Synthesis of a 1,3-Bis(indoaniline)-derived Calix[4]arene as an Optical Sensor for Calcium Ion

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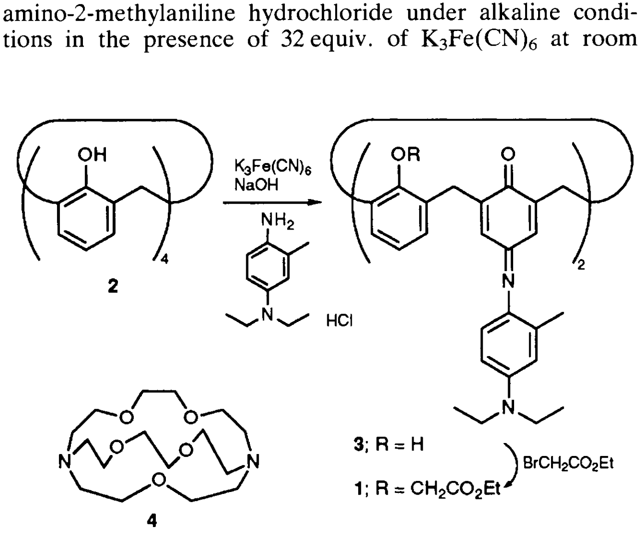
A new chromogenic artificial receptor, a 1,3-bis(indoaniline)-derived calix[4]arene, has been prepared, the ethyl acetate derivative of which shows a selective Ca^{2+}-induced pronounced colour change (wavelength change >100 nm) with an association constant of the order of 10^6 in 99% EtOH.

Human blood plasma usually contains Na^+, K^+, Mg^{2+} and Ca^{2+} ions.[1] The development of optical fibre sensors to measure the concentration of these biologically important cations has been of particular recent interest in clinical analysis.[2] Synthetic chromoionophores that give rise to specific colour changes on complexation with alkali and alkaline earth cations have been utilized as spectrophotometric analytical reagents for the detection of particular cations.[3] While chromogenic receptors for Na^+ and K^+ have been synthesized,[4] studies on Ca^{2+} are uncommon.[3a,5] Calixarenes are useful building blocks in the design of artificial receptors,[6] and with the aim of developing new types of optical receptor, there has been particular recent emphasis on the synthesis of 'chromogenic'[4e,f,4h,7] and 'fluorogenic'[8] calix[4]arenes. However, to the best of our knowledge, a calixarene derivative has not been used as an optical sensor for Ca^{2+}. The indoaniline chromophore system may be important in this area because its optical properties can be perturbed significantly by chemical stimuli. In particular, we have found that the quinone carbonyl group of indoaniline-type ligands strongly interacts with divalent metal ions to cause a colour change.[9] Our interest in chromogenic artificial receptors for the detection of Ca^{2+} led us to design the title compound **1** and to study its potential for use as an optical sensor for Ca^{2+}; we now report the results of these studies.

Condensing calix[4]arene **2**[10] with 16 equiv. of 4-diethylamino-2-methylaniline hydrochloride under alkaline conditions in the presence of 32 equiv. of $K_3Fe(CN)_6$ at room temperature afforded the 1,3-bis(indoaniline)-derived calix[4]arene **3** in 35% yield; ethoxycarbonylmethylation of **3** gave the ethyl acetate derivative **1**[†] in 62% yield.



Scheme 1

Compound **1** is blue [λ_{max} 609 nm (ε_{max} 35 000) in 99% EtOH]. However, as shown in Fig. 1, addition of $Ca(SCN)_2 \cdot 4H_2O$ to compound **1** in 99% EtOH solution causes a large bathochromic shift with an increase in absorption intensity. At a ratio of [Ca^{2+}] to [**1**] of 100 : 1, a new absorption band in the near-IR region at 719 nm was observed. Addition of NaSCN, KSCN or $Mg(ClO_4)_2$ caused only minor changes in the absorption spectra, suggesting that compound **1** exhibited a significant selectivity for Ca^{2+}. Use of the continuous variation method[11] indicated the formation of a 1 : 1 complex between **1** and Ca^{2+}.

IR spectroscopy was used in order to obtain insight into the coordination structure. The frequency of both C=O (ester) and C=O (quinone) absorptions for the Ca^{2+}–**1** complex are lower by 34–35 cm^{-1} than those of the free ligand, suggesting that compound **1** forms an encapsulated complex with Ca^{2+} on the lower rim of the calixarene unit. From these results,[‡] a rather specific Ca^{2+}-induced bathochromic shift could be explained on the basis of a well-tailored electrostatic interaction between the encapsulated cation and quinone carbonyl groups of the indoaniline chromophores. The excited state of the indoaniline chromophore might be more stabilized by the cation than the ground state.

The association constants (K) and binding free energies ($-\Delta G^\circ$) are summarized in Table 1. Compound **1** showed peak selectivity for Ca^{2+} with a ΔG° value of -9.39 kcal mol^{-1}, being comparable to that of the cryptand **4**.[14] It is noteworthy that high Ca^{2+} selectivity over Na^+ ($\Delta\Delta G^\circ = -3.16$ kcal mol^{-1}) is obtained, in spite of their similar ionic radii. This result can be interpreted in terms of ion–dipole interaction; because Ca^{2+} has higher charge density than Na^+ it should interact more strongly with polar donor groups.[15]

In conclusion, compound **1** is the first rationally designed chromogenic calixarene-type receptor for Ca^{2+}, and is more sensitive to Ca^{2+} than to Na^+, K^+ and Mg^{2+}, making it of potential use as an optical sensor for Ca^{2+} detection. We are attempting to obtain an X-ray structure of the Ca^{2+} complex,

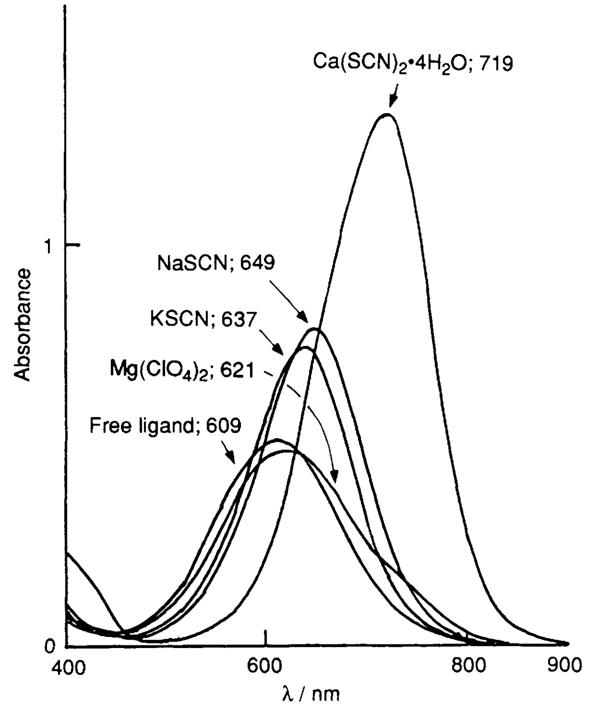


Fig. 1 Influence of added NaSCN, KSCN, $Mg(ClO_4)_2$ and $Ca(SCN)_2 \cdot 4H_2O$; [metal salt]/[**1**] = 100, [**1**] = 1.5×10^{-5} mol dm^{-3}

Table 1 Association constants (K^a) and binding free energies ($-\Delta G^\circ$) in 99% EtOH at 25 °C

	K/dm^3 mol^{-1} [$-\Delta G^\circ$/kcal mol^{-1}]^d			
Host	Na^+	K^+	Mg^{2+}	Ca^{2+}
1	3.7×10^4	3.2×10^{5b}	100 [2.73]	7.6×10^{6b}
	[6.23]	[7.51]	[2.73]	[9.39]
4	2.5×10^{5c}	8.9×10^{3c}	<100	8.9×10^{6c}

[a] Determined from a Benesi–Hildebrand plot.[12] [b] Determined by the Rose–Drago method.[13] [c] In water. [d] 1 cal = 4.184 J.

[†] The new compounds **1** and **3** were identified by NMR and mass spectroscopy, and elemental analysis. **1**: ^1H NMR ($CDCl_3$) δ 1.14–1.19 (18H, m), 2.29 (6H, s), 3.175–3.46 (12H, m), 4.02–4.25 (8H, m), 5.02–5.07 (4H, m), 6.43–6.66 (12H, m) and 7.03–7.14 (4H, m). **3**: ^1H NMR (CD_3OD–$CDCl_3$) δ 1.16 (12H, t), 2.23 (6H, s), 3.39 (8H, q), 3.70 (8H, s), 6.515–6.64 (8H, m), 6.88 (4H, d, J 7.26 Hz) and 7.15 (4H, s); ^{13}C NMR (CD_3OD–$CDCl_3$) δ 13.3, 19.5, 31.9, 45.7, 114.8, 121.7, 125.4, 128.8, 129.8, 143.0, 152.6 and 188.1.

[‡] In a control experiment, 4-(4-diethylamino-*o*-tolylimino)-2,6-dimethylcyclohexa-2,5-dienone shows no colour change with alkali and alkaline earth metal ions.

as well as to synthesize other types of chromogenic artificial receptor.

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