Synthesis, characterisation and metal ion binding properties of crown ethers incorporating 4,5-dioxyxanthones

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An efficient preparation of 4,5-dihydroxyxanthone, **5**, is described, and its incorporation into crown ethers with 18-, 21- and 24-membered macrocyclic arrays, **3** ($n = 3$, 4 and 5), and a model compound, 4,5-diethoxyxanthone, **10**. Metal ion complexation of the crowns causes a strong quenching of the highly fluorescent 4,5-diethoxyxanthone chromophore. Binding constants for complex formation with sodium, potassium, and caesium ions in methanolic solution have been measured by spectrofluorimetric and conductimetric methods and range from $<10^2$ for **3** ($n = 5$) binding sodium ion to 4.1×10^3 for **3** ($n = 4$) binding potassium ion. The behaviour of the 4,5-dioxyxanthones in aqueous sulfuric acid mixtures has been examined by UV spectroscopy and treatment of the data by the excess acidity method yields $-2.6 < \mathrm{p}K_\mathrm{a} < -2.3$ for the conjugate acids with $0.33 < m^* < 0.40$. The behaviour of the crowns containing 4,5-dioxyxanthones is compared with that of analogues containing 1,8-dioxyxanthones.

Introduction

The structure of xanthone (xanthen-9-one) (Fig. 1) and its photophysical properties suggest that its incorporation into crown ethers or related structures would yield ionophores with a number of desirable features. X-Ray crystallography[1] and electron diffraction[2] reveal a planar structure, and its dipole moment (3.11 D)[3] is consistent with a contributing dipolar form. Appropriate annulation of a polyethylene oxide chain could yield macrocycles with either xanthone oxygen in a position to participate in binding to guest species. Xanthone itself shows a double phosphorescence[4] which might be modified in the crowns and responsive to ion binding in ways dependent on the mode of incorporation of the xanthone.

We have already described the preparation,[5] structures,[6] and some properties of macrocycles with 18-, 21- and 24-membered rings based on 1,8-dioxyxanthone, **1** ($n = 3$, 4, 5). These have also been converted to the corresponding xanthydrols, **2**, and equilibria between these alcohols and their derived carbocations have been measured. The 1,8-dioxyxanthone-based crowns were not strongly fluorescent themselves, but showed strong fluorescence enhancement and appearance of a long lived delayed fluorescence upon binding to alkaline earth cations, especially Ba^{2+}, which make them suitable for construction of multi-sensory devices.[7] In this series, the ketonic oxygen of the xanthone residue lies within the macrocycle, and has near ideal placement and polarity for involvement in metal ion complexation (Fig. 2), and its close association with a bound metal ion is clearly a factor in the desirable photophysical behaviour of these crowns.

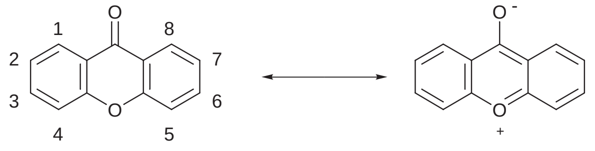


Fig. 1 Structure and contributing canonical forms of xanthone.

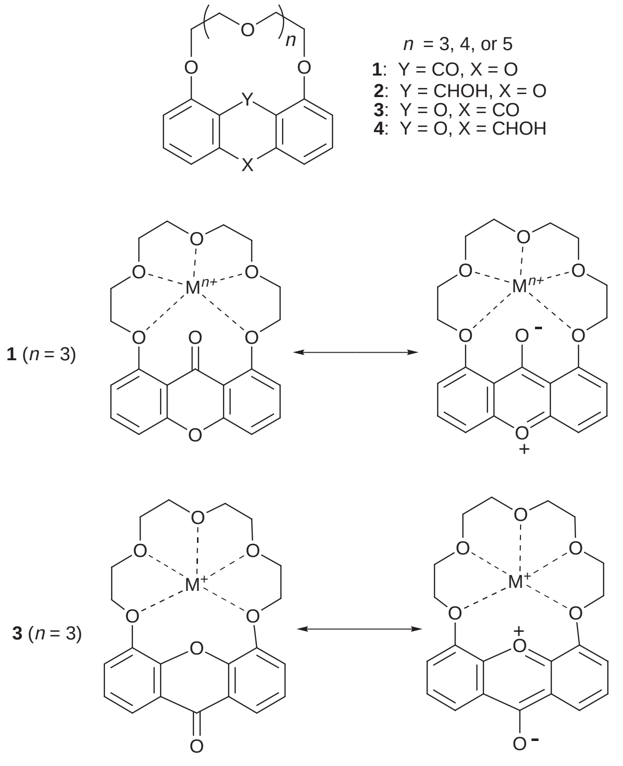
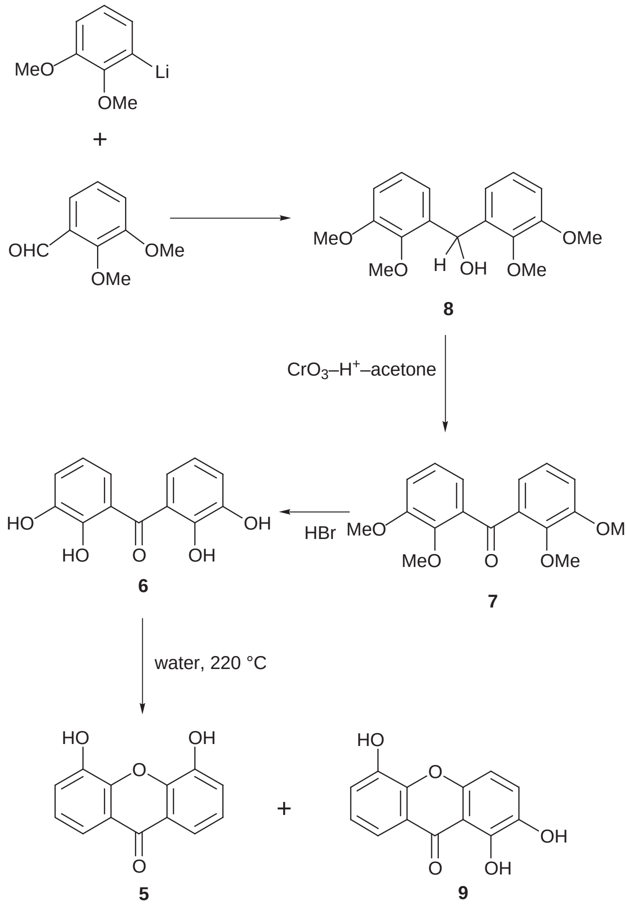


Fig. 2 Structures of crown ethers incorporating 1,8- and 4,5-dioxyxanthones and interactions in binding to metal ions.

Attachment of polyethylene oxide chains to the xanthone nucleus *via* its 4- and 5-positions would yield macrocycles incorporating the more electropositive ethereal xanthone oxygens in the crown macrocycle. This oxygen may be less basic than the carbonyl oxygen (and oxygens in simpler phenolic ethers) but the macrocycle thus formed would have the benefit of an uninterrupted set of –C–C–O– sequences. The consequences of such an arrangement on the binding properties and photophysical behaviour of such macrocycles in the presence and absence of metal ions is the topic of this paper, and we here describe the preparation and characterisation of 18-, 21- and 24-membered crowns incorporating the 4,5-dioxyxanthone residue, **3** (n = 3, 4 and 5).

Preparation and structures

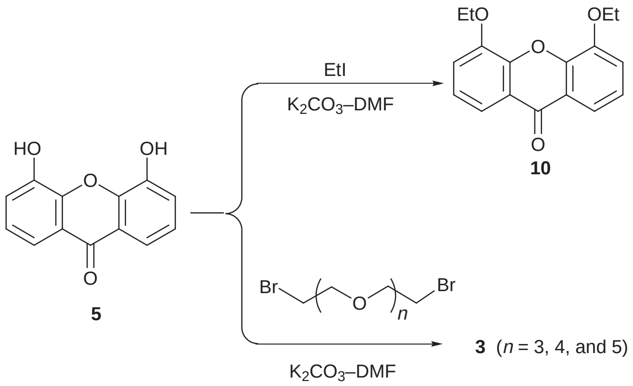
Synthesis is by attachment of an appropriate polyethylene oxide chain to 4,5-dihydroxyxanthone, **5** (Scheme 1). This is a known compound, first prepared by Finnegan and Merkel,[8] by heating 2,2′,3,3′-tetrahydroxybenzophenone **6** in water at 220–230 °C. This cyclization seemed promising, but a photo-Fries rearrangement employed by Finnegan and Merkel in their preparation of precursor **6** was low yielding and did not seem amenable to scale-up to give the amounts of 4,5-dihydroxyxanthone demanded by this work. We avoided this step by exploiting the directed lithiation of 1,2-dimethoxybenzene.[9] Coupling of the resulting organolithium with veratraldehyde yields 2,2′3,3′-tetramethoxybenzhydrol, **8**; Jones oxidation then provides 2,2′3,3′-tetramethoxybenzophenone, **7**, in high yield, and demethylation by hydrobromic acid yields the required cyclization precursor, **6**, efficiently (Scheme 1).



Scheme 1 Preparation of 4,5-dihydroxyxanthone.

First attempts to reproduce the hot water cyclizations[10] of Finnegan and Merkel did not cleanly yield the desired 4,5-dihydroxyxanthone, which is a profoundly intractable high melting (mp > 350 °C) solid. In small scale test reactions it was always the major product, but was accompanied by significant amounts of a second phenolic compound, separable as yellow crystals by sublimation from 4,5-dihydroxyxanthone. Mass spectrometry of the sublimate gave a molecular formula, $C_{13}H_8O_5$, its IR spectrum showed a band at 1649 cm^{-1}, and its ^{1}H NMR spectrum indicated the presence of one aromatic ring with three adjacent hydrogens and the other with two adjacent hydrogens. We speculated that this was a trihydroxyxanthone, probably **9**, arising from an air oxidation of one ring of the 2,2′,3,3′-tetrahydroxybenzophenone prior to cyclization. Formation of this by-product was almost completely suppressed when the reaction was run in buffered medium with hydroquinone added as an oxygen scavenger. Isolated yields of the 4,5-dihydroxyxanthone **5** were then greater than 90%, as a dark solid remaining after sublimation of all of the more volatile impurities. Further purification and characterisation was possible by conversion to its known diacetate.[8]

The alkylation of 4,5-dihydroxyxanthone with excess ethyl iodide in DMF with potassium carbonate provided a single detectable product, crystallising from ethanol as colourless needles, with a UV spectrum (methanol) showing maxima at 248 and 354 nm, and its IR spectrum showing a typical xanthone carbonyl stretching band at 1648 cm^{-1}. ^{1}H NMR spectroscopy confirmed the presence of ethoxy groups, and two doublets and a triplet (at 7.24, 7.30 and 7.91 ppm respectively) in the aromatic region, were consistent with the bis-*O*-alkylation in the anticipated 4,5-diethoxyxanthone **10**. The ^{13}C NMR spectrum showed the expected nine signals.



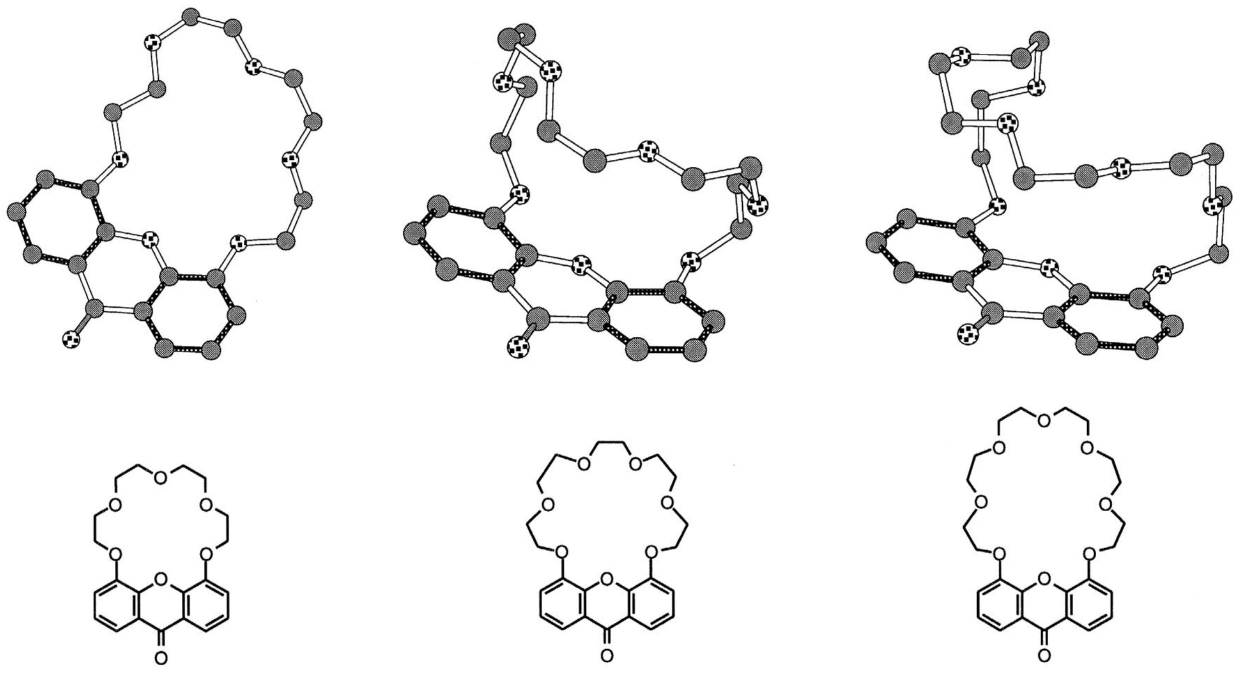
Scheme 2 Alkylations of 4,5-dihydroxyxanthone.

For preparations of the 18-, 21- and 24-membered rings, reactions with appropriate polyethylene dibromides in DMF were carried out following the pattern used earlier in cyclizations with 1,8-dioxyxanthone.[4] For preparation of 18- and 21-membered rings, the base was potassium carbonate. For the 24-membered ring, acceptable yields were only obtained with use of higher dilution, lower reaction temperature, and replacement of potassium carbonate by caesium carbonate. In all cases crystallised yields of macrocycle were over 40%. The aromatic regions of the ^{13}C and ^{1}H NMR spectra of these compounds were superimposable on that of 4,5-diethoxyxanthone, as were their UV spectra.

Attempts to produce crystals of **3** (n = 3, 4 or 5) or of **10** suitable for crystallography have not yet proved successful, but molecular mechanics calculations using the MM3 forcefield[11] (shown to reproduce well experimentally determined structural features in the 1,8-dioxyxanthone series[6]) have been carried out on all three crowns and the model 4,5-diethoxyxanthone. Minimum energy conformations and associated steric energies are shown in Fig. 3.

In 4,5-diethoxyxanthone **10**, the xanthone tricycle is planar, and the pendant ethyl groups are anti-coplanar to the central ring of the xanthone. There are, however, four low energy conformations (within 4.18 kJ mol^{-1} of global minimum) having different torsions about the exocyclic C–O bonds.

In the minimum energy conformation of **3** (n = 3), the xanthone is non-planar, with the central rings adopting a flattened boat conformation with an angle of 167° between the planes of the two benzenes of the xanthone. The sequences of torsion angles around bonds in the –O–C–C– repeating units in



3 ($n = 3$) $E_{\mathrm{steric}} = 206.6$ kJ mol^{-1} **3** ($n = 4$) $E_{\mathrm{steric}} = 231.7$ kJ mol^{-1} **3** ($n = 5$) $E_{\mathrm{steric}} = 256.1$ kJ mol^{-1}

Fig. 3 Minimum energy conformations of 4,5-dioxyxanthones and steric energies from molecular mechanics calculations.

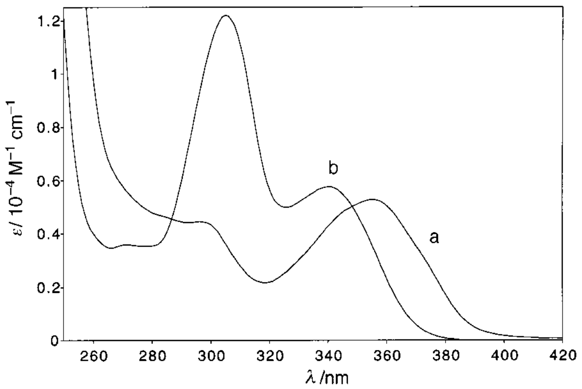


Fig. 4 UV spectra for methanol solutions of 4,5-diethoxyxanthone (trace a) and 1,8-diethoxyxanthone (trace b).

the polyethylene oxide parts of the macrocyclic array deviate from the ideal *anti–anti–gauche* sequence found in linear polyethylene glycols,[12] presumably reflecting the restrictions imposed by the xanthone structure on four contiguous bonds in each macrocycle. Seven additional low energy conformations are found and, notably, the next most stable conformation (0.7 kJ mol^{-1} above the global minimum) has a planar xanthone array and should be extensively populated at 25 °C. This pattern is repeated in the structures of **3** ($n = 4$) and **3** ($n = 5$) where the global minima have non-planar xanthones with interplane angles in the xanthone of 168° and 172° respectively, but in both cases there is a closely lying second structure with a planar xanthone array.

The xanthone arrays in all the 4,5-dioxyxanthone derivatives are more nearly planar than in the corresponding 1,8-dioxyxanthones, and differ from them in having energetically accessible conformations with planar xanthones. This presumably reflects the absence in the former of the >C=O group which would parallel C–O bond dipoles at adjacent 1- and 8-positions in the planar conformations of the latter.

Absorption spectra, luminescence spectra and excited-state lifetimes

The absorption spectra in methanol solution of the 4,5-dioxyxanthone crowns, **3** ($n = 3$, 4 and 5) and model compound **10** are very similar ($\lambda_{\mathrm{max}} = 355$ nm and $\varepsilon_{\mathrm{max}} = 5700$ M^{-1} cm^{-1}). All, however, differ markedly from the analogous 1,8-dioxyxanthone derivatives and Fig. 4 compares the UV spectra of corresponding compounds of each series.

Even more pronounced differences are found in the fluorescence spectra of the two different families of dioxyxanthone derivatives. In contrast to the 1,8-dioxyxanthone derivatives whose fluorescence intensity is very weak, all the 4,5-dioxyxanthone derivatives are strongly fluorescent even at room temperature ($\lambda_{\mathrm{max}} = 437$ nm, $\varphi_{\mathrm{em}} = 0.3$). For 1,8-dioxyxanthone derivatives and related crowns, the low fluorescence quantum yield was explained[7] in terms of ground state conformations (found in the X-ray crystal structures) containing a non-planar xanthone chromophore whose first excited state was a non-emitting n–π* state. Binding of the crowns incorporating 1,8-dioxyxanthones, **1** ($n = 3$, 4 and 5), to alkali earth cations yielded highly fluorescent complexes, and it was suggested that metal ion incorporation stabilised conformations containing planar xanthones whose lowest excited state is probably a π–π* state. As discussed earlier, molecular modelling shows that the most stable conformation of 4,5-diethoxyxanthone **10** incorporates a planar xanthone array, and that the crowns also can accommodate such arrays, so that the close similarity of the absorption and fluorescence spectra of **10** and **3** ($n = 3$, 4 and 5) reflects the close similarity in their xanthone chromophore structures. In the case of **10** and **3** ($n = 3$, 4 and 5), in deaerated solution, no delayed luminescence was observed (as was the case for the complexed 1,8-dioxyxanthone crown ethers) indicating that in the 4,5-dioxyxanthones the energy gap between the fluorescent lowest singlet state and the lower lying triplet state is higher, and cannot be overcome even at room temperature.

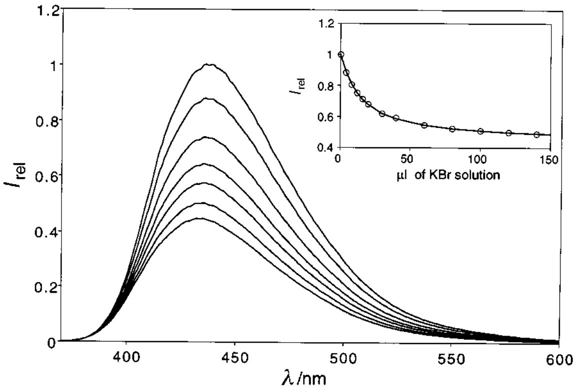


Fig. 5 Fluorescence quenching in response to addition of potassium bromide to a methanolic solution of **3** ($n = 3$).

Table 1 Stability constants and luminescence properties of complexes formed between 4,5-dioxyxanthone based crown ethers and sodium, potassium and caesium ions in methanol at 25 °C

4,5-Dioxyxanthone	Ion	K_{ass}/M^{-1}	I_{rel}	t/ns
10	Na^+		100	12.0
3 ($n = 3$)	Na^+	0.8 (±0.3) × 10^3	46 (±1)	5.0
3 ($n = 4$)	Na^+	0.3 (±0.1) × 10^3	30 (±1)	3.0
3 ($n = 5$)	Na^+	<0.2 × 10^3		
10	K^+		100	12.0
3 ($n = 3$)	K^+	2.0 (±0.1) × 10^3	30 (±1)	5.0
3 ($n = 4$)	K^+	4.1 (±0.1) × 10^3	39 (±1)	4.5
3 ($n = 5$)	K^+	1.6 (±0.3) × 10^3	36 (±1)	4.0
10	Cs^+		100	12.0
3 ($n = 3$)	Cs^+	1.4 (±0.3) × 10^3	32 (±1)	3.0
3 ($n = 4$)	Cs^+	2.6 (±0.2) × 10^3	25 (±2)	2.0
3 ($n = 5$)	Cs^+	3.4 (±0.2) × 10^3	38 (±2)	3.0

Binding to metal ions

The effects of added metal ions on the ^1H NMR spectra of methanolic solutions of **3** ($n = 3$) were briefly examined. This crown incorporates an 18-crown-6 and might be expected to bind K^+ and Ba^{2+}. Even with large excesses of potassium or barium bromide, however, changes in chemical shifts and line shapes were difficult to detect and measure. Effects of added ions on the UV spectra of methanolic solutions were also small, and neither of these spectroscopic methods was well adapted to quantitative measuring of the binding constants for these crowns.

Stronger effects were observed on the fluorescence spectra, where the intensity of the band showed a strong quenching upon addition of sodium, potassium or caesium bromide, accompanied by a reduction in the fluorescence lifetime. The dependence of fluorescence intensity on the amount of metal ion added to a methanol solution of the crown (as exemplified in Fig. 5) followed an isotherm anticipated for 1 : 1 binding[13] of metal ion and crown, and we associate the quenching with complex formation [eqn. (1)].

$$\text{Crown} + M^{n+} \underset{}{\overset{K_{ass}}{\rightleftharpoons}} [\text{Crown} : M]^{n+} \qquad (1)$$

Values of association constants extracted from the curves are also presented in Table 1 and were in excellent agreement with measurements using conductivity changes observed on the addition of the crowns to methanolic metal ion solutions for both bromides and perchlorates of these ions.

The fluorescence spectra of the crowns were not affected by addition of the alkali earth metal ions; neither were changes observed in the conductivity experiments, showing that the constants for binding between **3** ($n = 3$, 4 and 5) and the alkali earth metal ions are below 200 M^{-1}.

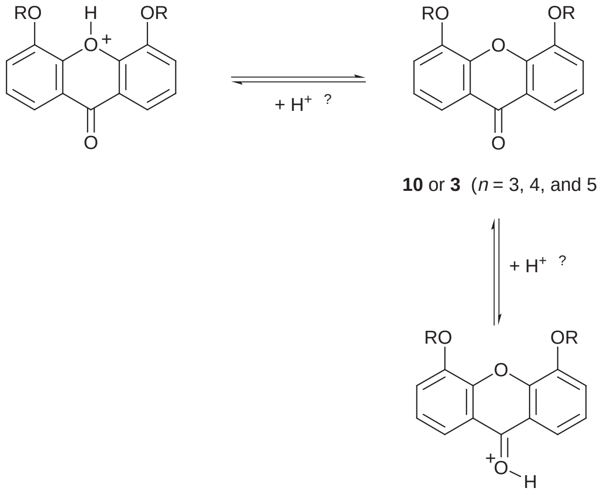


Fig. 6 Possible protonation sites in 4,5-dioxyxanthones.

The decrease in fluorescence intensity of the crown ethers upon complexation can be attributed to a change in the structure of the xanthone chromophore induced by the presence of a positive charge near the ethereal oxygen atom of the central xanthone ring. Co-ordination of the metal ion at this oxygen would destabilise the planar conformation in which through-conjugation from oxygen lone pairs to the xanthone carbonyl places positive charge on that atom, and enhances folding of the xanthone with production of a non-emitting n–π* first excited state. The effect of metal ion binding on the chromophore is thus exactly the opposite to that observed in the 1,8-dioxyxanthone based crowns.

The 4,5-dioxyxanthones **3** ($n = 3$, 4 and 5) may be regarded as modified dibenzo-annulated crown ethers, and we briefly compare their binding constants with those of the familiar dibenzo-18-crown-6, dibenzo-21-crown-7 and dibenzo-24-crown-8.[14] The 4,5-dioxyxanthones are less effective ligands for sodium (ionic radius = 0.95 Å) by a factor of at least 10. With larger potassium and caesium ions (ionic radii = 1.33 and 1.69 Å) binding constants for the same ring sizes are again less for the 4,5-dioxyxanthones but by less than a power of ten. This reduction is surprisingly small in view of the unfavourable polarity of the ethereal xanthone oxygen, and the rigidity associated with restriction of no less than seven adjacent atoms of the macrocycle by their incorporation into the xanthone tricycle.

Acid–base behaviour

Dilute acid solutions of the 4,5-dioxyxanthone crowns, **3** ($n = 3$, 4 and 5), and model compound, **10**, are colourless, showing characteristic UV absorptions with λ_{max} at 250 (log $\varepsilon = 4.42$), 292 (shoulder, 3.45) and 362 (3.50) nm, resembling the spectra in methanol solution shown earlier. Solutions in strong acid (aq. 90% H_2SO_4) are yellow, and the spectra develop new absorptions at $\lambda_{max} = 272$ (4.55), 330 (3.99), 366 (shoulder, 3.56) and 440 (3.42) nm. Under these conditions also, the fluorescence band of the 4,5-dioxyxanthone crowns, **3** ($n = 3$, 4 and 5), and of the model compound, **10** are no longer present, while a lower energy band ($\lambda_{max} = 552$ nm) appears. Dilution and extraction of the acid solutions recovers the xanthones, and we associate the colour changes with formation in solution of their conjugate acids.

Protonation of xanthone itself, believed to be on the carbonyl oxygen, yields intensely fluorescent ions.[15] The behaviour of the 4,5-dioxyxanthone derivatives thus appears atypical, raising the possibility that their protonation involves the ethereal rather than the carbonyl oxygen of the xanthone (Fig. 6). Certainly the pendant oxygens positioned *meta* relative

Table 2 pK_a and m^* values for the 4,5-dioxyxanthones, **3** ($n = 3$, 4 and 5) and model compound, **10**, using the excess acidity function

4,5-Dioxyxanthone	m^*	pK_a
10	0.40	−2.6 (±0.2)
3 ($n = 3$)	0.35	−2.5 (±0.2)
3 ($n = 4$)	0.33	−2.3 (±0.2)
3 ($n = 5$)	0.40	−2.5 (±0.2)

to the carbonyl group are expected to reduce its basicity [σ_m (MeO) = +0.10],[16] by induction, while possibly providing additional internal solvation to stabilise a proton co-ordinated at the ethereal oxygen.

Spectra were examined in a series of sulfuric acid mixtures of varying strength, and extents of protonation were followed by measuring the absorption at 272 nm for solutions of crown or model compound. Plots of log I against acid strength as measured by H_o[17] were linear, but had slopes between 0.4 and 0.6, showing that these ketones were not behaving as Hammett bases.[18] The data were therefore treated using the excess acidity (X) method[19] to obtain acidity constants, K_a, for the conjugate acids (BH^+) referred to dilute aqueous solution [eqn. (2)]. The appropriate relationship, eqn. (3), uses both m^*

$$BH^+ \underset{}{\overset{K_a}{\rightleftharpoons}} B + H^+ \qquad (2)$$

$$\log I - \log c_{H^+} = m^*X + pK_a \qquad (3)$$

and pK_a as parameters to be determined, and the values obtained are presented in Table 2.

In practical terms these compounds require *ca.* 65% sulfuric acid for half protonation. They have $-2.6 < pK_a < -2.3$, and $0.33 < m^* < 0.40$, and show no trend that we can discern between ring size and basicity. They are considerably more basic than xanthone itself (pK_a reported as −4.81[2]), and are less basic than the corresponding compounds of the 1,8-dioxyxanthone series, **1** ($n = 3$, 4 and 5) where $-2.37 < pK_a < -1.78$ and m^* values are close to 1. The difference in values of m^* between the series indicates significantly different demands for solvation around the protonation site, and may be consistent with a change in the protonation site. However, even with a series of substituted benzophenones[20] where carbonyl protonation is expected to occur constantly on carbonyl oxygen, wide variations in values of m^* have been found, and a conclusion has not yet been reached.

Conclusions

The search for new chemosensors presents one of the more challenging of current chemical problems. Luminescent sensors have particular advantages in their sensitivity and ease of measurement.[21] The 4,5-dioxyxanthone base crowns described here and the isomeric 1,8-dioxyxanthones described earlier[7] have both shown desirable behaviour. Although the binding of the 4,5-dioxyxanthones to potassium ions was disappointingly small, the absence of binding to the alkali earth ions of the same ionic size is a useful selectivity. Indeed, there is a complementarity between the binding and luminescence responses of the 1,8-dioxyxanthone series and the 4,5-dioxyxanthones which may be exploitable in the construction of multi-sensory devices to yield concentrations of these ions in complex mixtures.[22]

Experimental

Proton NMR spectra were recorded on a Varian Gemini-200 (200 MHz) spectrometer or a Varian Unity-500 (500 MHz) spectrometer, and carbon-13 NMR spectra were recorded on a Brüker AC-300 (75 MHz). Infrared spectra were recorded on an ATI Mattson Genesis Series FTIR and were run as films evaporated from deuteriated chloroform or as KBr discs. Ultraviolet absorption spectra were recorded on a Hewlett Diode-array Spectrophotometer (Manchester) or a Perkin-Elmer λ16 (Bologna). The fluorescence lifetimes (uncertainty ±5%) were obtained with an Edinburgh single-photon counting apparatus, in which the flash lamp was filled with D_2. In order to allow comparison of emission intensities, corrections for instrumental response, inner filter effects, and phototube sensitivity were performed.[23] A correction for differences in the refraction index was introduced when necessary. Mass spectra were recorded on a Kratos MS25 or a Fisons VG Trio 2000. Modes of ionisation are indicated as follows: electron impact (EI), positive chemical ionisation (+CI/NH_3) and fast atom bombardment (FAB). Melting points were recorded on a Kofler heated stage microscope and are uncorrected. All temperatures are quoted in degrees Celsius (°C). Thin layer chromatography (TLC) was carried out on Polygram Sil G/UV_{254} 0.25 mm silica gel plates with solvent systems as indicated. Analytical HPLC was carried out using: Waters 510 HPLC pump, Waters 'Z' module with 4 μ ODS Nova-Pak 100 × 8 mm column, Perkin-Elmer LC480 Diode Array System with detection at 255 nm, premixed degassed solvent system 75:25 MeOH–H_2O, flow rate 2 ml min^{-1}, injections as stated. Elemental analyses were carried out at the micro-analytical laboratories at the University of Manchester under the direction of Mr M. Hart.

2,2′,3,3′-Tetramethoxydiphenylmethanol, 8

1,2-Dimethoxybenzene (49.24 g; 0.357 mol) was dissolved in dry THF (500 ml) in a two litre round-bottomed flask fitted with a septum cap under nitrogen and with stirring.[8] The reaction vessel was cooled to −78 °C and *n*-butyllithium solution (199 ml of 1.61 M solution in hexane; 0.32 mol) was added by syringe. The reaction was then stirred at room temperature for 3 hours, before cooling to −78 °C and adding dropwise a solution of 2,3-dimethoxybenzaldehyde (53.12 g, 0.32 mol) in THF (150 ml). The reaction was stirred at room temperature overnight until it appeared clear orange in colour, then hydrolysed by addition of water (200 ml). The organic phase was separated and the aqueous phase extracted with ether (3 × 50 ml). The combined organic phases were dried (Na_2SO_4) and evaporation under reduced pressure then gave a viscous orange liquid, (84.06 g, 86%) (Found: C, 67.7; H, 6.2%. $C_{17}H_{20}O_5$ requires C, 67.5; H, 6.0%); λ_{max} (CH_2Cl_2)/nm (log ε), 274 (3.72), 316 (3.01); ν_{max} ($CDCl_3$)/cm^{-1} 3448, 2937, 2834, 1266, 1082, 1006, 944, 791, 751; δ_H (200 MHz; $CDCl_3$) 3.07 (1H, d, J 6), 3.70 (6H, s), 3.85 (6H, s), 6.35 (1H, d, J 6), 6.8–7.1 (6H, m); *m/z* (EI) 304 (M^+, 45), 273 (26), 165 (100), 151 (73%); (+CI/NH_3) 304 (29), 287 (100), 165 (11%).

2,2′,3,3′-Tetramethoxybenzophenone, 7

Crude 2,2′,3,3′-tetramethoxydiphenylmethanol (70 g) was dissolved in dry acetone (700 ml). The reaction was cooled to 5 °C and Jones reagent (0.27 g CrO_3 per ml aq. H_2SO_4)[24] was added dropwise until a persistent orange colour was seen (~60 ml). Excess oxidant was destroyed by addition of propan-2-ol, the reaction mixture was filtered, and the chromium residues washed with ether. The combined organics were then stirred with saturated aqueous sodium bicarbonate solution, before separation, drying over Na_2SO_4, and evaporation. The crude product was recrystallized twice from absolute ethanol to produce the 2,2′,3,3′-tetramethoxybenzophenone in fine white needle shaped crystals (40.0 g, 41%, based on 2,3-dimethoxybenzaldehyde in first stage); mp 98 °C (Found: C, 67.2; H, 6.0%. $C_{17}H_{18}O_5$ requires C, 67.5; H, 5.96%); λ_{max} (CH_2Cl_2)/nm (log ε), 258 (4.33), 306 (3.86); ν_{max} ($CDCl_3$)/cm^{-1} 1665, 1473, 1266, 1002, 783, 755; δ_H (200 MHz; $CDCl_3$) 3.60 (6H, s), 3.90 (6H, s), 7.0–7.1 (6H, m); *m/z* (EI) 302 (M^+, 25), 165 (78), 151 (100%); (+CI/NH_3) 320 (3), 304 (35), 303 (100), 287 (20%).

2,2′,3,3′-Tetrahydroxybenzophenone, 6

To 2,2′,3,3′-tetramethoxybenzophenone, **7** (1.0 g, 3.3 mmol) (in a 50 ml round-bottomed flask) was added glacial acetic acid (15 ml), with stirring, followed by 60% HBr (10 ml) and the mixture was heated under reflux for 6 hours. The reaction was then cooled and a red precipitate which had formed was filtered off. Water (35 ml) was then added and the mixture extracted with chloroform until the extracts were almost colourless. The combined organic extracts were dried (Na$_2$SO$_4$), and the solvent evaporated to leave a greenish viscous liquid which formed bright yellow crystals on addition of water (20 ml) and cooling. (0.757 g, 93%); mp 120–121 °C (lit.[7] 121–122 °C) (Found: C 62.9; H, 3.94%. C$_{13}$H$_{10}$O$_5$ requires C, 63.4; H, 4.06%); λ_{max} (abs. EtOH)/nm (log ε), 232 (3.88), 280 (3.97), 354 (3.44); ν_{max} (CDCl$_3$)/cm^{-1} 3550–3100, 1625, 1580, 1451, 1248, 1226, 852, 748; δ_H (200 MHz; CDCl$_3$) 5.80 (2H, s), 6.88 (2H, t, *J* 9), 7.22 (4H, m), 10.70 (2H, s); *m*/*z* (EI) 246 (M$^+$, 9), 137 (51), 136 (36%); (+CI/NH$_3$) 264 (6), 247 (51), 134 (100), 117 (40%).

4,5-Dihydroxyxanthone, 5

A buffer of ionic strength 0.01 was prepared from acetic acid (2.4 g, 2.28 ml, 0.04 mol), and sodium acetate (0.82 g, 0.01 mol), placed in a 100 ml volumetric flask and diluted with water up to the mark. 2,2′,3,3′-Tetrahydroxybenzophenone, **6** (1.0 g, 4.07 mmol), hydroquinone (1.0 g, 9.08 mmol), and the buffer (8 ml) were added to a stainless steel bomb and blanketed with nitrogen. The bomb was sealed and heated for 17 h at 220 °C. After cooling, the bomb was opened, the contents emptied into a round-bottomed flask and water evaporated under reduced pressure. The reaction mixture was then sublimed (170 °C, 15 mmHg, for 30 minutes) to remove hydroquinone, leaving a dark gritty product (0.87 g, 94%); mp >320 °C (lit.[8] >350 °C); ν_{max} (KBr)/cm^{-1} 3341, 2922, 1645, 1603, 1499, 1466, 1292, 1153, 1075, 1025, 738; δ_H (500 MHz; DMSO-d$_6$) 7.38 (2H, t, *J* 8), 7.44 (2H, d, *J* 8), 7.70 (2H, d, *J* 8); *m*/*z* (EI) 229 (14), 228 (100), 200 (10), 171 (7%); (+CI/NH$_3$) 245 (14), 230 (11), 229 (100%). Crude 4,5-dihydroxyxanthone, **5** (344 mg) was dissolved in methanol (250 ml) in a conical flask. Activated charcoal (25 mg) was added and the mixture refluxed for 5 minutes. The solution was filtered hot through celite, and the methanol was removed *in vacuo* yielding a light green product (304 mg, 88%).

In initial reactions run on *ca.* 0.1 g samples of **6** in unbuffered medium, without added hydroquinone, sublimation at 170 °C, 15 mmHg, for 30 minutes yielded yellow crystals of *1,2,5-trihydroxyxanthone*, **9**, ν_{max} (KBr)/cm^{-1}; δ_H (500 MHz; CDCl$_3$) 7.69 (<1H, d, *J* 9), 7.51 (2H, d, *J* 9), 7.35 (1H, t, *J* 8), 7.08 (1H, d, *J* 8); *m*/*z* (EI) 244 (5).

4,5-Diacetoxyxanthone

Decolourised 4,5-dihydroxyxanthone, **5** (0.200 g, 0.88 mmol), acetic anhydride (10 ml) and pyridine (1 ml) were refluxed for 5 h. Evaporation under vacuum yielded crystals which were collected by filtration, rinsed with ethanol and dried under vacuum (160 mg, 58%); mp 262–270 °C (lit.[8] 263–268 °C); λ_{max} (abs. EtOH)/nm (log ε), 246 (3.79), 268 (3.7), 338 (3.69); ν_{max} (CDCl$_3$)/cm^{-1} 2918, 2850, 1764, 1672, 1482, 1479, 1371, 1192, 1022, 876, 753; δ_H (200 MHz; CDCl$_3$) 2.44 (6H, s), 7.40 (2H, t, *J* 8), 7.53 (2H, d, *J* 7.5), 8.22 (2H, d, *J* 7.5); δ_C (75 MHz; CDCl$_3$) 20.55, 123.06, 123.90, 124.31, 128.18, 139.20, 147.70, 168.0, 175.98; *m*/*z* (EI) 312 (M$^+$, 4), 270 (15), 229 (13), 228 (100), 171 (5%); (+CI) 330 (30), 313 (100), 285 (5), 29 (7), 228 (9%).

4,5-Diethoxyxanthone, 10

Decolourised, crude 4,5-dihydroxyxanthone, **5** (0.27 g, 1.18×10^{-3} mol), anhydrous potassium carbonate (0.54 g, 3.87×10^{-3} mol), DMF (70 ml) and iodoethane (0.34 ml, 4.77×10^{-3} mol) were refluxed under nitrogen for 2.5 h. After cooling, the solution was filtered, diluted with water (50 ml) and extracted with chloroform. Drying (Na$_2$SO$_4$) and evaporation yielded a brown crude product which was taken up in THF and passed through a short column of silica. Evaporation and recrystallisation from ethanol yielded fine beige needles, (0.15 g, 45%); mp 204–206 °C (Found: C, 71.88; H, 5.63%. C$_{17}$H$_{16}$O$_4$ requires C, 71.83; H, 5.63%); λ_{max} (CH$_3$CN)/nm (log ε), 240 (shoulder, 4.34), 248 (4.46), 286 (shoulder, 3.49), 354 (3.62); ν_{max} (CDCl$_3$)/cm^{-1} 2973, 2903, 1658, 1598, 1496, 1445, 1405, 1356, 1330, 1285, 1227, 1112, 1072, 1017, 912, 743; δ_H (200 MHz; CD$_3$CN) 1.60 (6H, t, *J* 6.3), 4.27 (4H, q, *J* 8), 7.28 (4H, m), 7.91 (2H, d, *J* 8); δ_C (75 MHz; CDCl$_3$) 14.81, 65.42, 117.29, 117.66, 122.61, 123.57, 146.82, 148.38, 177.31; *m*/*z* (EI) 285 (26), 284 (M$^+$, 97), 270 (5), 256 (17), 255 (10), 229 (15), 228 (100), 227 (15), 190 (10), 171 (23), 115 (24%); (+CI/NH$_3$) 302 (2), 287 (5), 286 (35), 285 (100), 271 (9).

1,11-Dibromo-3,6,9-trioxaundecane, 1,14-dibromo-3,6,9,12-tetraoxatetradecane and 1,17-dibromo-3,6,9,12,15-pentaoxaheptadecane

These dibromides were prepared from the corresponding polyethyleneglycols using previously described methods.[4]

1,11-(4,5-Dioxyxanthone)-3,6,9-trioxaundecane,[†] 3 (*n* = 3). Decolourised 4,5-dihydroxyxanthone, **5** (0.3 g, 1.3×10^{-3} mol), and anhydrous potassium carbonate (0.6 g, 4.3×10^{-3} mol) were dissolved in DMF (60 ml) in a 250 ml round-bottomed flask fitted with a reflux condenser, septum cap, nitrogen atmosphere and stirring. 1,11-Dibromo-3,6,9-trioxaundecane (0.64 g, 2×10^{-3} mol) was added by syringe and the mixture refluxed overnight. After cooling, the solution was filtered, most of the DMF distilled off under reduced pressure, the residue diluted with water (30 ml). Extraction with chloroform (3 × 40 ml), drying (Na$_2$SO$_4$), and evaporation yielded crude product, and recrystallization from acetonitrile gave beige needles (0.29 g, 56%); mp 168–171 °C (Found: C, 65.3; H, 5.6%. C$_{21}$H$_{22}$O$_7$ requires C, 65.3; H, 5.7%); λ_{max} (CH$_3$CN)/nm (log ε), 240 (shoulder, 4.39), 248 (4.5), 284 (shoulder, 5.53), 354 (3.65); ν_{max} (CDCl$_3$)/cm^{-1} 3548, 3335, 2919, 2877, 1648, 1617, 1592, 1487, 1359, 1283, 1241, 1129, 1072, 913, 746; δ_H (200 MHz; CDCl$_3$) 3.81 (4H, m), 3.86 (4H, m), 4.10 (4H, t, *J* 3), 4.33 (4H, t, *J* 3), 7.28 (m), 7.93 (2H, d, *J* 8); δ_C (75 MHz; CDCl$_3$) 70.27, 70.59, 71.70, 72.58, 117.37, 118.50, 123.35, 124.23, 147.31, 148.92, 177.74; *m*/*z* (EI) 386 (M$^+$, 35), 255 (20), 254 (92), 228 (28), 225 (26%); (+CI/NH$_3$) 404 (100), 387 (32%).

1,14-(4,5-Dioxyxanthone)-3,6,9,12-tetraoxatetradecane,[‡] 3 (*n* = 4). Reaction of decolourised 4,5-dihydroxyxanthone, **5** (0.3 g, 1.3×10^{-3} mol), anhydrous potassium carbonate (0.6 g, 4.3×10^{-3} mol), DMF (60 ml) and 1,14-dibromo-3,6,9,12-tetraoxatetradecane (0.72 g, 1.97×10^{-3} mol) as described above yielded a crude product (0.3 g, 53%) which was purified by column chromatography (basic alumina, tetrahydrofuran) to yield an off-white solid which was washed with ether and dried in air (0.25 g, 44%); mp 127–129 °C (Found: C, 61.65; H, 5.99%. C$_{23}$H$_{26}$O$_8$·H$_2$O requires C, 61.61; H, 6.25%); λ_{max} (CH$_3$CN)/nm (log ε), 240 (shoulder, 4.38), 248 (4.5), 288 (shoulder, 3.69), 354 (3.73); ν_{max} (CDCl$_3$)/cm^{-1} 3336, 2923, 2857, 1655, 1598, 1495, 1445, 1354, 1329, 1285, 1226, 1133, 1114, 1076, 1023, 747; δ_H (200 MHz; CD$_3$CN) 3.58 (4H, s), 3.61–3.72 (8H, m), 3.95 (4H, t, *J* 5), 4.39 (4H, t, *J* 5), 7.3–7.43 (4H, m), 7.81 (2H, d, *J* 8); δ_C (75 MHz; CDCl$_3$) 69.60, 69.78, 70.82, 71.18, 71.38, 117.36, 117.94, 122.57, 123.45, 146.61, 147.97, 176.93; *m*/*z* (EI) 430

[†] IUPAC name: 2,3,5,6,8,9,11,12-Octahydro[1,4,7,10,13,16]hexaoxacyclooctadeca[2,3,4,5,6-*defg*]xanthen-17-one.

[‡] IUPAC name: 8,9,11,12,14,15,17,18,20,21-Decahydro[1,4,7,10,13,16,19]heptaoxacyclohenicosa[2,3,4,5,6-*defg*]xanthen-20-one.

(M^+, 16), 386 (3), 342 (6), 298 (8), 255 (27), 254 (100), 253 (18), 228 (36), 226 (18), 225 (40%); (+CI/NH_3) 448 (100), 431 (16), 430 (3), 404 (6), 360 (8), 343 (7), 330 (33), 299 (10%).

1,17-(4,5-Dioxyxanthone)-3,6,9,12,15-pentaoxaheptadecane,§ 3 (*n* = 5). Decolourised, crude 4,5-dihydroxyxanthone, **5** (0.1 g, 4.386×10^{-4} mol), anhydrous caesium carbonate (0.34 g, 1.76×10^{-3} mol), DMF (60 ml), and 1,17-dibromo-3,6,9,12,15-pentaoxaheptadecane (0.27 g, 6.62×10^{-4} mol) were heated together under nitrogen at 120 °C for 72 h. Evaporation, aqueous dilution and chloroform extraction as before yielded a brown liquid which was applied to a basic alumina column. Elution with tetrahydrofuran yielded an off-white solid, which was washed with ether and dried in air (84.5 mg, 41%); mp 102–105 °C (Found: C, 62.96; H, 6.43%. $C_{25}H_{30}O_9$ requires C, 63.29; H, 6.3%); λ_{max} (CH_3CN)/nm (log ε), 240 (shoulder, 4.34), 248 (4.45), 284 (shoulder, 5.52), 354 (3.59); ν_{max} ($CDCl_3$)/cm^{-1} 2918, 2870, 1658, 1598, 1496, 1446, 1353, 1328, 1285, 1227, 1117, 1076, 1043, 1025, 746; δ_H (200 MHz; CD_3CN) 3.55 (8H, s), 3.60–3.75 (8H, m), 3.95 (4H, t, *J* 5), 4.35 (4H, t, *J* 5), 7.32–7.45 (4H, m), 7.79 (2H, d, *J* 7.6); δ_C (75 MHz; $CDCl_3$) 69.80, 69.94, 70.65, 70.92, 70.98, 71.42, 117.77, 118.15, 122.69, 123.60, 146.86, 148.21, 177.18; *m*/*z* (EI) 474 (M^+, 8), 255 (21), 254 (78), 253 (18), 228 (40), 226 (38%); (+CI/NH_3) 493 (26), 492 (100), 475 (15), 374 (38), 278 (55%).

Measurement of acid–base equilibria

Aqueous sulfuric acid mixtures of known strength were made up according to Rochester[25] and stock solutions of the xanthones (*ca.* 4.2×10^{-3} M in acetonitrile). Aqueous acid solutions (3.0 ml) were pipetted into 1 cm quartz cells and a background UV spectrum collected. The xanthone was then added by micropipette (20 µl of stock acetonitrile solution) to the active cell, which was stirred briefly before recording a UV spectrum and recording absorbance at 272 nm. Each experiment was repeated three times, and the acidity of the protonated xanthones was determined as described in the text.

Measurement of binding constants with metal ions

a) By conductimetry.[26] The conductivity measurements were carried out in a stirred glass thermostatted conductivity cell, connected across a fast response AC conductivity bridge,[27] which in turn was connected to a digital voltmeter to obtain a voltage reading proportional to the conductivity of the solution in the cell. All solutions and the cell were thermostatted at 35 °C and the temperature in the conductivity cell was constant to ±0.01 °C during the titration. In a typical experiment, a solution of potassium bromide in anhydrous methanol (15.0 ml of 2.4×10^{-4} M) was placed in the cell. The crown ether **3** ($n = 4$) (5.350 mg) was weighed into a 5 ml volumetric flask and made up to the mark with 5 ml of the methanolic potassium bromide solution from the cell and the flask was sonicated to effect solution. A voltage reading, V, was taken from the cell then the crown solution was added in 100 µl aliquots and measurements taken after each addition. Readings were then fitted to the relationship $V = M_{tot}\Lambda_{MX} + x(\Lambda_{MCr} - \Lambda_{MX})$, where M_{tot} is the total metal ion concentration and x is the concentration of the complex. Here, Λ_{MX} and Λ_{MCr} are proportionality constants between the voltage (in mV) and the concentration of the uncomplexed and complexed metal ion respectively.

b) By spectrofluorimetry. Emission spectra were run for solutions of the crown ethers in methanol (3.0 ml of 1×10^{-4} M at 25 °C), by excitation of the solution at an isosbestic point. Aliquots of salt solution (10 µl of 1×10^{-2} M) were added and intensities recorded at the maximum of the emission band. Readings were then fitted to the relationship $I_{corr} = C_{cr}\varphi_{Cr} + x\,\varphi_{MCr}$, where C_{cr} and x are the concentrations of the uncomplexed and complexed crown, and φ_{Cr} and φ_{MCr} are proportionality constants between the corrected emission intensity (in arbitrary units) and the concentration of uncomplexed and complexed crown ether respectively.

For both conductimetry and spectrofluorimetry, x satisfies the usual binding expression where Cr_{tot} is the total concentration of crown and M_{tot} is the total metal ion concentration: $x^2 - (Cr_{tot} + M_{tot} + 1/K)x + M_{tot}Cr_{tot} = 0$. Values of the binding constants, K, were obtained by simulation of the data using both K and Λ_{MCrX} as adjustable parameters using a Newton–Raphson procedure[28] to minimise the sum of squares of the residuals.

Empirical force field calculations

The molecular modelling package was Macromodel 4.5,[29] running on a Silicon Graphics 4D 240 GTX work station. The MM3* force field of Allinger *et al.*[11] was used for calculations with no modification of parameters. The Monte Carlo method of conformational searching was used, and energy minimisations used the truncated Newton conjugate gradient (TCNG) method.

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References

1 S. C. Biswas and R. K. Sen, *Indian J. Pure Appl. Phys.*, 1969, **7**, 408; S. Onuma, K. Iijima and I. Ohnishi, *Acta Crystallogr., Sect. C*, 1990, **46**, 1725.

2 K. Iijima, T. Misu, S. Ohnishi and S. Omuma, *J. Mol. Struct.*, 1989, **213**, 263.

3 C. G. Le Fevre and R. J. W. Le Fevre, *J. Chem. Soc.*, 1937, 196; Z. Aixenshtat, E. Klein, H. Weider-Feilchenfeld and E. D. Bergman, *Isr. J. Chem.*, 1972, **10**, 753.

4 H. J. Pownall and W. W. Mantulin, *Mol. Phys.*, 1976, **31**, 1393; J. C. Scaiano, *J. Am. Chem. Soc.*, 1980, **102**, 7747.

5 B. G. Cox, O. S. Mills, N. J. Mooney, P. M. Robinson and C. I. F. Watt, *J. Chem. Soc., Perkin Trans. 2*, 1995, 697.

6 R. S. Beddoes, B. G. Cox, O. S. Mills, N. J. Mooney, C. I. F. Watt, D. Kirkland and D. Martin, *J. Chem. Soc., Perkin Trans. 2*, 1996, 2091.

7 L. Prodi, F. Bolletta, N. Zaccheroni, C. I. F. Watt and N. J. Mooney, *Chem. Eur. J.*, 1998, **4**, 1090.

8 R. A. Finnegan and K. E. Merkel, *J. Org. Chem.*, 1972, **37**, 2986.

9 K.-H. Bolze, H.-D. Dell and H. Janse, *Liebigs Ann Chem.*, 1967, **709**, 63.

10 For recent comments on reactions in supercritical water see A. R. Katritsky, S. M. Allen and M. Siskin, *Acc. Chem. Res.*, 1996, **29**, 399.

11 N. L. Allinger, Z. S. Zhu and K. Chen, *J. Am. Chem. Soc.*, 1992, **114**, 6120.

12 K. Matsuzaki and H. Ito, *J. Polym. Sci., Part B: Polym. Phys.*, 1974, **12**, 2507; H. Weiser, G. Laidlaw, P. J. Kruger and H. Fuhrer, *Spectrochim. Acta, Part A*, 1968, **24**, 1055.

13 *Binding Constants: The Measurement of Molecular Complex Stabilities*, K. A. Connors, Wiley Interscience, New York, 1987, ch. 2.

14 H. K. Frensdorff, *J. Am. Chem. Soc.*, 1971, **93**, 600; Y. Takeda and H. Yano, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 866 and 1980, **53**, 1720; R. M. Izatt, G. A. Clark, J. D. Lamb, J. E. King and J. J. Christensen, *Thermochim. Acta*, 1986, **97**, 115.

15 J. F. Ireland and P. A. H. Wyatt, *J. Chem. Soc., Faraday Trans. 1*, 1972, **68**, 1053; R. Rusakowicz, G. W. Byers and P. A. Leermakers, *J. Am. Chem. Soc.*, 1971, **93**, 3263; D. Weir and J. C. Scaiano, *Tetrahedron*, 1987, **43**, 1617.

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§ IUPAC name: 8,9,11,12,14,15,17,18,20,21,23,24-Dodecahydro[1,4,7,10,13,16,19,22]octaoxacyclotetraicosa[2,3,4,5,6-*defg*]xanthen-23-one.

16 O. Exner, in *Correlation Analysis in Chemistry*, *Recent Advances*, N. B. Chapman and J. Shorter, Eds., Plenum Press, New York, 1978, ch. 10.

17 Values of H_o taken from C. D. Johnson, A. R. Katritzsky and S. A. Shapiro, *J. Am. Chem. Soc.*, 1969, **91**, 6654.

18 L. P. Hammett and A. J. Deyrup, *J. Am. Chem. Soc.*, 1932, **43**, 2721.

19 R. A. Cox, *Acc. Chem. Res.*, 1987, **20**, 27; also reviewed by A. Bagno, G. Scorrano and R. A. More O'Ferrall, *Rev. Chem. Intermed.*, 1987, **7**, 313.

20 A. Levi, G. Modena and G. Scorrano, *J. Am. Chem. Soc.*, 1974, **96**, 6585.

21 *Fluorescent Chemosensors for Ion and Molecule Recognition*, A. W. Czarnik, Ed., ACS, Washington DC, 1992; A. P. de Silva, H. Q. N. Gunarantne, T. Gunnlaugsson, A. J. M. Huxley, C. P. McCoy, J. T. Rademacher and T. E. Rice, *Chem. Rev.*, 1997, **97**, 1515.

22 C. di Natale, J. A. J. Brunink, F. Bungaro, F. Davide, A. D'Amico, R. Paolesse, T. Boschi, M. Faccio and G. Ferri, *Meas. Sci. Technol.*, 1996, **7**, 1103; Y. G. Vlasov, *Anal. Chem.*, 1997, **87**, 261.

23 A. Credi and L. Prodi, *Spectrochim. Acta*, *Part A*, 1998, **54**, 159.

24 C. Djerassi, R. R. Engle and A. Bowers, *J. Org. Chem.*, 1956, **21**, 1547.

25 *Acidity Functions*, C. H. Rochester, Academic Press, London and New York, 1970.

26 Method of Y. Takeda, H. Yano, M. Ishibashi and H. Isozumi, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 72; Y. Takeda and H. Yano, *ibid.*, 1980, **53**, 1720.

27 A. C. Knipe, D. McLean and R. L. Tranter, *Sci. Instrum.*, 1974, **4**, 586.

28 *Computational Methods for Determination of Formation Constants*, ed. D. J. Leggett, Plenum Press, London and New York, 1985, ch. 1.

29 F. H. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, C. Caulfield, G. Chang, T. Hendrojson and W. C. Still, *J. Comput. Chem.*, 1990, **11**, 440.

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