b*)] were mirror images of each other, indicating that the compounds from the first and second fractions were optical isomers.

The fluorescence spectrum of the first fraction was identical with that of the second fraction. Fig. 2(*a*) shows the fluorescence spectrum of the isomer from the first HPLC fraction. It shows a dual emission resulting from a pyrene monomer (*ca.* 390 nm) and excimer (480 nm),[6] while the fluorescence spectrum of pyrene at the same concentration as **2** afforded only monomer emissions [Fig. 2(*b*)]. The intensity ratio of the monomer/excimer emission **2** was less affected by the concentration in the range from 10^{-4} to 10^{-7} mol dm^{-3}. This indicates that the excimer emission results from an intramolecular excimer, not from an intermolecular excimer.

We examined the fluorescence properties of two enantiomers (the first and second fractions of **2**) toward three chiral guests in the $CHCl_3$–EtOH (30 : 1) at 25 °C. We found that the intensity of the excimer emission of **2** (3.9 μmol dm^{-3}) increased up to 2-fold by addition of L-phenylalanine methyl ester, L-alanine methyl ester or L-phenylglycinol in the presence of Na^+ (76 μmol dm^{-3}). However, differences in the fluorescence intensities between the two isomers of **2** in the presence of the



Scheme 1 *Reagents and conditions:* i, pyren-1-ylmethyl iodoacetate, K_2CO_3, THF, 15 h

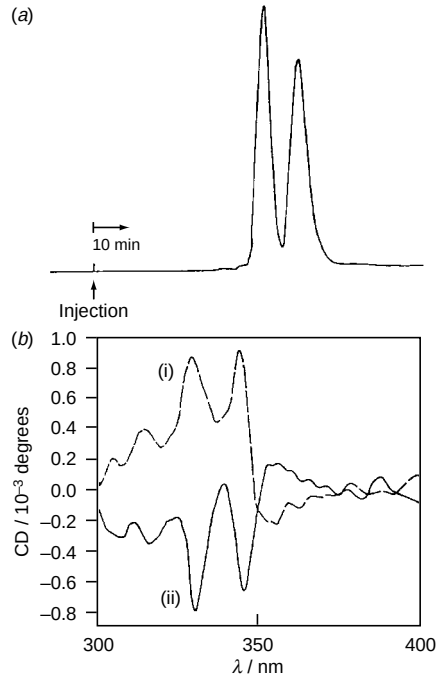


Fig. 1 (*a*) An HPLC chromatogram for optical resolution of racemic **2**. Column: Chiracel OD (0.46 × 25 cm); eluent: hexane–Pr^{i}OH (95 : 5); flow rate: 0.2 ml min^{-1}; T = 40 °C. (*b*) CD spectra of the enatiometric pair of **2** ($CHCl_3$, 25 °C): (i) first fraction, (ii) second fraction.

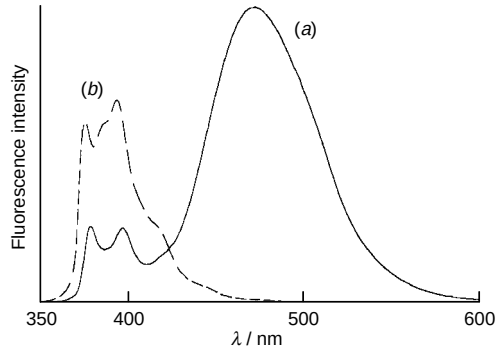


Fig. 2 Fluorescence spectra of the isomer (first fraction) of **2** and pyrene in $CHCl_3$ at 25 °C: (*a*) [**2**] = 3.9 μmol dm^{-3}, (*b*) [pyrene] = 3.9 μmol dm^{-3}

chiral guests were too small to evaluate the chiral discriminating ability of **2**.

To the best of our knowledge, compound **2** is the first example of a tri-*O*-alkylated fluorescent chiral calix[4]arene (ABBH type). So far, $Ba(OH)_2$ and BaO have been the only bases that stop the *O*-alkylation reaction at the tri-*O*-substituted stage.[7] Shinkai and co-workers have reported an inherently chiral calix[4]arene of the ABBH type *via* tri-*O*-alkylation of calix[4]arenes using $Ba(OH)_2$, where an excess amount of alkyl halide (*ca*. 10 equiv.) was used to accomplish alkylation.[4a,c] We found that a tri-*O*-alkylated chiral calix[4]arene **2** with a cone conformation could be easily prepared by a stoichiometric reaction with **1** and pyren-1-ylmethyl iodoacetate in the presence of K_2CO_3. Since chiral calix[4]arene **2** has a phenolic OH group, further modifications of **2** can be easily carried out. Applications for chiral calix[4]arene **2** are the subject of ongoing investigation in our laboratory.

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Notes and References

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‡ Compound **1** was synthesized by refluxing *p-tert*-butylcalix[4]arene (1 g, 1.5 mmol) and ethyl bromoacetate (171 μl, 1.5 mmol) in the presence of K_2CO_3 (0.213 g, 1.5 mmol) in anhydrous THF for 15 h.

§ *Selected data* for **2**: $\delta_H(CDCl_3)$ 0.820, 0.823, 1.27, 1.29 (s, 4 × 18 H, CMe_3), 1.10 (t, 3 H, OCH_2CH_3), 4.08 (m, 2 H, OCH_2CH_3), 4.08 (m, 2 H, OCH_2CH_3), 3.05, 3.17, 3.18, 3.19, 4.22, 4.31, 4.88, 4.89, (d, 2 H × 8, $ArCH_2Ar$), 4.43, 4.69 (dd, 2 H, OCH_2CO), 4.49, 4.56 (dd, 2 H, OCH_2CO), 5.19, 5.20 (s, 2 × 1 H, OCH_2CO), 5.68, 5.69 (s, 2 × 1 H, pyrene-CH_2), 5.75 (s, 2 H, pyrene-CH_2), 6.48–7.06 (m, 8 H, ArH), 6.64 (s, 1 H, ArOH), 7.83–8.13 (m, 18 H, pyrene); *m/z* (FD-MS) 1278 (M^+).

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