

# Structures and complexing properties of crown ethers incorporating 1,8-dioxyxanthenes

2 PERKIN

Roy S. Beddoes,<sup>a</sup> Brian G. Cox,<sup>b</sup> Owen S. Mills,<sup>a</sup> Nichola J. Mooney,<sup>a</sup> C. Ian F. Watt<sup>\*a</sup> and (in part) David Kirkland<sup>a</sup> and Daryl Martin<sup>a</sup>

<sup>a</sup> Department of Chemistry, University of Manchester, Manchester, UK M13 9PL

<sup>b</sup> Zeneca FCMO, North of England Works, PO Box A38, Huddersfield, UK HD2 1FF

The X-ray crystal structures of three crown ethers containing the 1,8-dioxyxanthone residue are reported. 1,8-[3,6,9-Trixaundecane-1,11-diyl]dioxy]xanthone, **1** ( $n = 3$ ), and 1,8-[(3,6,9,12,15-pentaoxaheptadecane-1,17-diyl]dioxy]xanthone, **1** ( $n = 5$ ), have been crystallized from acetonitrile and their crystals shown to incorporate acetonitrile. Crystals of the former also contain water which forms a tight hydrogen-bonded bridge between the xanthone carbonyl oxygen and the most remote oxygen of the 18-membered macrocycles. Crystals of 1,8-[(3,6,9,12-tetraoxatetradecane-1,14-diyl]dioxy]xanthone, **1** ( $n = 4$ ), from toluene do not incorporate solvent molecules.

Earlier UV measurements for the basicity of the carbonyl oxygen for these crowns and for 1,8-diethoxyxanthone have been re-examined using the excess acidity method and revised values of  $pK_a$  and  $m^*$  are reported. The UV spectra of methanolic solutions of the ketones show shifts with added strontium or barium salts and these are associated with complex formation which places the metal ion in close proximity to the carbonyl oxygen. Binding constants for formation of complexes are reported.

## Introduction

We have recently prepared a series of crowns by alkylation of the readily available 1,8-dihydroxyxanthone (1,8-dihydroxyxanthene-9-one) with polyethylene glycol dibromides to afford acceptable yields of the annelated xanthenes.<sup>1</sup> Reduction yields xanthyls, which exist in equilibrium with the corresponding xanthylium ions in dilute aqueous acid. Studies of structure and reactivity of these compounds are now in progress and we report here an examination of the structures and some properties of the xanthenes, **1** ( $n = 3, 4$  and  $5$ ), whose macrocyclic arrays contain 18, 21 and 24 atoms, respectively (Fig. 1). Four contiguous bonds in these rings are shared with the xanthone residue and therefore restricted in their conformational freedom. Xanthone itself is reported to be planar<sup>2</sup> in its crystal structure, with all its heavy atoms within 0.03 Å of their best plane. It also has a dipole moment<sup>3</sup> (2.95 D) rather higher than additivity schemes would predict, consistent with a contributing dipolar pyrylium 4-oxide form of the central ring which provides an endomacrocyclic polar residue which might participate in macrocycle binding to either ionic or molecular species.

## X-Ray crystallographic studies

Crystallization solvents ranging from aqueous methanol to hydrocarbon mixtures were examined in attempting to prepare crystals of the xanthone-containing crowns. No attempt was made to prepare particular inclusion compounds; rather, we sought the solvents which most quickly yielded material for X-ray crystallographic study. In the event, crystallization from acetonitrile yielded suitable crystals for **1** ( $n = 3$ ) and **1** ( $n = 5$ ). The crystals of **1** ( $n = 5$ ) were air stable, but those of **1** ( $n = 3$ ) first developed powdery surfaces then slowly decayed to non- or micro-crystalline material. This decay was slow enough to permit data collection, but there was large intensity loss and the structure was solved by extending the number of phase sets tried by direct methods after correction for intensity loss. Even so, the structure of **1** ( $n = 3$ ) is the poorest of the three reported because of this decomposition. Crystals of **1** ( $n = 4$ ) were obtained only after considerable experimentation, and with

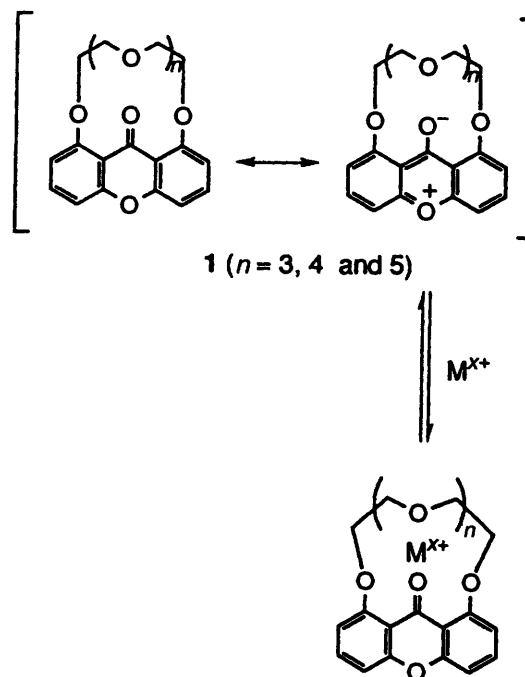


Fig. 1 Structure and canonical forms of xanthenes **1** ( $n = 3, 4$  and  $5$ )

some difficulty, by slow evaporation of a dilute toluene solution.

All three crown ethers were found to contain non-planar xanthone arrays. While atoms of either benzene ring in the xanthenes and the C- and O-atom of the central ring are near co-planar (mean deviation from best plane  $< 0.04$  Å), the two sides of the molecule are not in the same plane, so that it hinges along the central ring C---O line with this ring adopting a flattened boat conformation. Angles between the planes ( $\alpha$ ) range from 172 to 163°. Presumably folding occurs to relieve what would otherwise be severe non-bonded and dipole-dipole interactions between coplanar and parallel carbonyl groups and the C-O bonds at the 1- and 8-positions carrying links

**Table 1** Comparison of structural features in X-ray crystal structures of **1** ( $n = 3, 4$  and  $5$ )

Feature	Ketone		
	<b>1</b> ( $n = 3$ )	<b>1</b> ( $n = 4$ )	<b>1</b> ( $n = 5$ )
$r(\text{C}=\text{O})/\text{\AA}$	1.21 (2)	1.222(3)	1.221(4)
$\Sigma$ angles at $\text{C}=\text{O}$ carbon/ $^\circ$	360	359.9	359.8
Mean aliphatic $r(\text{C}-\text{C})/\text{\AA}$	1.483	1.480	1.496
Angles at attachment $\text{O}-\text{C}-\text{C}/^\circ$	116, 112	116.6, 116.4	117.0, 116.4
Mean $\text{O}-\text{C}-\text{C}-\text{O}$ torsion angles/ $^\circ$	69	76.0	71.8
Mean $\text{C}-\text{O}-\text{C}-\text{C}$ torsion angles/ $^\circ$	173.1	165.5 (1 at 102)	172.9
$\text{C}-\text{O}-\text{C}-\text{C}$ attachment/ $^\circ$	174.5	176.8	175.8
Angle of xanthone planes ( $\alpha$ )/ $^\circ$	165.6	162.7	173.7
$\text{O}=\text{C}-\text{C}=\text{C}$ torsions/ $^\circ$	-21, 19	18.4, -21.8	16.1, -14.4
$\text{C}=\text{O} \cdots \text{O}$ intramolecular contacts/ $\text{\AA}$	2.714, 4.450, 4.702, 4.306, 2.697	2.729, 4.695, 5.434, 6.154, 4.725, 2.705	2.679, 4.747, 6.129, 7.011, 6.180, 4.789, 2.697
Bound molecule contacts/ $\text{\AA}$	Water	—	Acetonitrile
	O8-O1 2.873	—	O9-Me 3.132
	O8-O4 2.864	—	O1-Me 3.878
	Acetonitrile	—	O2-Me 3.591
	O1-Me 3.454	—	O3-Me 3.656
	O2-Me 3.528	—	O4-Me 4.228
	O3-Me 3.506	—	O5-Me 3.604
	O4-Me 3.434	—	O6-Me 3.457
	O5-Me 3.404	—	O7-Me 3.704
	O6-Me 3.434	—	—

to the macrocyclic array. Even so,  $\text{C}=\text{O} \cdots \text{O}$  distances are uncomfortably close (mean, 2.703  $\text{\AA}$ ). Within the polyethylene glycol portions of the macrocycles, bond lengths and angles are similar to those found in other crown ethers. As in many other such structures, the aliphatic  $\text{C}-\text{C}$  bond lengths (mean, 1.486  $\text{\AA}$ ) are shorter than the standard single bond length.<sup>4</sup>

Details of these and other features of the X-ray crystal structures are collected in Table 1 and we now comment briefly on the features of each. We also make comparison with structures calculated using the MM3 empirical force field<sup>5</sup> as implemented in Macromodel 4.5,<sup>6</sup> (MM3\*) and note that the MM2<sup>7</sup> implementation did not reproduce the fold in the calculated structures of any of the crown xanthenes or indeed of 1,8-diethoxyxanthone.

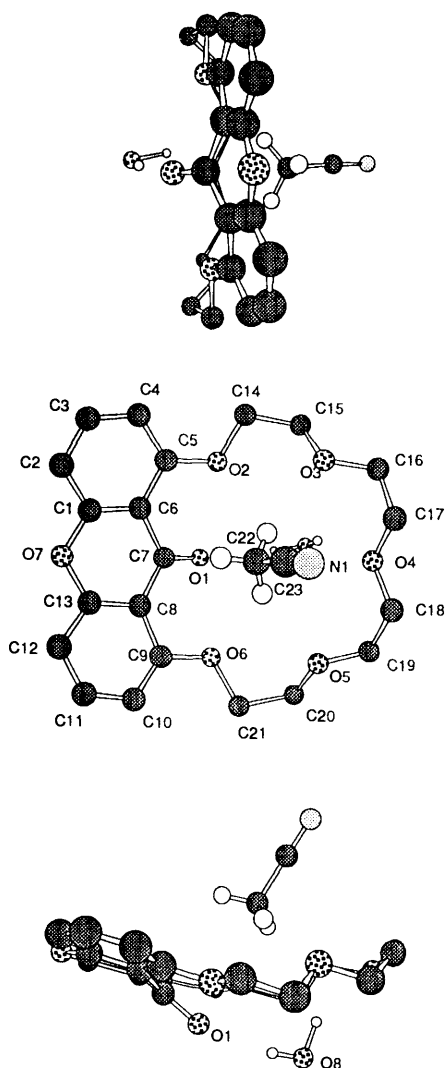
**Structure of **1** ( $n = 3$ ).** The compound crystallized from acetonitrile as a 1:1:1 complex of **1** ( $n = 3$ ), acetonitrile and water. Water was not added during crystallization and probably arises from atmospheric moisture absorbed during crystallization. The complexes crystallize as centrosymmetric dimers with each complex (Fig. 2) having approximate mirror symmetry with the plane running through the carbonyl group of the xanthone residue. As noted earlier, the 1,8-dioxyxanthone unit is non-planar, with a 165° fold about the  $\text{C} \cdots \text{O}$  line of the central ring. This directs the carbonyl oxygen out of the mean plane of the macrocyclic array, and the water molecule forms a hydrogen-bonded bridge between the carbonyl oxygen and the remotest ethereal oxygen [ $d(\text{O} \cdots \text{O}) = 4.702 \text{\AA}$ ] of the polyethylene bridge. Distances from the oxygen of the water to the carbonyl and ethereal oxygens are 2.873 and 2.864  $\text{\AA}$ , respectively, consistent with strong hydrogen bonds.<sup>8</sup> Usually, hydrogen bonds to ethereal oxygen are measurably shorter than those to carbonyl oxygen,<sup>9</sup> but here the hydrogen bond distances are almost equal, possibly reflecting the unusually high basicity of this carbonyl oxygen. The  $\text{O} \cdots \text{H} \cdots \text{O}$  arrays are non-linear with angles at the hydrogens of 167 and 145°, respectively. In the macrocycle, all torsion angles about  $\text{C}-\text{C}$  bonds lie between 65 and 70°, and those about  $\text{C}-\text{O}$  bonds are close to 180°, so that the presence of the water molecule does not interfere with the preferred alternating gauche-anti-sequence of torsional arrangements about  $\text{C}-\text{C}$ <sup>10</sup> and  $\text{C}-\text{O}$ <sup>11</sup> bonds in this part of the macrocycle.

The ability of **1** ( $n = 3$ ) to bind a water molecule contrasts interestingly with that of the simplest 18-membered ring crown,

18-crown-6, which has a poor cavity fit for a single water molecule.<sup>12</sup> A binary hydrate, 18-crown-6·6H<sub>2</sub>O, has been recently described,<sup>13</sup> and has a crown ether with near  $D_{3d}$  symmetry, with water molecules hydrogen bonding across O1-O7 on one face and across O10-O16 on the other. Other binary water containing complexes are observed, with additional hydrogen bonding molecules such as phenols, oximes<sup>14</sup> and carboxylic acids.<sup>15</sup> In the case of our xanthone, the internally directed carbonyl oxygen appears to provide the necessary additional bridging point, and indeed, similar accommodation of water has been found in 18-membered ring bis-lactones.<sup>16</sup>

An empirical force field calculation, with a full conformational search, on **1** ( $n = 3$ ) minus the bound water and acetonitrile, gave as the global energy minimum energy conformation ( $E_{\text{steric}} = 198.35 \text{ kJ mol}^{-1}$ ) a symmetrical structure closely resembling that found in the crystal. The next most energetic conformation found was nearly 5  $\text{kJ mol}^{-1}$  higher in energy and was one of a family of eight conformations ( $203.34 < E_{\text{steric}} < 207.69 \text{ kJ mol}^{-1}$ ) in which symmetry was absent. In the global minimum energy conformation, the sequence of torsional angles in the polyether portion of the crystal structure was well reproduced, as was the fold of the xanthone portion. The distance between carbonyl oxygen and remote ethereal oxygen (4.801  $\text{\AA}$ ) is quite close to that found in the crystal (4.701  $\text{\AA}$ ) where these two atoms are hydrogen-bonded to the guest water molecule. Introduction of a water molecule to the calculated structure and reminimization resulted in only minor adjustments of angles and distances, suggesting a pre-organization<sup>17</sup> of the host array to accept its guest water molecule.

The acetonitrile molecule is 'perched' on the opposite side of the mean plane of the macrocycle array from the water molecule, on the 'in' side of the fold of the xanthone unit. Two of the three methyl hydrogens are directed between oxygens of the macrocycle giving relatively close  $\text{C}-\text{H} \cdots \text{O}$  approaches [ $3.40 < d(\text{C} \cdots \text{O}) < 3.55 \text{\AA}$ ] which might be regarded as weak hydrogen bonds,<sup>18</sup> or equally well as an attractive dipole-dipole interaction. The bonding situation closely resembles that found in acetonitrile-18-crown-6 complexes<sup>15</sup> where the crown adopts  $D_{3d}$  symmetry and there are close approaches between hydrogens of the methyl of the nitrile and ethereal oxygens. Such forces are much weaker than the conventional hydrogen



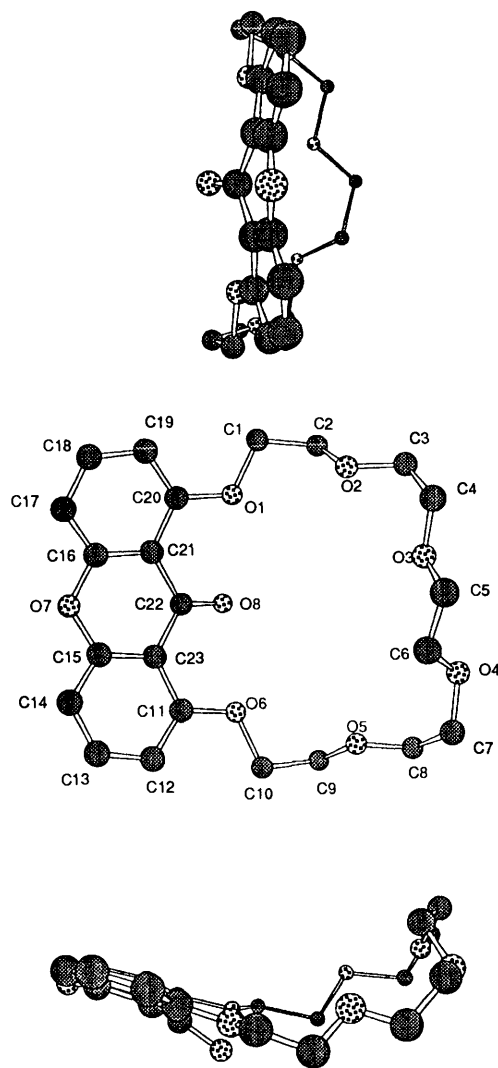
**Fig. 2** Orthogonal views of the X-ray crystal structure of the acetonitrile-water complex of **1** ( $n = 3$ ); hydrogens have been omitted for clarity

bond involving lone pair interaction, and indeed, the decay of the crystals of **1** ( $n = 3$ ) seems to be associated with loss of weakly bound acetonitrile.

**Structure of 1** ( $n = 4$ ). Crystals of **1** ( $n = 4$ ) grown from toluene contain no complexed molecules. The structure of the crown is shown in Fig. 3. The fold in the xanthone again directs the carbonyl oxygen out of the mean plane of the macrocyclic array. There is no plane of symmetry, but the ring forms an open near square, with the xanthone residue and atom sets O1–C1–C2–O2–C3, C4–O3–C5–C6–O4–C7 and C8–O5–C9–C10–O6 of the polyethylene glycol portion forming the edges. The conformations about C–C and C–O bonds in this portion are recognizably gauche and anti but average torsion angles ( $76.4^\circ$  for C–C and  $164.8^\circ$  for C–O) show that there are deviations from the ideal values. One notably small torsional angle of  $102^\circ$  at O3–C4 occurs at one corner of the square.

Vacant cavities in crown ethers have a tendency to collapse thus maximizing favourable  $\text{CH}\cdots\text{O} <$  interactions,<sup>19</sup> but in this structure the open cavity seems to be maintained by the rigid xanthone unit, although it is notable that the thermal motion of atoms does increase with distance from xanthone. It may also be significant that the deviation from planarity in the xanthone unit in this structure ( $\alpha = 162.7^\circ$ ) is the largest we have found in these three structures.

The molecular mechanics gave a global minimum energy conformation ( $E_{\text{steric}} = 229.8 \text{ kJ mol}^{-1}$ ) closely resembling that found in the crystal. Again the fold in the xanthone unit was



**Fig. 3** Orthogonal views of the X-ray crystal structure of **1** ( $n = 4$ ); hydrogens have been omitted for clarity

reproduced, as was the sequence of torsional angles about C–C and C–O bonds in the polyethylene glycol unit. As is to be expected with the larger ring, this is a more flexible array than **1** ( $n = 3$ ) and in the conformational search, no less than 38 conformations were found with energies within  $10 \text{ kJ mol}^{-1}$  of the global minimum.

**Structure of 1** ( $n = 5$ ). This compound crystallizes from acetonitrile as a 1:1 complex with acetonitrile. Views of the structure are shown in Fig. 4. Like **1** ( $n = 3$ ), the complex shows an approximate plane of symmetry running through the carbonyl of the xanthone and the remotest ethereal oxygen (O4), but lies in a general cell position of the centrosymmetric space group. The xanthone unit is again folded, but has the smallest fold angle ( $\alpha = 172^\circ$ ) of the three crowns studied, possibly reflecting the occupancy of the cavity. The conformations about C–C and C–O bonds in the polyethylene glycol portion are comfortably alternating gauche- and anti-conformations with average dihedral angles of  $71.8^\circ$  for C–C and  $172.9^\circ$  for C–O bonds, with no one torsion deviating by more than  $4^\circ$  from these values. Thermal motion of the atoms of the macrocyclic ring increases with distance from the xanthone residue, but does not become large enough to indicate local disorder.

In the 24-membered macrocycle, oxygen atoms O1, O3, O5 and O7 occupy the corners of a square, and the intervening three glycol units and the xanthone lie alternately above and below this plane in a distorted tennis ball seam arrangement.

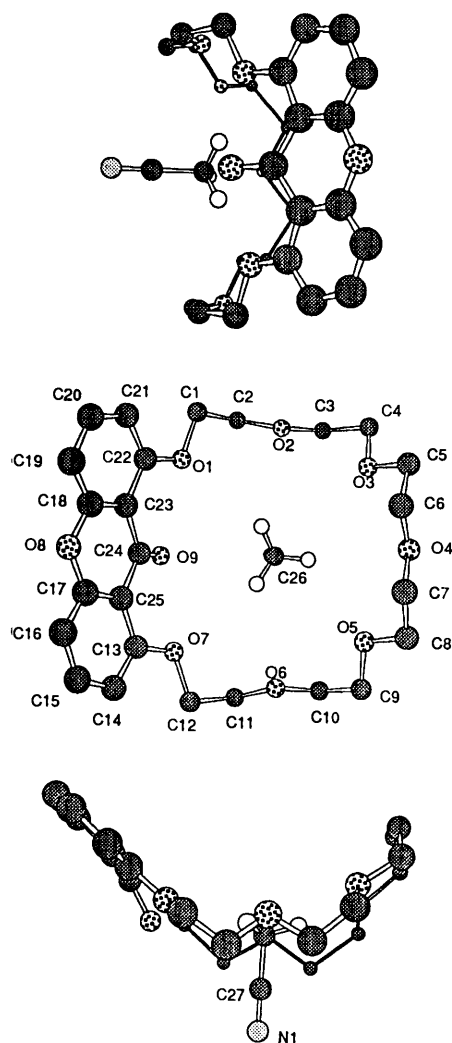


Fig. 4 Orthogonal views of the X-ray crystal structure of the acetonitrile complex of 1 ( $n = 5$ ); hydrogens have been omitted for clarity

The guest acetonitrile lies in the mirror plane with the  $C\equiv N$  directed on the same side of the array as the carbonyl oxygen, so that the methyl group is nicely cupped by the two sides of the tennis ball array, and presumably bound by dipolar interaction between the electropositive methyl group and the electronegative oxygens of the macrocycle.<sup>20</sup> The conformation of the methyl of the acetonitrile is such that the carbonyl oxygen bisects an  $H-C-H$  angle so that the closest heavy atom non-bonded approach is between the carbonyl oxygen and the methyl group carbon [ $d(C=O\cdots C27) = 3.132 \text{ \AA}$ ]. This arrangement directs these methyl group hydrogens between  $O1$  and  $O2$  on one side of the molecule, and  $O6$  and  $O7$  on the other with  $C-H\cdots O$  approaches of *ca.*  $2.8 \text{ \AA}$ . The third methyl hydrogen has longer contacts; *ca.*  $3.0 \text{ \AA}$  with  $O5$  and  $O3$ . All these distances are larger than the sums of the van der Waal's radii.

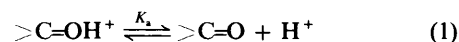
The general arrangement of the macrocycle has not been found in the structures of unoccupied 24-crown-8 compounds, such as dibenzo-24-crown-8,<sup>21</sup> but has been observed in cationic rhodium complexes of dibenzo-24-crown-8.<sup>22</sup>

Molecular mechanics calculations on this macrocycle, minus its complexed acetonitrile, relaxing from the X-ray coordinates found a minimum energy conformation ( $E_{steric} = 253.08 \text{ kJ mol}^{-1}$ ) which retained the symmetry of the complex and the sequence of torsional angles in the polyether portion. The most noticeable feature of the relaxation was the alteration of the fold angle of the xanthone residue to place the carbonyl oxygen on the opposite side of the mean plane of the macrocyclic array.

This reduces the separation between the carbonyl oxygen ( $O9$ ) and macrocycle remote oxygen ( $O4$ ) from  $7.016 \text{ \AA}$  in the crystal structure to  $6.043 \text{ \AA}$  in the calculated structure, and positions the carbonyl oxygen to replace some attractive intermolecular  $C-H\cdots O$  interactions between acetonitrile hydrogens and ethereal oxygens with attractive intramolecular interactions between the carbonyl oxygen and ethylene glycol  $C-H$  residues in the macrocycle. A full conformational search found no lower energy conformation, and again the structure seems to have a degree of pre-organization for formation of its acetonitrile complex. The next most energetic conformation was an unsymmetrical one ( $E_{steric} = 257.79 \text{ kJ mol}^{-1}$ ) in which the ring cavity had collapsed, presumably to maximize transannular  $C-H\cdots O$  interactions<sup>19</sup> across the polyether portion of the molecule, and was one of a family of similar conformations. A second symmetrical conformation, closely resembling the global minimum but with the carbonyl oxygen pointing out of the macrocycle, had  $E_{steric} = 261.7 \text{ kJ mol}^{-1}$ .

#### Solution studies

**Acid-base behaviour.** In our earlier work<sup>1</sup> we reported an examination of the acid-base behaviour of these ketones using UV spectrometric methods. 1,8-Diethoxyxanthone and the crown ketones show indistinguishable spectra in ethanol solution, with  $\lambda_m = 240 \text{ nm}$  ( $\log \epsilon = 4.26$ ),  $304 \text{ nm}$  ( $\log \epsilon = 3.90$ ) and  $338 \text{ nm}$  ( $\log \epsilon = 3.57$ ). Solutions in 80% sulfuric acid are yellow and show bands at  $272 \text{ nm}$  ( $\log \epsilon = 4.56$ ),  $319 \text{ nm}$  ( $\log \epsilon = 3.77$ ),  $368 \text{ nm}$  ( $\log \epsilon = 4.05$ ) and  $438 \text{ nm}$  ( $\log \epsilon = 3.63$ ), changes which are reasonably associated with reversible protonation on carbonyl oxygen [reaction (1)]. Values for the



acidity constants ( $-1.93 > pK_a > -2.12$ ) of the protonated ketones were extracted from plots of absorbance changes of solutions in different sulfuric acid mixtures against acid strength, given by  $H_o$ ,<sup>23</sup> by fitting a standard titration curve. This procedure assumes, unjustifiably, that these ketones behave as Hammett bases, *i.e.* that  $m = 1$  in eqn. (2) where  $I$  is

$$\log I = mH_o + pK_a \quad (2)$$

the indicator ratio and  $m$  is the ratio of activity coefficients of the ketone and Hammett bases.<sup>24</sup>

We have re-examined our data using the excess acidity ( $X$ ) method,<sup>25</sup> which makes the less drastic assumption that there is proportionality between the activity coefficient ratios, but treats the constant of proportionality as a parameter to be determined. The appropriate relationship, which yields true thermodynamic values for the acidity constants of the ketone conjugate acids referred to dilute aqueous solution, is given by eqn. (3), where  $m^*$  and  $pK_a$  are both parameters to be

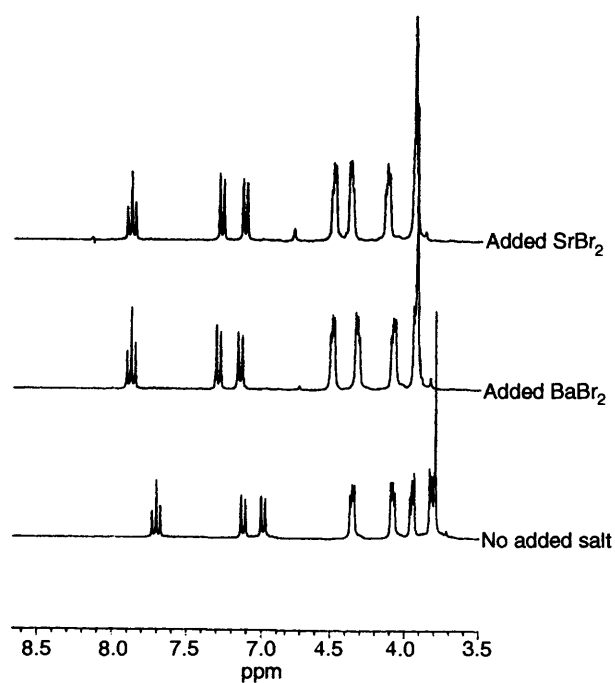
$$\log I - \log c_{H^+} = m^*X + pK_a \quad (3)$$

determined. In practice, values of  $m^*$  are found to be close to 1 and the revised  $pK_a$  values (Table 2) differ from our earlier published values by less than  $0.2 pK_a$  units. The xanthenes are considerably more basic than 2,4,4'-trimethoxy- and 2,2',4,4'-tetramethoxy-benzophenone ( $m^* = 1.11$  and  $1.06$ , respectively, and  $pK_a = -3.58$  and  $-3.89$ ).<sup>26</sup> The macrocyclic arrays attached through the 1- and 8-positions do not appear to have a strong effect on the protonation equilibria or on the solvation demand of the cations as indicated by the constancy of  $m^*$  values for the crowns and for the model 1,8-diethoxyxanthone.

**Association with metal ions.** We have examined the effects of added metal ions on UV spectra of methanolic solutions of the crowns. With lithium and sodium bromide, we could find no changes. With potassium and caesium bromide, small effects

**Table 2**  $pK_a$  and  $m^*$  values for ionizations of the xanthenes in aqueous sulfuric acid mixtures, and binding constants for complex formation between xanthone crowns and barium and strontium ions in methanol

Xanthone	Acid-base behaviour		$\log K_{\text{ass}}$	
	$m^*$	$pK_a$	$\text{Sr}^{2+}$	$\text{Ba}^{2+}$
1,8-Diethoxy	0.92 ( $\pm 0.13$ )	-1.93 ( $\pm 0.17$ )	—	—
<b>1</b> ( $n = 3$ )	0.93 ( $\pm 0.14$ )	-1.85 ( $\pm 0.18$ )	2.77 ( $\pm 0.16$ )	3.16 ( $\pm 0.09$ )
<b>1</b> ( $n = 4$ )	1.02 ( $\pm 0.06$ )	-2.05 ( $\pm 0.08$ )	4.48 ( $\pm 0.06$ )	4.68 ( $\pm 0.05$ )
<b>1</b> ( $n = 5$ )	1.16 ( $\pm 0.08$ )	-2.31 ( $\pm 0.11$ )	3.15 ( $\pm 0.21$ )	4.98 ( $\pm 0.06$ )



**Fig. 5** Proton NMR spectra of methanolic solutions **1** ( $n = 4$ ) in absence and presence of excess added  $\text{BaBr}_2$  and  $\text{SrBr}_2$

were evident. With added barium bromide, however, the effects were easily observed, and most marked in the case of the 24-membered ring ketone, **1** ( $n = 5$ ), with shifts to longer wavelengths and increased absorption coefficients reminiscent of those induced by protonation. Superimposed spectra showed isosbestic points at 286, 311, 330 and 349 nm. Similar, but less marked behaviour was observed for the other crown ketones, and for additions of strontium bromide. Proton NMR spectra of methanolic solutions of the ketones show downfield shifts of between 0.2 and 0.3 ppm in signals from the ethylene oxide units of the macrocycle, and of 0.2 ppm in signals from the xanthone unit, on addition of the salts as exemplified in Fig. 5 for **1** ( $n = 4$ ). Both phenomena are consistent with complex formation, placing the metal ions within the macrocycle in close proximity to the carbonyl oxygen as depicted in Fig. 1.

The changes in the UV spectra offered a convenient method of determining the extent of complex formation, and binding constants [eqn. (4)] are listed in Table 2. For the larger  $\text{Ba}^{2+}$



ion ( $r = 1.35 \text{ \AA}$ ), binding constants increase with ring size, although the change between 21- and 24-membered rings is not large. For the smaller  $\text{Sr}^{2+}$  ion ( $r = 1.13 \text{ \AA}$ ), the binding constant is largest for the 21-membered ring of **1** ( $n = 4$ ), and indeed this ring binds  $\text{Ba}^{2+}$  and  $\text{Sr}^{2+}$  about equally, despite their different ionic radii. In X-ray crystal structures of barium and strontium crown ether complexes,<sup>27</sup> typical  $\text{M}^{2+} \cdots \text{O}$  distances range from 2.8 to 2.93  $\text{\AA}$  for barium and 2.66 to 2.72  $\text{\AA}$

for strontium, and the results of the simple docking of these ions with the crowns, using their X-ray crystal structure geometries, do not agree with the pattern of binding constants. The best fit is between **1** ( $n = 3$ ) and barium; for strontium, this smallest ring is just a little too large, and for both ions, the fit becomes progressively poorer with increasing ring size. Clearly, the higher conformational mobility of the larger arrays must also be taken into account in modelling complex formation.

In absolute terms, the binding constants for the 18-membered ring are *ca.*  $10^2$  less than those for dibenzo-18-crown-6 with the same ions.<sup>28</sup> Similar reductions in binding constants are found in other crowns with carbonyl groups replacing a ring oxygen<sup>29</sup> and have been associated with the altered steric requirements and the reduced basicity of carbonyl as opposed to ethereal oxygen.

We were a little surprised at the absence of a strong effect on UV spectra by added potassium ion; its ionic radius (1.33  $\text{\AA}$ ) is very close to that of barium, and crowns which bind barium usually also bind potassium.<sup>30</sup> It is possible that the crowns do indeed bind potassium as efficiently as barium, but that the binding of the singly charged potassium ion does not perturb the electronic energy levels of the xanthone to the same extent as the doubly charged barium ion. Further measurements and modelling studies are to be undertaken.

**Complex formation with amides and catalysis of amide hydrolyses.** One of our interests is the possibility that these and related crowns may catalyse hydrolyses of simple carboxylic acid derivatives, and the finding that these crowns did indeed form complexes with neutral molecules<sup>31</sup> in their crystals was encouraging. We therefore examined  $^1\text{H}$  NMR spectra of the crowns in  $\text{CD}_3\text{CN}$  solution, in the presence and absence of varying amounts of added acetamide, but found no shifts indicative of complex formation. Variation of temperature (+70 to -30  $^\circ\text{C}$ ) did not induce any spectral changes other than those which could be associated with slowing of conformational motion in the polyethylene glycol portions of the molecule. Neither did we detect any effect on rates of hydrolyses of toluamide in buffered aqueous acetic acid. Disappearance of the amide showed good first-order behaviour, but was extremely slow. In the absence of crown,  $k_{\text{obs}} = 4.48 \times 10^{-5} \text{ s}^{-1}$  at 170  $^\circ\text{C}$  ( $t_{\frac{1}{2}} = 4.3 \text{ h}$ ). With  $10^{-4} \text{ M}$  added crowns **1** ( $n = 3, 4$  and  $5$ ), values of  $k_{\text{obs}}$  were  $4.42 \times 10^{-5}$ ,  $4.58 \times 10^{-5}$  and  $4.31 \times 10^{-5} \text{ s}^{-1}$ , respectively, and with  $10^{-4} \text{ M}$  1,8-diethoxyxanthone,  $k_{\text{obs}}$  was  $4.39 \times 10^{-5} \text{ s}^{-1}$ , with 95% confidence limits of  $\pm \text{ca. } 10\%$  in all cases. In practice, values of  $k_{\text{cat}}/k_{\text{uncat}}$  would have to be greater than 500 for detectable effects for these hydrolyses.

## Experimental

### Crystallography

Empirical absorption corrections were applied using the program DIFABS<sup>32</sup> and the resulting transmission factors are tabulated below. The data were corrected for Lorentz and polarization effects.

In all cases, structures were solved by direct methods.<sup>33</sup> Non-hydrogen atoms were refined anisotropically, except for **1** ( $n = 3$ ) where data were sparse. Hydrogen atoms were included in

**Table 3** Crystal data for **1** ( $n = 3$ ), **1** ( $n = 4$ ) and **1** ( $n = 5$ )

Parameter	<b>1</b> ( $n = 3$ )	<b>1</b> ( $n = 4$ )	<b>1</b> ( $n = 5$ )
Empirical formula	C <sub>23</sub> H <sub>27</sub> NO <sub>8</sub>	C <sub>23</sub> H <sub>26</sub> O <sub>8</sub>	C <sub>27</sub> H <sub>33</sub> NO <sub>9</sub>
Formula weight	445.47	430.45	515.56
Crystal colour and habit	Colourless, prisms	Pale yellow, prisms	Colourless, prisms
Crystal dimensions/mm	0.15 × 0.35 × 0.35	0.50 × 0.55 × 0.70	0.4 × 0.50 × 0.55
Crystal system	Triclinic	Monoclinic	Orthorhombic
Number of reflections for unit cell	25	25	25
Determination (2θ range)	(19.7–20.9°)	(39.5–44.2°)	(34.5–38.0°)
ω-Scan peak width at half height	0.38	0.16	0.22
Lattice parameters			
<i>a</i> /Å	11.144(8)	11.696(2)	19.122(3)
<i>b</i> /Å	13.41(2)	13.912(3)	30.993(6)
<i>c</i> /Å	8.182(4)	13.043(3)	9.009(1)
α/°	90.41(8)		
β/°	105.88(5)	98.67(2)	
γ/°	106.91(8)		
<i>V</i> /Å <sup>3</sup>	1120(2)	2098(1)	5339(2)
Space group	<i>P</i> $\bar{1}$ (#2)	<i>P</i> 2 <sub>1</sub> / <i>n</i> (#4)	<i>Pccn</i> (#56)
<i>Z</i>	2	4	8
<i>D</i> <sub>c</sub> /g cm <sup>-3</sup>	1.321	1.363	1.283
<i>F</i> <sub>000</sub>	472	912	2192
μ/cm <sup>-1</sup>	0.94 (Mo-Kα)	8.19 (Cu-Kα)	7.64 (Cu-Kα)

**Table 4** Intensity measurements, solution and refinement

Parameter	<b>1</b> ( $n = 3$ )	<b>1</b> ( $n = 4$ )	<b>1</b> ( $n = 5$ )
Diffractometer	Rigaku AFC6S	Rigaku AFC5R	Rigaku AFC5R
Radiation	Mo-Kα	Cu-Kα	Cu-Kα
λ/Å	0.710 69	1.541 78	1.541 78
<i>T</i> /°C	20	22	21
Take-off angle/°	6.0	6.0	6.0
Detector aperture:			
horizontal × vertical/mm	6.0 × 6.0	6.0 × 6.0	6.0 × 6.0
Crystal-detector distance/cm	40	40	40
Scan type	ω	ω/2θ	ω/2θ
Scan rate/° min <sup>-1</sup>	4.0 (in ω)	32.0 (in ω)	32.0 (in ω)
	3 rescans	2 rescans	2 rescans
Scan width/°	(0.92 + 0.30 tan θ)	(1.42 + 0.30 tan θ)	(1.10 + 0.30 tan θ)
2θ <sub>max</sub>	40.0	120.1	120.1
Number of reflections			
Total	2045	3450	4501
Unique	1899 ( <i>R</i> <sub>int</sub> = 0.042)	3271 ( <i>R</i> <sub>int</sub> = 0.068)	4499 ( <i>R</i> <sub>int</sub> = 0.108)
Ranges of			
<i>h</i>	0 to 8	–12 to 13	0 to 21
<i>k</i>	–12 to 12	–8 to 15	0 to 34
<i>l</i>	–7 to 7	–14 to 13	0 to 10
Transmission factors	0.76–1.44	0.95–1.07	0.83–1.13
	Decay (–85.00%)	Decay (–3.51%)	Decay (–7.50%)
<i>p</i> -Factor	0.06	0.02	0.02
No. of observations [ <i>I</i> > 3.00σ( <i>I</i> )]	790	2662	2859
No. of variables	174	280	334
Reflection/parameter	4.54	9.51	8.56
Residuals: <i>R</i> , <i>R</i> <sub>w</sub>	0.085, 0.105	0.050, 0.066	0.064, 0.078
Goodness of fit indicator	2.53	3.62	3.34
Max. shift in final cycle	< 0.01	< 0.01	< 0.01
Max. peak in final diff. map/e <sup>-</sup> Å <sup>-3</sup>	0.32	0.28	0.49
Min. peak in final diff. map/e <sup>-</sup> Å <sup>-3</sup>	–0.29	–0.17	–0.19

the structure factor calculation in idealized positions (C–H = 0.95 Å) and were assigned isotropic thermal parameters 20% greater than the equivalent *B* value of the atom to which they were bonded. The refinements were full-matrix least squares with the function minimized  $\sum w(|F_o| - |F_c|)^2$  where  $w = 4F_o^2/\sigma^2(F_o^2)$ . The weighting scheme was based on the counting statistics and included a factor (*p*) to down weight intense reflections. Plots of  $\sum w(|F_o| - |F_c|)^2$  versus  $|F_o|$ , reflection order in data collection,  $\sin \theta/\lambda$ , and various classes of indices showed no unusual trends.

Neutral atom scattering factors were taken from Cromer and Waber.<sup>34</sup> Anomalous dispersion effects,<sup>35</sup> were included in *F*<sub>calc</sub> values for Δ*f*' and Δ*f*" were those of Cromer.<sup>36</sup> All calculations were carried out using the TEXSAN crystallo-

graphic computing package<sup>37</sup> of the Molecular Structure Corporation. Molecular and crystal structure diagrams were prepared using either PLUTO<sup>38</sup> or ORTEP<sup>39</sup> plotting packages.

Crystal data, and further details of both measurements and refinements are presented in Table 3 and Table 4. Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC).†

† For details of the deposition scheme, see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 2*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and reference no. 188/19.

### Empirical force field calculations

The molecular modelling package Macromodel 4.5,<sup>6</sup> running on a Silicon Graphics 4D 240 GTX work station was used. The MM3\* force field of Allinger *et al.*<sup>5</sup> was used for calculations with no modification of parameters.

### Hydrolyses of toluamide

The reaction medium was 1 : 1 v/v acetic acid–water made up at 25 °C. A stock solution containing toluamide (0.003 M), benzoic acid (0.002 M as internal reference) and sodium acetate (0.10 M) was used for all determinations.

For a typical kinetic experiment, the appropriate xanthone was added to a portion of the stock solution to make its concentration 0.0001 M. This solution was then divided and sealed into 10 glass ampules. Nine of these were transferred into a constant temperature bath at 170 °C (refluxing decane) and the clock started. At known times of over three half-lives of the reaction (*ca.* 12 h), a tube was removed and cooled in ice then stored at 10 °C. When all samples were removed, they were opened and analysed by HPLC on an ODS Novopak column (8NVC185m P516A02), eluting with 50:50 methanol–water containing 0.5% acetic acid, on a Waters X-module fitted with a PE LC-480 diode array detector. Reactant and product (toluamide and toluic acid) and the internal reference (benzoic acid) were fully resolved, and no other materials were detected. Changes in absorbance at 260 nm were used to follow changes in concentrations. Good first-order fits were found for growth of decay of toluamide, and first-order rate constants were obtained from non-linear regression analysis of the curve to the data.

### Metal binding studies

A series of 0.1 M methanolic metal ion solutions were prepared by dissolving an appropriate weighed amount of the bromide in freshly distilled methanol. Weaker solutions were then prepared by successive dilutions. Stock solutions (*ca.* 10<sup>-4</sup> M) of the crown ketones were prepared by dissolving a weighed amount of the crown (between 2 and 4 mg) in 100 ml of methanol. A UV spectrum was then run on the crown solution in 1 cm cells containing 3 ml of the crown ether solution. Aliquots of salt solution (5 to 10 µl) were then added by microsyringe and spectra rerecorded. Absorbances were all less than 1.5. Temperatures were uncontrolled but were between 27 and 30 °C.

The UV data was fitted to  $A_{\text{exp}} = \epsilon_{\text{cr}} C_{\text{tot}} - \delta\epsilon C_{\text{cm}}$ , where  $A_{\text{exp}}$  is the experimental absorbance,  $\epsilon_{\text{cr}}$  the extinction of the uncomplexed crown,  $C_{\text{tot}}$  the total concentration of the crown and  $\delta\epsilon$  is the difference in extinction coefficient between free and bound crown at the observing wavelength.  $C_{\text{cm}}$  is the concentration of the metal ion complex and satisfies the usual binding expression in eqn. (5) where  $M_{\text{tot}}$  is the total concen-

$$C_{\text{cm}}^2 - (C_{\text{tot}} + M_{\text{tot}} + 1/K)C_{\text{cm}} + M_{\text{tot}}C_{\text{tot}} = 0 \quad (5)$$

tration of added metal ion. Estimates of extinction coefficient changes on complex formation were made from spectra of the crowns run in a series of concentrated metal ion solutions (0.01 to 0.05 M) where spectra were not dependent on ion concentration. Equilibrium constants,  $K$ , were then obtained by simulation of the data with both  $K$  and  $\delta\epsilon$  as adjustable parameters, using a Newton–Raphson procedure<sup>40</sup> to minimize the sum of squares of residuals.

### Acknowledgements

We thank SERC and Zeneca Specialties for a studentship (N. M.). Additional generous financial support and advice was provided by Zeneca plc.

### References

- 1 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.
- 2 S. C. Biswas and R. K. Sen, *Indian J. Pure and Appl. Physics*, 1982, **20**, 414.
- 3 C. G. Le Fèvre and R. J. W. Le Fèvre, *J. Chem. Soc.*, 1937, 196.
- 4 M. Mercer and M. R. Truter, *J. Chem. Soc., Dalton Trans.*, 1973, 2469; J. D. Dunitz and P. Seiler, *Acta Cryst.*, 1973, **B29**, 599.
- 5 N. L. Allinger, Z. S. Zhu and K. Chen., *J. Am. Chem. Soc.*, 1992, **114**, 6120 and references therein.
- 6 F. J. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, C. Caulfield, G. Chang, T. Hendrojon and W. C. Still, *J. Comput. Chem.*, 1990, **11**, 440.
- 7 J. T. Sprague, J. C. Tai, Y. Tuh, and N. L. Allinger, *J. Comput. Chem.*, 1987, **8**, 81.
- 8 G. A. Jeffrey and W. Saenger, *Hydrogen Bonding in Biological Structure*, Springer-Verlag, Berlin 1991.
- 9 T. Steiner, *J. Chem. Soc., Chem. Commun.*, 1994, 2341.
- 10 K. Matsuzaki and H. Ito., *J. Polym. Sci. Physics*, 1974, **12**, 2507.
- 11 H. Weiser, W. G. Laidlaw, P. J. Kruger and H. Fuhrer, *Spectrochimica Acta*, 1968, **24A**, 1055.
- 12 B. L. Allwood, S. E. Fuller, P. C. Y. K. Nong, A. M. Z. Slawin, J. F. Stoddart and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1984, 1356; F. Vogtle, W. M. Muller and W. H. Watson, *Top. Curr. Chem.*, 1984, **125**, 131; R. D. Rogers, P. D. Richards and E. J. Voss, *J. Inclusion Phenom.*, 1988, **6**, 65; R. L. Garrell, J. C. Smyth, F. R. Fronczek, R. Gandour, *J. Inclusion Phenom.*, 1988, **6**, 73.
- 13 D. Mootz, A. Albert, S. Schaefer and D. Staben, *J. Am. Chem. Soc.*, 1994, **116**, 12045.
- 14 F. Vogtle and W. M. Muller, *Chem. Ber.*, 1981, **114**, 3179.
- 15 A. Elbasaouny, H. J. Brugge, K. Von Deuten, M. Dickel, A. Knochel, K. U. Koch, J. Kopf, D. Melzer and G. Rudolph, *J. Am. Chem. Soc.*, 1983, **105**, 6568.
- 16 G. R. Newkome, F. R. Fronczek and D. Kholi, *Acta Crystallogr., Sect. B*, 1981, **37**, 2114.
- 17 D. J. Cram, T. Kaneda, R. C. Helgeson, S. Bruce Brown, C. B. Knobler, E. Maverick and K. N. Trueblood, *J. Am. Chem. Soc.*, 1985, **107**, 3645; D. J. Cram, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1009.
- 18 T. Steiner and W. Sanger, *J. Am. Chem. Soc.*, 1992, **114**, 10146.
- 19 M. J. Bovill, D. J. Chadwick, I. O. Sutherland and D. Watkin, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1529; E. Maverick, P. Seiler, W. B. Schweizer and J. D. Dunitz, *Acta Crystallogr., Sect. B*, 1980, **36**, 615; J. Dale, *Isr. J. Chem.*, 1980, **20**, 3; G. Wipff, P. Weiner and P. Kollman, *J. Am. Chem. Soc.*, 1982, **104**, 3249.
- 20 E. M. D. Keegstra, A. L. Spek, J. W. Zwikker and L. W. Jenneskens, *J. Chem. Soc., Chem. Commun.*, 1994, 1633; D. S. Reddy, B. S. Goud, K. Pannersevam and G. R. Desiraju, *J. Chem. Soc., Chem. Commun.*, 1993, 663; R. Taylor and O. Kennard, *Acc. Chem. Res.*, 1984, **17**, 320.
- 21 I. R. Hanson, D. L. Hughes and M. R. Truter, *J. Chem. Soc., Perkin Trans. 2*, 1976, 972.
- 22 H. M. Colquhoun, S. M. Doughty, J. F. Stoddart, A. M. Z. Slawin and D. J. Williams, *J. Chem. Soc., Dalton Trans.*, 1986, 1639.
- 23  $H_0$  values from C. D. Johnson, A. R. Katritzsky and S. A. Shapiro, *J. Am. Chem. Soc.*, 1969, **91**, 6654.
- 24 L. P. Hammett and A. J. Deyrup, *J. Am. Chem. Soc.*, 1932, **43**, 2721.
- 25 For recent reviews see (a) R. A. Cox, *Acc. Chem. Res.*, 1987, **20**, 27; (b) A. Bagno, G. Scorrano and R. A. More O'Ferrall, *Rev. Chem. Intermed.*, 1987, **7**, 313.
- 26 A. Levi, G. Modena and G. Scorrano, *J. Am. Chem. Soc.*, 1974, **91**, 6585.
- 27 N. Poonia and A. V. Bajaj, *Chem. Rev.*, 1979, **79**, 389.
- 28 R. M. Izatt, G. A. Clark, J. D. Lamb, J. E. King and J. J. Christensen, *Thermochim. Acta*, 1986, **97**, 115.
- 29 K. Sighara, H. Kamiya, M. Yamaguchi, T. Kaneda and S. Misumi, *Tetrahedron Lett.*, 1981, **22**, 1619; G. D. Beresford and J. F. Stoddart, *Tetrahedron Lett.*, 1980, **21**, 867.
- 30 X. X. Zhang, A. V. Bordunov, J. S. Bradshaw, N. K. Dalley, X. Kou and R. M. Izatt, *J. Am. Chem. Soc.*, 1995, **117**, 11507.
- 31 R. M. Izatt, J. S. Bradshaw, K. Pawlak, R. L. Bruening and B. J. Tabet, *Chem. Rev.*, 1992, **92**, 1261.
- 32 N. Walker and D. Stuart, *Acta Crystallogr., Sect. A*, 1983, **38**, 158.
- 33 G. M. Sheldrick, SHELXS86, in *Crystallographic Computing*, eds. G. M. Sheldrick, C. Krueher and R. Goddard, Oxford University Press, Oxford, 1985, p. 175.
- 34 D. T. Cromer and J. T. Waber, *International Tables for X-Ray Crystallography*, Kynoch, Birmingham, 1974, vol. IV, table 2.2a.

- 35 J. A. Ibers and W. C. Hamilton, *Acta Crystallogr.*, 1964, 17, 781.
- 36 D. T. Cromer, *International Tables for X-Ray Crystallography*, Kynoch, Birmingham, 1974, vol. IV, Table 2.3.1.
- 37 TEXSAN-TEXRAY Structure Analysis Package, Molecular Structure Corporation, 1985.
- 38 S. Motherwell and W. Clegg, PLUTO, Program for Plotting Molecular and Crystal Structures, University of Cambridge, England, 1978.
- 39 C. K. Johnson, ORTEP II, Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, 1976.
- 40 *Computational Methods for Determination of Formation Constants*, ed. D. J. Leggett, Plenum, London and New York, 1985, ch. 1.

*Paper 6/030001*

*Received 29th April 1996*

*Accepted 30th May 1996*