A Chromogenic Reagent for Calcium. The Importance of Ion-pairing in Cation Selection

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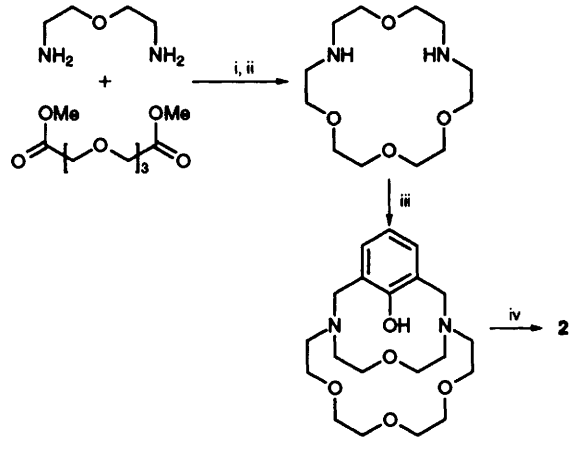
The chromoionophore **2** has been synthesised from the corresponding diaza 18-crown-6 in two steps in good overall yield, and the reagent **2** extracts calcium cations from aqueous solutions in the pH range 7–9 with moderately high selectivity as compared with sodium and with high selectivity as compared with other cations of biological interest; the series of apparently similar reagents **2**, **3** and **4** shows very wide variation in Na^+/Ca^{2+} selectivity.

A number of chromogenic reagents for Li^+, Na^+ and K^+ have been described[1–3] which are soluble in organic solvents and potentially suitable for use in optical fibre sensors. Similar chromogenic reagents for Ca^{2+} are uncommon although a number of fluorescent reagents have been described[4] which are suitable for use in aqueous solution, and neutral crown ether derivatives have been reported[5] which show high Ca^{2+}/Na^+ selectivity in aqueous solution. Recently a chromogenic derivative of calix[4]arene has been shown[6] to have moderately high Ca^{2+}/Na^+ selectivity (ratio of K_as 205) and Ca^{2+}/K^+ selectivity (ratio of K_as 24) in organic solvents. However, no chromogenic reagent has yet been reported which extracts Ca^{2+} from an aqueous phase into an organic phase, as required for an optical fibre sensor of a type which has been described,[7] with high selectivity as compared with Na^+ and K^+.

The simple chromogenic reagent **1** shows[7] modest selectivity for the extraction of Ca^{2+} as compared with K^+ and Na^+ and this, together with recent work on Na^+ and Li^+ selective regents,[2,3] suggested that a chromogenic reagent based upon a phenolic cryptand rather than a crown ether structure might show enhanced sensitivity and selectivity for Ca^{2+}. This has been found to be the case. The azophenol dye **2**, synthesised as outlined in Scheme 1, represents a relatively small structural variation upon the compounds **3** and **4** described in the earlier work but the extraction coefficients for cations of biological interest (Table 1) show a remarkable change in the Ca^{2+}/Na^+ selectivity. The new reagent **2** shows better selectivity for Ca^{2+}, as compared with both Na^+ and K^+, than the reagent[6] based upon calix[4]arene and Ca^{2+} is extracted efficiently into the organic phase. The ionophores **2** show no detectable extraction of Mg^{2+} in concentrations of up to 1 mol dm^{-3} from the aqueous phase, up to pH 9, into the organic phase.

Modification of the reagent **2** to improve the selectivity for Ca^{2+} is currently under investigation, meanwhile the reagent **2** appears to be the most suitable chromogenic reagent that is available for use in an optical fibre sensor for calcium and it may be prepared by a simple route from available starting materials. The change in Ca^{2+}/Na^+ selectivity in the series of compounds **2** and **4** is unexpected since the cavity size in all three cryptands is expected to be similar. This expectation is supported by molecular mechanics calculations for all three compounds and their sodium and calcium complexes. In all but one case the distances between hetero atoms (O and N) and the complexed cation (Na^+ or Ca^{2+}) is similar (O–M^+ 2.33–2.52 Å and N–M^+ 2.71–2.84 Å) in minimum energy conformations of the complexes based upon extensive conformational searching (the exception is the Na^+ complex of **2** which has one N–Na^+ distance of 3.27 Å).

The change in Ca^{2+}/Na^+ selectivity by a factor of $>10^6$ in this series of related chromoionophores appears to be largely a consequence of two factors. Na^+ binding increases in the series **2** to **4** as a result of greater preorganisation and greater screening of the Na^+ cation from the organic solvent phase. The decrease in Ca^{2+} binding in the same series **2** to **4** is probably due to a reduction in the exposure of the Ca^{2+} cation to the Cl^- counter ion required to neutralise the positive charge. Thus the Ca^{2+} complex of **2** leaves the cation completely exposed to the counter ion whereas it is almost totally screened in **4**. This effect is evidently more important than the increased preorganisation of the cavity which would



Scheme 1 Synthesis of chromogenic reagent **2**. *Reagents and conditions* (yields): i, MeOH, room temp., 3 d, reflux 24 h (47%); ii, $BH_3{\cdot}SMe_2$ in THF (99%); iii, 2,6-bisbromomethylanisole, MeCN, reflux 24 h (75%); iv, *p*-nitrophenyldiazonium chloride, NaOH, 0 °C (84%).

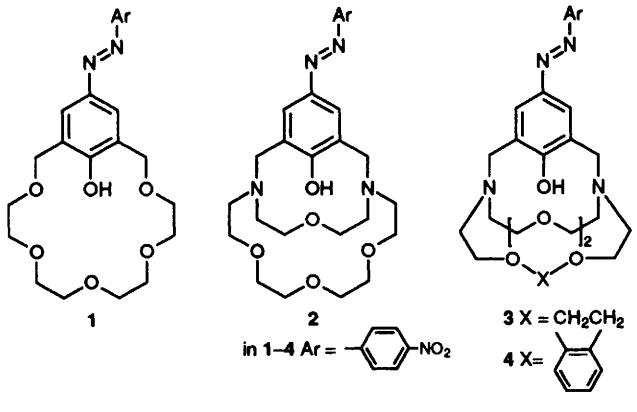


Table 1 Extraction coefficients and selectivities for chromoionophores **2**, **3** and **4**

Cation	$Log_{10}K_e^a$ for compounds		
	2	**3**[b]	**4**[b]
Ca^{2+}	−5.7[d]	−7.9	−9.4
Na^+	−8.5	−6.7	−5.8
K^+	−9.3	−9.3	−9.6

[a] For a solution of **2** at *ca.* 10^{-5} to 10^{-4} mol dm^{-3} in $CHCl_3$ and solutions of metal chlorides at 10^{-4} to 1 mol dm^{-3} in water generally using either a tris(hydroxy-methyl)methylamine–HCl buffer or a diethanolamine-HCl buffer. K_e is based upon changes in absorption at *ca.* 400 and *ca.* 550 nm for Na^+ and K^+, and *ca.* 400 and *ca.* 490 nm for Ca^{2+}. [b] Taken from refs. 2 and 3. [c] $K_e = [H^+]_{aq}[M^+Cl^-]_{org}/[M^+]_{aq}{\cdot}[ClH]_{org}$ (where the subscripts aq and org refer to the aqueous and organic phases respectively and ClH refers to the ionisable chromoionophore). [d] Best results were obtained using a diethanolamine–HCl buffer for concentrated solutions of $CaCl_2$.

have a similar effect upon both cations. The complexation of K^+, which does not fit well into the cavity and does not require ion-pairing, is very little affected by the structural changes. Thus the accommodation of a required counter ion can be an important factor in the design of ionophores.

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