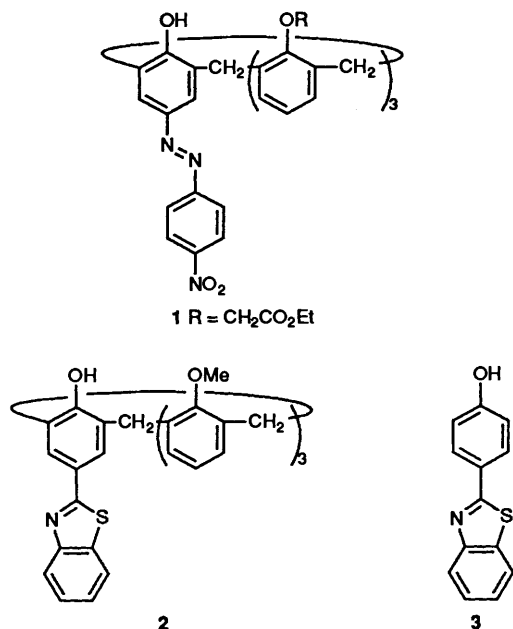# Fluorogenic Calix[4]arene

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5-Benzothiazol-1-yl-28-hydroxy-25,26,27-trimethoxycalix[4]arene has been synthesized: this compound acted as a novel fluorogenic calix[4]arene showing 'perfect' Li$^+$-selectivity.
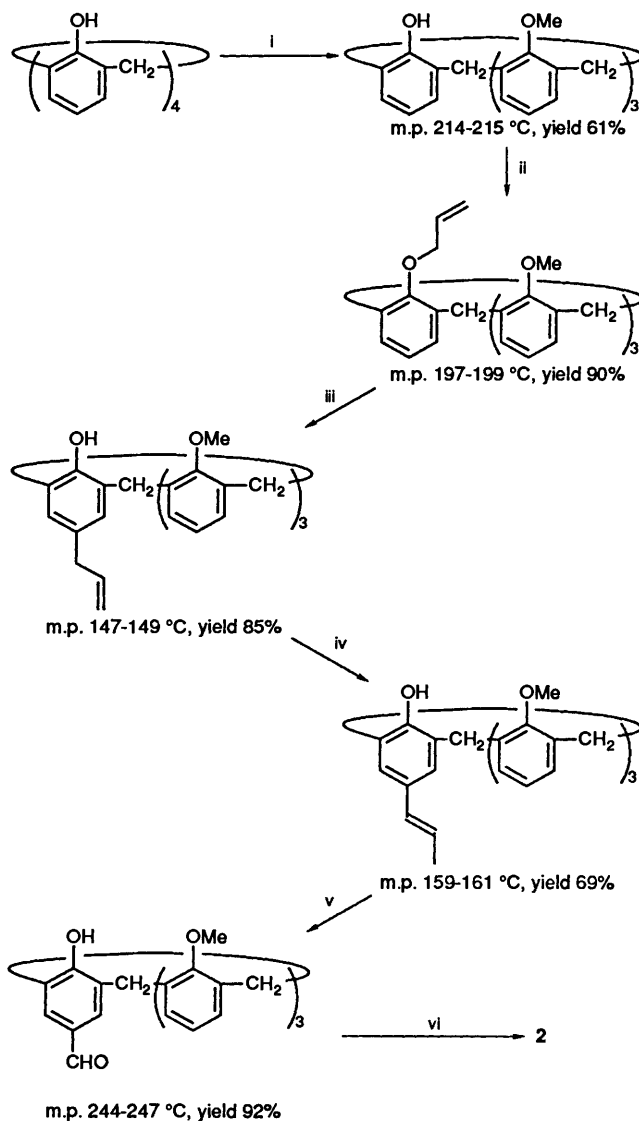
Spectroscopic detection of metal ions is of importance both in classical analytical chemistry and in the molecular design of ion sensors and signal transformations. The latter are well represented by a family of so-called 'chromogenic crown ethers': the metal-induced colouration process serves as a transducer of the chemical signal (*i.e.*, metal concentrations) to the physical signal (*i.e.*, spectral parameters).[1] Calixarenes, which appeared after crown ethers and cyclodextrins as the third generation of inclusion compounds, are capable of selective metal-binding if the OH groups on the lower rim are appropriately modified.[2-7] It seems to us, therefore, that calixarenes have latent potential as a basic skeleton for the design of 'chromogenic calixarenes'. In particular, they have the structural merit that the OH group is directly usable as a metal-induced dissociation group. We have previously synthesized an ionophoric calix[4]arene 1 which has a 4-(4-nitrophenyl)azophenol unit.[8,9] Upon metal-binding this compound showed a new absorption maximum at *ca.* 600 nm and high Li$^+$ selectivity. We here extend this concept to the molecular design of a 'fluorogenic calix[4]arene', a trace amount of metal ion being detected more sensitively by a

1 R = CH₂CO₂Et

2   3

m.p. 214-215 °C, yield 61%

m.p. 197-199 °C, yield 90%

m.p. 147-149 °C, yield 85%

m.p. 159-161 °C, yield 69%

m.p. 244-247 °C, yield 92%

Scheme 1 *Reagents:* i, Me₂SO₄, BaO, Ba(OH)₂·8H₂O in DMF; ii, CH₂=CHCH₂Br, NaH in THF; iii, reflux in *N*,*N*-dimethylaniline; iv, Bu^{t}OK in THF; v, O₃ in CHCl₃; vi, *o*-aminothiophenol in acetic acid

fluorescence spectroscopic method rather than an absorption one.[10]

We chose benzothiazole as a fluorophore and the fluorogenic calix[4]arene 2 was synthesized according to Scheme 1. The compound was identified on the basis of IR and NMR spectral evidence† and elemental analysis. Compound 3 was used as a reference.

We first determined the pK_a of 3 by phototitration [in water–ethanol = 9:1 (v/v) at 30 °C, μ = 0.1; λ$_{max}$ 318 nm for neutral 3

and 351 nm for dissociated 3]. The pK_a was estimated to be 8.60. Although the pK_a for 2 could not be determined because of its

† M.p. 231-233 °C, yield 63%; ν$_{max}$(Nujol)/cm^{-1} 3300 (OH); δ(CDCl₃, 30 °C, 400 MHz) for cone 2, 3.29, 3.50, 4.36 and 4.39 (2 H each 4 × d, ArCH₂Ar), 3.85 and 3.98 (6 H and 3 H, s each, CH₃O), 6.5–8.1 (15 H, m, ArH); for partial cone 2, 3.42, 3.84 and 4.11 (2 H, 4 H and 2 H, 3 × d, ArCH₂Ar), 3.13 and 3.76 (3 H and 6 H, s each, CH₃O) and 6.5–8.1 (15 H, m, ArH). The mol ratio of cone *vs.* partial cone is 3.1:1.0.
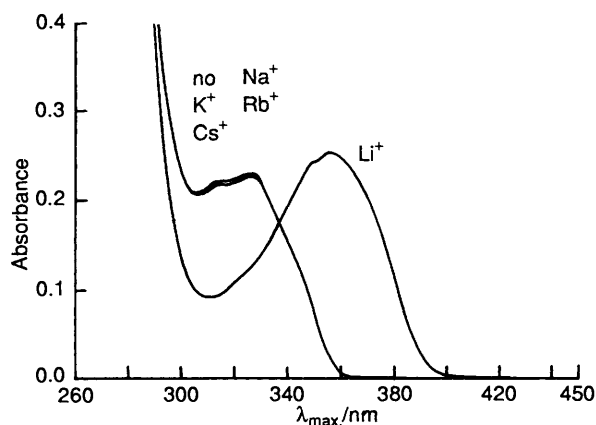
Fig. 1 Absorption spectra of 2 after solid(MClO₄)-liquid(chloroform) two-phase solvent extraction: 30 °C, [2] = 1.0 × 10⁻⁵ mol dm⁻³, [NEt₃]/[2] = 10⁴. The solution was shaken vigorously for 2 min at 30 °C, which was enough to attain the extraction equilibrium.
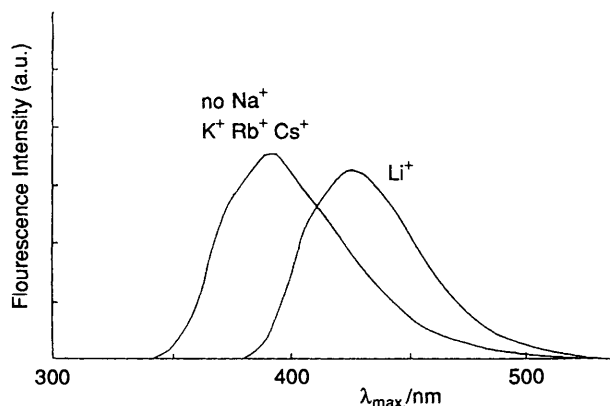

Fig. 2 Fluorescence spectra of 2 after solid(MClO₄)-liquid(chloroform) two-phase solvent extraction: 30 °C, [2] = 1.0 × 10⁻⁶ mol dm⁻³, [NEt₃]/[2] = 10⁴. The excitation wavelength is 332 nm which is the isosbestic point of the absorption spectra observed for two-phase solvent extraction of LiClO₄ in the presence of triethylamine ([NEt₃]/ [2] = 0 ~ 10⁴). It was confirmed that under the present measurement conditions triethylamine does not quench the fluorescence of 2.

poor solubility in water, it is presumed that the pK_a value for the phenol unit was similar.

In chloroform at 30 °C, compounds 2 and 3 had absorption maxima at 327 and 310 nm, respectively. The absorption spectra were scarcely affected by the addition of triethylamine (up to [triethylamine]/[2 or 3] = 10³). This implies that in chloroform the basicity of triethylamine is not strong enough to dissociate the OH groups in 2 and 3. In the absence of triethylamine, alkali perchlorates (MClO₄:M = Li, Na, K, Rb and Cs) added as solid salts into the chloroform solution were not extracted and the absorption spectra were unaffected. In the presence of triethylamine, in contrast, only LiClO₄ could change the absorption spectrum of 2 (Fig. 1). The new absorption maximum (356 nm) increased with increasing triethylamine concentration and reached a saturation value above [triethylamine]/[2] = 10². These results show that 2 also acts as a Li⁺-selective chromogenic calix[4]arene. Such a Li⁺-induced spectral change was not observed for 3. This indicates that the ionophoric cavity constructed on the lower rim of calix[4]arene plays a crucial role in the chromogenic behaviour.

We here tested to see if 2 acted as a 'fluorogenic calix[4]arene'. In chloroform 2 gave a fluorescence maximum at 391 nm (excitation 332 nm), which was scarcely affected by the addition of triethylamine. The fluorescence spectra were measured after solvent extraction in the presence of triethylamine and alkali perchlorates (solid). In the presence of LiClO₄ a new fluorescence maximum appeared at 422 nm while the band at 391 nm almost disappeared (Fig. 2). In contrast, such a spectral change was not induced by alkali perchlorates other than LiClO₄. The results establish that 2 acts as a 'perfect' Li⁺-selective fluorogenic calix[4]arene.

In order to confirm that 2 acted equally well as a 'perfect' Li⁺-selective ionophore in an homogeneous system, we measured the absorption spectra in a chloroform–DMSO (97.5:2.5, v/v) mixed solvent ([2] = 1.0 × 10⁻⁵ mol dm⁻³, [NEt₃] = 0.10 mol dm⁻³, [MClO₄] = 2.0 × 10⁻⁴ mol dm⁻³ (M = Li, Na and K; the solubility of Rb and Cs was not enough to do this experiment). As expected, a new absorption maximum (359 nm) appeared only when LiClO₄ was added. The association constant was estimated to be 1100 dm³ mol⁻¹.*

To obtain further insights into the dissociation process we

measured the ¹H spectra of 2 in CDCl₃ at 30 °C. Compound 2 exists as an equilibrium mixture of cones and partial cones (3.1:1.0 mol ratio) as evidenced by the splitting pattern of the ArCH₂Ar methylene protons:[11,12] two pairs of doublets for cone [δ_H = 3.50 and 4.39 (J 13.3 Hz) for one pair and 3.29 and 4.36 ppm (J 12.9 Hz) for another pair] and two pairs of doublets, one with the large chemical shift difference and another with the small chemical shift difference [δ 3.42 and 4.11 ppm (J 13.7 Hz) and δ_H 3.84, br s]. In partial cone 2 two MeO protons appeared at δ 3.76 and one MeO proton appeared at δ 3.13. The upfield shift of one MeO indicates that the anisole unit distal to the phenol unit is inverted and the MeO protons shift to higher magnetic field as a result of the shielding effect of the benzene rings. Addition of triethylamine ([NEt₃]/[2] = 100; above this ratio it became difficult to isolate the peaks of 2 from those of triethylamine) induced a decrease of the peak strength of the OH proton (δ 6.57).

Addition of LiClO₄ (solid) gave new peaks assignable to dissociated partial cone 2 (δ 3.34 and 3.91, J 13.1 Hz; δ 3.75 and 3.80, J 14.4 Hz): the ratio of cone:partial cone:dissociated partial cone (as a Li⁺ complex) = 1.0:0:5.4.

The above observations are shown as in Scheme 2. When we
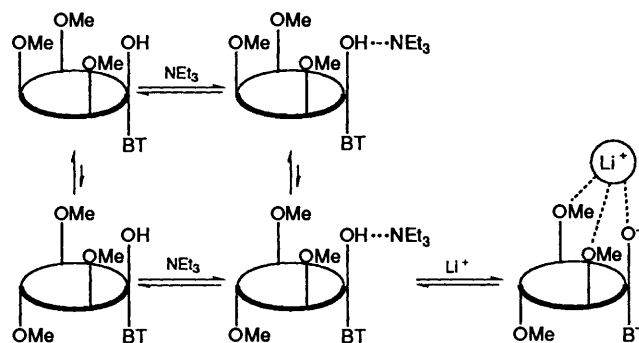
Scheme 2 BT denotes benzthiazole

designed compound 2, we expected as a working hypothesis that cone 2 would form a stable complex with Li⁺ because it can be stabilized by three methoxy oxygens and one oxide anion. Contrary to our expectation, the ¹H NMR data revealed that partial cone 2 forms a more stable complex with Li⁺.

It is not yet clear why the Li⁺·2 complex adopts a partial cone conformation rather than a cone conformation. We previously found that tetra-O-methylated calix[4]arenes, which exist as a

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* The dissociation process is expressed by 2 OH + LiClO₄ + NEt₃ ⟶ 2 O⁻Li⁺ + Et₃NH⁺ClO₄⁻. For the sake of the simplicity the association constant is herein defined as $K = [2\ O^-Li^+]/[2\ OH][LiClO_4]$.

mixture of cone and partial cone under an equilibrium, bind Li^+ ion and the complexes exactly adopt a cone conformation with four methoxy oxygens coordinating to Li^+ ion.[13] We now consider that Li^+ cation forms a tight ion-pair with the phenoxide anion and the position is too far for the distal methoxy group to coordinate.

In conclusion, compound **2** designed using the calix[4]arene skeleton serves as a novel fluorogenic ionophore with the 'perfect' Li^+-selectivity. Undoubtedly, the high Li^+-selectivity stems from the rigid ring structure of calix[4]arene.

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