# A Novel Pyridinium Betaine Derivative of a Phenolic Cryptand

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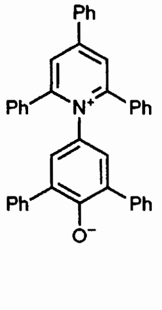
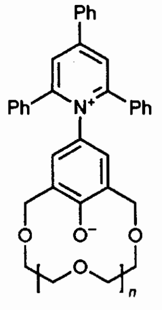
The novel pyridinium *N*-phenoxide betaine has been synthesised as its NaCl adduct **4** which has solvatochromic properties that are similar to those of the classic solvatochromic reagent **1** (Reichardt's dye); the derived hydrochloride salt **5** extracts $Na^+$ highly selectively from aqueous solutions into dichloromethane to form the purple NaCl adduct **4**.

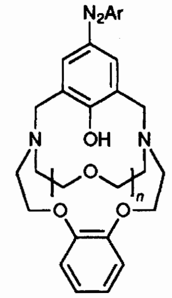
Pyridinium *N*-phenoxide betaine dyes, such as **1**, have been shown, primarily through the work of Reichardt and his coworkers,[1] to have a long wavelength charge transfer absorption band. The position and intensity of this band are dependent upon solvent polarity (solvatochromism) and surface charge density of added cations (halochromism).[2] Since charge separation in the betaine **1** is reduced in the excited state the shifts are hypsochromic (to shorter wavelength) with increasing solvent polarity or in the presence of metal cations of increasing surface charge density as in the



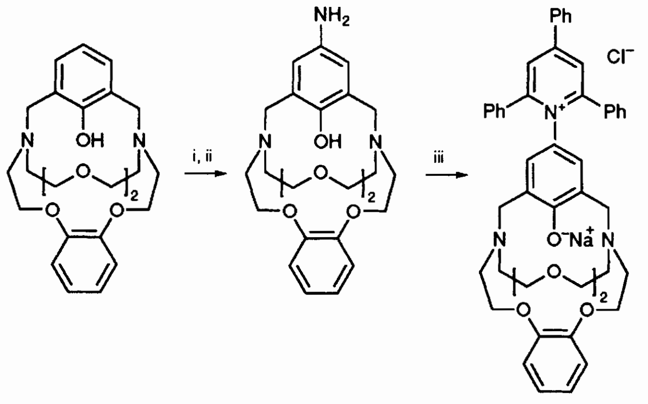
**1**



**2** $n$ = 2, 3 or 4



**3** $n$ = 1 or 2



**4**

**Scheme 1** Synthesis of phenolic cryptand salt **4**. *Reagents and conditions*: i, $HNO_3$, $NaNO_2$, $CHCl_3$–$H_2O$; ii, $H_2$, Pd–C, MeOH; iii, 2,4,6-triphenylpyrylium tetrafluoroborate, NaOAc, MeOH; extraction into 3 mol dm$^{-3}$ HCl followed by neutralisation ($NaHCO_3$), extraction into $CH_2Cl_2$, and washing with aqueous NaCl.

sequence of physiologically important cations $K^+$, $Na^+$, $Li^+$, $Ca^{2+}$ and $Mg^{2+}$.

The classic example **1** of this group of dyes gives rise to the widely used $E_T(30)$ scale[1] for solvent polarity. A range of structural variations of the reagent **1** have been reported including the crown ether modified dyes **2** which were described[3] in a recent publication. The dyes **2** show enhanced negative halochromism as compared with **1** and show some cation selectivity in the formation of complexes in a single solvent phase. However in two-phase systems, such as water–dichloromethane, although the crown ether derivatives **2** largely remain in the organic phase, cation extraction from the aqueous phase is accompanied[4] by a pronounced decrease in absorbance which is only slightly cation-selective, although it is more marked for cations with a high surface charge density such as $Mg^{2+}$. This effect is possibly a consequence of the residual hydration shell of the extracted cation since it appears to be absent[3] from cation complexation in a single-phase system. The dyes **2** do not show the selectivity required for sensing cations in biological samples but it was evident that the incorporation of a selective ionophore into the betaine structure might give a product with the required properties. The recent discovery[5] that the phenolic cryptand dyes **3** have very high selectivity suggested that analogous betaine dyes would be appropriate.

A betaine of this type was prepared as the NaCl adduct **4** using the route outlined in Scheme 1, but conventional deprotonation of the hydrochloride salt **5** failed to give a stable pyridinium betaine **6** (compounds **4** and **5** were characterised by MS, $^1H$ and $^{13}C$ NMR and elemental analysis of crystalline solvates). However reaction of **5** with sodium hydrogen carbonate gave the sodium chloride adduct **4** of the betaine **6** as a purple crystalline solid which was readily purified. The betaine **6** could be generated as a solution in propan-2-ol and other solvents by reaction of the salt **5** with tetramethylammonium hydroxide.

The salt **4** showed solvatochromic properties, which are reported in Table 1. The absorption spectrum of the sodium salt **4** in acetonitrile ($\lambda_{max}$ 544 nm, ε 3050) is rather similar to

**Table 1** Halochromism and solvatochromism of salt **4** and betaines **2** ($n$ = 3) and **6**

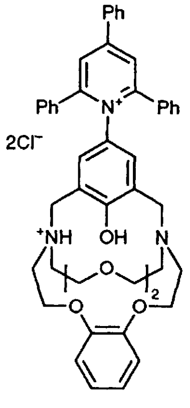
| | Charge transfer band, $\lambda_{max}$/nm | | | | Charge transfer band, $\lambda_{max}$/nm | | |
|---|---|---|---|---|---|---|---|
| Solvent[a] | **2** ($n$ = 3) | **6** | **4** | Solvent[a] | **2** ($n$ = 3) | **6** | **4** |
| Water | 433 | | 394 | $Me_2SO$ | 603 | | 548 |
| MeOH | 477 | | 486 | $Me_2CO$ | 620 | 680 | 556 |
| EtOH | 484 | | 493 | $ClCH_2CH_2Cl$ | 643 | | 582 |
| Pr$^n$OH | 506 | 606 | 500 | $CH_2Cl_2$ | 647 | | 580 |
| Bu$^n$OH | 512 | 626 | 504 | Pyridine | 663 | 736 | 580 |
| Pr$^i$OH | 532 | 666 | 486 | $CHCl_3$ | 668 | | 518 |
| Bu$^s$OH | 545 | 644 | 486 | $MeCO_2Et$ | | 702 | 544 |
| MeCN | 588[b] | 680 | 544 | Tetrahydrofuran | | | 554 |

[a] Solvents are listed in a sequence of increasing $E_T(30)$ values. [b] In this solvent the corresponding $Na^+$ complex has $\lambda_{max}$ 464 nm.

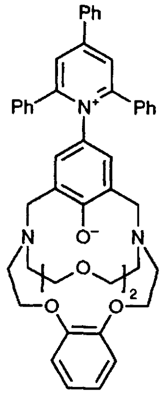
**Table 2** Extraction coefficients[a] and selectivities for chromogenic reagents **3** ($n$ = 2) and **5**

| | $\log_{10}K_e$, cryptand **3** ($n$ = 2) | | | | $\log_{10}K_e$, cryptand **5** | | | |
|---|---|---|---|---|---|---|---|---|
| | $Li^+$ | $Na^+$ | $K^+$ | $Ca^{2+}$ | $Li^+$ | $Na^+$ | $K^+$ | $Ca^{2+}$ |
| pH 7.0 | | −5.8 | | | | −6.1 | | |
| pH 8.0 | | −5.8 | | | | −6.3 | | |
| pH 9.0 | −9.5 | −5.8 | −9.6 | −9.4 | −9.3[b] | −6.5 | | |
| pH 10.5 | | | | | | (−6.5) | <−11.3[c] | *ca.* −10.6[d] |

[a] $K_e$ is defined as in ref. 5 for **3** and as the equilibrium constant for the two phase process: $(\mathbf{6}\text{–H})^+ \; M^{n+} \rightleftharpoons \mathbf{6}\cdot M^{n+} + H^+$. [b] Based upon the similar absorption intensities for extraction of 1 mol dm$^{-3}$ $Li^+$ (absorbance at 536 nm) and $10^{-3}$ mol dm$^{-3}$ $Na^+$ (absorbance at 570 nm). [c] Based upon similar absorption intensities for extraction of 1 mol dm$^{-3}$ $Ca^{2+}$ (absorbance at 474 nm) and $5 \times 10^{-5}$ mol dm$^{-3}$ $Na^+$ (absorbance at 570 nm). [d] Based upon similar absorption intensities at 570 nm for extraction of 1 mol dm$^{-3}$ KCl (99.99% purity) and $10^{-5}$ mol dm$^{-3}$ $Na^+$.



**5**



**6**

that of the dyes **2** in the same solvent[3] but the spectrum of the betaine **6** in propan-2-ol ($\lambda_{max}$ 666 nm, ε *ca.* 3000), a solvent with a moderately high value of $E_T(30)$ [$E_T(30)$ 48.6 kcal mol$^{-1}$; 1 cal = 4.184 J], shows a significant shift to longer wavelength as compared with the betaines **2** ($\lambda_{max}$ 532–537 nm) in the same solvent, presumably a consequence of the phenolate oxygen lying, at least in part, in the environment provided by the surrounding cryptand system possibly analogous to tetrahydrofuran [$E_T(30)$ 37.4 kcal mol$^{-1}$]. As expected the betaine **6** is solvatochromic but it could only be generated in a limited range of solvents. The negative halochromism due to $Na^+$ complexation is very pronounced with differences in $\lambda_{max}$ for the salt **4** and the betaine **6** ranging from 106 to 180 nm; details are reported in Table 1.

Salts analogous to **4** were not formed by other alkali metal salts in accord with the expected cation selectivity[5] of the phenolic cryptand system. This selectivity was further illustrated by extraction experiments using the salt **5** in a two phase system (aqueous tris buffer at pH 7–10.5 and dichloromethane). The formation of the salt **4** in the organic phase was monitored from its absorption spectrum ($\lambda_{max}$ 570 nm); the values of the derived extraction coefficient $K_e$ (Table 2) may be compared with those of the dye **3** ($n = 2$). The $Na^+$ complex **4** has a relatively high absorbance (ε *ca.* 1500) even in the wet organic phase suggesting that the hydration shell of the cation is absent in the complex, in contrast with the complexes of the crown ether derivatives **2** formed under similar conditions. The extraction of $K^+$ and $Ca^{2+}$ is negligible in the pH range 7–9 but $Li^+$ is extracted to a small extent at pH 9 ($\log_{10} K_e$ *ca.* −9.3). The $Li^+$ salt has an absorption spectrum ($\lambda_{max}$ 536 nm) that is consistent with the expected greater negative halochromism of the $Li^+$ cation as compared with $Na^+$. At pH 10.5 there is evidence for slight extraction of $Ca^{2+}$ and the $Ca^{2+}$ salt has an absorption spectrum ($\lambda_{max}$ 474 nm) which shows the expected large hypsochromic shift as compared with $Li^+$ and $Na^+$; the absorbance for $Ca^{2+}$ at 1 mol dm$^{-3}$ in the aqueous phase is comparable with that given by $4 \times 10^{-5}$ mol dm$^{-3}$ $Na^+$. There is also a slight response from 1 mol dm$^{-3}$ $K^+$ at pH 10.5, comparable with that from $10^{-5}$ mol dm$^{-3}$ $Na^+$, but this may just be a consequence of $Na^+$ as an impurity in the sample of KCl used for the experiment. These results of extraction experiments are summarised in Table 2 in terms of estimated values of $\log_{10} K_e$. The relative selectivities, based upon aqueous solutions of the chloride salts, for $Na^+$ as compared with other cations of physiological importance are $Na^+/Li^+$ $10^3$, $Na^+/K^+ > 10^5$, $Na^+/Ca^{2+}$ *ca.* $2 \times 10^4$, and $Na^+/Mg^{2+}$ is too large to be measured.

This exceptional selectivity and sensitivity of the salt **5** towards $Na^+$, combined with the solvatochromic properties of the $Na^+$ complex **4**, indicate that it is a novel chromogenic reagent for $Na^+$. Its behaviour contrasts with that of other highly selective chromogenic reagents[6] in that it also indicates the polarity of the environment of the complexed cation.

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