Effect of Metal Ion Complexation on the Rate of the Alkaline Ester Hydrolysis of 4'-(4-Nitrophenoxycarbonyl)benzo-15-crown-5 in Ethanol–Water Mixtures

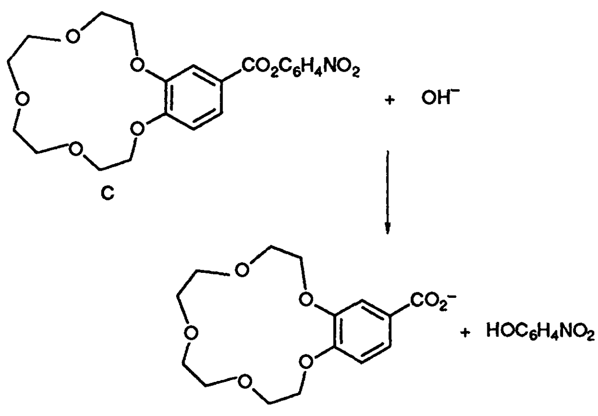
Robert J. M. Hedderwick,* Frank Hibbert* and (the late) Victor Gold
Department of Chemistry, King's College London, Strand, London WC2R 2LS, UK

The second-order rate coefficient for the hydroxide ion-promoted hydrolysis of 4'-(4-nitrophenoxycarbonyl)benzo-15-crown-5 in 54% (w/w) ethanol–water is increased by addition of NaCl, KCl, RbCl and CsCl. For each salt a limiting value of the rate coefficient is reached at high concentrations of salt. The limiting values are up to two times higher than the rate coefficient in the absence of salt and decrease in the order $Na^+ > K^+ > Rb^+ > Cs^+$. For reaction in the presence of K^+ the limiting value decreases as the solvent is changed from 54% to 49% and to 39% (w/w) ethanol–water. The kinetic results are compatible with the formation of a complex between the crown ester and the metal ion which is more susceptible to alkaline hydrolysis than the uncomplexed crown ester. The crown ester is unable to bind Li^+ and the presence of LiCl results in a small reduction in the rate. For the other cations, the results have been analysed to give values for the equilibrium constant for complex formation (K) and the rate coefficient (k^0_c) for hydrolysis of the crown ester/cation complexes. After allowance is made for electrolyte effects, it is found that the rate coefficients (corrected to infinite dilution) for hydrolysis of the crown ester/cation complexes are seven to twelve times greater than that for hydrolysis of the uncomplexed crown ester. The trends in the values of K and k^0_c with cation size and solvent are discussed.

Details of the binding of metal ions and small molecules to crown compounds are well established.[1,2] In the present work the effect of metal ion binding on the chemical reactivity of a crown ether containing a reactive site is investigated. There has been only limited study of this aspect of the behaviour of crown ethers. In acetonitrile as solvent, the rate of nucleophilic attack by piperidine on an ester linked to a crown ether is increased by metal ion binding to the crown ether,[3] an effect explained by the proximity of the charged metal ion to the reaction site. In the reaction of 4-nitrophenol with benzoic anhydride in acetonitrile, the effectiveness of catalysis by a pyridine moiety attached to a crown ether ring is reduced by metal ion binding to the crown ether.[3]

The effect of metal ion binding on the reactivity of sites incorporated as part of a crown ether ring has also been studied. For example, crown ethers having an acetal linkage undergo a hydrogen ion-catalysed ring opening in 60% (v/v) dioxane–water and the rate of this reaction is strongly depressed by the addition of metal ions which are able to bind to the crown ether.[4] In contrast, the rate of the hydroxide ion-promoted ring opening of a 19-crown-6 molecule with a malonate ester linkage is enhanced[5] by complex formation with Na^+, K^+, Rb^+ and Cs^+.

We wish to report kinetic results, in ethanol–water mixtures, of the effect of metal ion binding on the alkaline hydrolysis of a substituted benzo-15-crown-5 possessing an ester group (C), eqn. (1). The choice of ethanol–water for studying the hydrolysis was dictated by the need for an aqueous medium in which metal ion binding occurs at moderate salt concentrations, so that corrections for changes in activity coefficients with the concentration of salt can be estimated from the Debye–Hückel theory. Benzo-15-crown-5, the parent crown ether of the substrate, is known[6] to bind Na^+, K^+, Rb^+ and Cs^+.



(1)

Experimental

Materials.—A synthesis of 4'-(4-nitrophenoxycarbonyl)benzo-15-crown-5 has been published.[7] Our procedure initially followed a similar route: benzo-15-crown-5 (prepared by reaction of 1,2-dihydroxybenzene and tetraethylene glycol dichloride[1]) was converted[8] to 4'-formylbenzo-15-crown-5 which was oxidised[9] to yield 4'-carboxybenzo-15-crown-5. The conditions for the final esterification step to give 4'-(4-nitrophenoxycarbonyl)benzo-15-crown-5 were, however, different from the published procedure. This step was accomplished[9] by allowing 4'-carboxybenzo-15-crown-5 (1.8 mmol) to react with oxalyl chloride (11 mmol) in dichloromethane (10 cm^3) containing dry pyridine (0.05 cm^3) at room temperature for 6 h. The solvent was removed under reduced pressure without heating and further portions of dichloromethane (2 × 7.5 cm^3) were added and removed in a similar way. The residue, 4'-chlorocarbonylbenzo-15-crown-5, was dissolved in a solution of 4-nitrophenol (1.7 mmol) in dry pyridine (2 cm^3) and allowed to stand overnight. Water (0.5 cm^3) was added and reaction was allowed to proceed for 30 min, when a saturated solution of sodium hydrogen carbonate (10 cm^3) containing ice was added to the solution. The reaction mixture was extracted with dichloromethane. The organic extracts were reduced to give an oil and after repeated addition and evaporation of toluene to remove pyridine as an azeotrope, the resulting white solid was recrystallised from ethanol. The pure product (m.p. 140 °C; lit.[7] 139–140 °C) was identified as 4'-(4- nitrophenoxycarbonyl)benzo-15-crown-5 by its NMR spectrum $\delta(CDCl_3)$ 4.0 (m, 16 H, CH_2) and 7.0–8.4 (m, 7H, Ar).

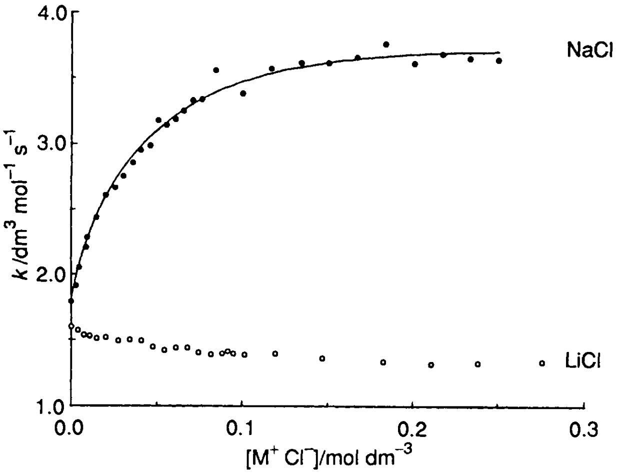


Fig. 1 Second-order rate coefficients (k) for the alkaline hydrolysis of 4′-(4-nitrophenoxycarbonyl)benzo-15-crown-5 in 54% (w/w) ethanol–water in the presence of lithium and sodium chloride. The points are experimental values and the curve through the data for NaCl is the best fit to the mechanism shown in eqns. (2)–(4).

Lithium, rubidium and caesium chlorides (reagent grade) and sodium and potassium chlorides (Analar grade) were dried under vacuum before use. The concentrations of metal chloride solutions made up by weight were checked by potentiometric titration against aqueous silver nitrate. Aqueous ethanol solvents were made up by weight from distilled water and 99.7% ethanol (James Burroughs, AR quality). Lithium hydroxide solutions were made up by weight and standardised with standard aqueous hydrochloric acid.

Kinetic Measurements.—The effect of LiCl, NaCl, KCl, RbCl and CsCl on the rate of the alkaline hydrolysis of 4′-(4-nitrophenoxycarbonyl)benzo-15-crown-5 was examined in 54% (w/w) ethanol–water. Salt concentrations up to 0.25 mol dm^{-3} were used. Stock solutions of the crown ester and the alkali metal chlorides were made up in an ethanol–water mixture which had been prepared by weight in a 2 dm^3 batch. The same solvent preparation was used for studying the whole of the concentration range for any one salt to ensure an identical solvent composition.

The reaction solutions were prepared by placing 1.5 cm^3 of the stock crown ester solution into a quartz cuvette, together with the appropriate volume of salt solution to give the required final concentration of salt. The solution was then made up to a volume of 3.0 cm^3. Volumes were delivered using calibrated syringes. The reaction mixture was thermostatted at 25 °C in the cell compartment of a Unicam SP 8-100 spectrophotometer and, to initiate the hydrolysis, 0.015 cm^3 of aqueous LiOH was added. The initial concentrations of lithium hydroxide and crown ester in the reaction solution were typically 1.5×10^{-3} and 5.0×10^{-5} mol dm^{-3}, respectively.

The hydrolysis was monitored by observing the increase in absorbance with time at 400 nm, corresponding to formation of 4-nitrophenolate ion. The total change in absorbance corresponded accurately to that expected for formation of an equimolar concentration of 4-nitrophenolate from 4′-(4-nitrophenoxycarbonyl)benzo-15-crown-5. The reaction was pseudo first-order under the conditions employed, and a non-linear least-squares method was used to obtain an exponential fit to the data. Correlation coefficients for the fit were generally better than 0.9999 for over two half-lives. At each salt concentration, three determinations of the rate coefficient were made, together with a simultaneous measurement of the rate coefficient in the absence of salt. The three determinations of the rate coefficient at each salt concentration gave a standard deviation of < 1.5% and the *ca.* 25 determinations of the rate coefficient in the absence of salt for each solvent preparation gave a standard deviation of < 2%. For the different solvent preparations made up for studies with each salt a standard deviation of 4% was found. Values of the second-order rate coefficients at each salt concentration were calculated by dividing the first-order rate coefficient by the hydroxide ion concentration.

Results and Discussion

The variation of the observed second-order rate coefficient (k) for alkaline hydrolysis of 4′-(4-nitrophenoxycarbonyl)benzo-15-crown-5 with the concentration of NaCl and LiCl in 54% (w/w) ethanol–water is shown in Fig. 1.[10] The variations of k with concentration of KCl, RbCl and CsCl were similar to that for NaCl, except that the limiting values of k reached at high concentrations of the metal chlorides increased in the order CsCl < RbCl < KCl < NaCl. The effect of KCl on the rate of hydrolysis in 49% and 39% (w/w) ethanol–water was also investigated. The dependence of k on the concentration of KCl was similar to that in 54% (w/w) ethanol–water but the value of the limiting rate increased in the order 39% < 49% < 54%. The increase in the rate of alkaline hydrolysis on adding Na$^+$, K$^+$, Rb$^+$ or Cs$^+$ is compatible with the formation of a crown ester/cation complex which is more reactive than the uncomplexed crown ester. The rate increases because the fraction of the crown ester that is complexed increases with the concentration of the cation. The effect of each metal ion on the rate coefficient for alkaline hydrolysis is illustrated by the magnitude of the ratio $k_{0.2}/k_f$ in which $k_{0.2}$ is the value of the rate coefficient (k) for each salt at a concentration of 0.2 mol dm^{-3} and k_f is the value in the absence of salt, see Table 1. For LiCl the results are compatible with negligible binding of Li$^+$ by the crown moiety, and the decrease in k with salt concentration is due to a small electrolyte effect on the reaction of the uncomplexed crown ester with hydroxide ion.

The kinetic results for the variation of k with metal chloride concentration in solutions of NaCl, KCl, RbCl and CsCl can be explained in terms of the mechanism summarised in eqns. (2)–(4). It is assumed that the equilibrium between 4′-(4-nitrophenoxycarbonyl)benzo-15-crown-5 and each metal ion, for which the equilibrium constant is given by eqn. (5), is established rapidly. The rate of disappearance of 4′-(4-nitrophenoxycarbonyl)benzo-15-crown-5 is given by eqn. (6) where the total (complexed and uncomplexed) concentration of substrate [C$_{st}$] is less than that of hydroxide ion and the cation (M$^+$). The rate coefficient k can then be expressed as the sum, eqn. (7). Combining eqns. (5) and (7) gives eqn. (8) which

$$\mathrm{C} + \mathrm{OH}^- \xrightarrow{k_f} \text{products} \qquad (2)$$

$$\mathrm{C} + \mathrm{M}^+ \overset{K}{\rightleftharpoons} \mathrm{CM}^+ \qquad (3)$$

$$\mathrm{CM}^+ + \mathrm{OH}^- \xrightarrow{k_c} \text{products} \qquad (4)$$

$$K = [\mathrm{CM}^+]/[\mathrm{C}][\mathrm{M}^+] \qquad (5)$$

$$-\mathrm{d}[\mathrm{C}_{st}]/\mathrm{d}t = -\{\mathrm{d}[\mathrm{C}]/\mathrm{d}t + \mathrm{d}[\mathrm{CM}^+]/\mathrm{d}t\} \qquad (6)$$

$$k = (k_f[\mathrm{C}] + k_c[\mathrm{CM}^+])/[\mathrm{C}_{st}] \qquad (7)$$

$$k = (k_f + k_cK[\mathrm{M}^+])/(1 + K[\mathrm{M}^+]) \qquad (8)$$

Table 1 Effect of alkali metal chlorides on the kinetics of hydrolysis of 4′-(4-nitrophenoxycarbonyl)benzo-15-crown-5

Solvent EtOH–H_2O (w/w)	Relative permittivity	Salt	k_f/dm^3 mol^{-1} s^{-1}	$k_{0.2}$/dm^3 mol^{-1} s^{-1}	$k_{0.2}/k_f$	K/dm^3 mol^{-1}	k^0_c/dm^3 mol^{-1} s^{-1}	k^0_c/k_f
54%	46.8	LiCl	1.60	1.33	0.83	—	—	—
54%	46.8	NaCl	1.79	3.68	2.06	4.5	21	12
54%	46.8	KCl	1.68	3.11	1.85	4.5	18	11
54%	46.8	RbCl	1.66	2.50	1.51	2.0	19	12
54%	46.8	CsCl	1.75	2.19	1.25	[a]	[a]	
49%	49.8	KCl	1.62	2.78	1.72	4.0	14	9
39%	55.6	KCl	1.44	2.13	1.48	2.5	11	7

[a] The effect of CsCl on the value of k was too small to allow values of k^0_c and K to be derived.

predicts a curved dependence of the second-order rate coefficient (k) on metal ion concentration, reaching a limit, $k = k_c$, at high concentrations of M^+ corresponding to reaction of fully complexed 4′-(4-nitrophenoxycarbonyl)benzo-15-crown-5. Although the experimental behaviour is qualitatively similar to that predicted by eqn. (8), to calculate values of K and k_c from the results it is necessary to make corrections for the effect on the rate coefficients of changing ionic strength as the salt concentration is varied from 0–0.25 mol dm^{-3}. Reaction (4) between the crown ester/cation complex and hydroxide ion is subject to a primary kinetic electrolyte effect. The value of the rate coefficient at hypothetical zero ionic strength (k^0_c) is related to the value under the experimental conditions at finite ionic strength (k_c) by eqn. (9) where y_{OH^-}, y_{CM^+} and $y_{\ddagger}$ denote

$$k_c = k^0_c(y_{OH^-}y_{CM^+}/y_{\ddagger}) \qquad (9)$$

the activity coefficients of the hydroxide ion, complexed metal ion and the reaction transition state, respectively. The transition state has zero net charge and the activity coefficient $y_{\ddagger}$ is taken as unity. To calculate the value of $y_{OH^-}y_{CM^+}$ it is assumed that this can be approximated by the Debye–Hückel theory expression, eqn. (10).[11] The parameters A and B are defined by eqn. (11) where ε_r is the relative permittivity of the medium

$$\log_{10} y_{CM^+}y_{OH^-} = -ZA[M^+]^{\frac{1}{2}}/(1 + B\mathring{a}[M^+]^{\frac{1}{2}}) \qquad (10)$$

$$\left.\begin{aligned} A &= 1.82 \times 10^6(\varepsilon_r T)^{-\frac{3}{2}} \\ B &= 50.29 \times 10^{10}(\varepsilon_r T)^{-\frac{1}{2}} \end{aligned}\right\} \qquad (11)$$

and T is the temperature. In eqn. (10), $\mathring{a}$ is the ion-size parameter and the value $\mathring{a} = 4 \times 10^{-10}$ m is taken for all metal chlorides. In addition to the correction for a change in activity coefficients with ionic strength, a further small correction is required because the concentration of free metal ions and the value of the ionic strengths of the solutions will be different from their stoichiometric values due to the formation of ion-pairs, eqn. (12). Values of ion pair association constants, eqn. (13), were

$$M^+ + Cl^- \rightleftharpoons (M^+Cl^-) \qquad (12)$$

$$K_{pair} = [(M^+Cl^-)]/[M^+][Cl^-] \qquad (13)$$

interpolated from the values measured conductimetrically for metal chlorides in ethanol–water mixtures.[12]

Eqn. (8) contains two unknown parameters, k_c and K. The value of k_f was measured in solutions in the absence of metal chlorides and it was assumed that the effect of varying ionic strength on the value of k_f was negligible. This assumption is justified because the contribution of k_f to the observed rate coefficient is most significant at low salt concentrations where electrolyte effects are small, and because the value of k in the presence of LiCl (a non-complexing salt) shows only a small decrease from 1.60–1.34 dm^3 mol^{-1} s^{-1} as the concentration of LiCl is varied from 0–0.28 mol dm^{-3}. Values of the second-order rate coefficients k at different concentrations of M^+ were calculated using eqn (8), taking into account electrolyte effects, eqns. (9) and (10), and ion-pairing, eqn. (13), and fitted to the experimentally-determined values of k by a step-wise iterative adjustment of k^0_c and K. The best-fit values of k^0_c and K are given in Table 1. The points in Fig. 1 for NaCl are experimental values and the curve is generated from the above equations using the values of k^0_c and K for NaCl given in Table 1. Fits to the data for KCl and RbCl were equally good to that shown for NaCl but the effect of CsCl on the rate was too small to permit values of k^0_c and K to be derived.

The shape of the plots of k *vs.* salt concentration arises because the reactive crown ester/cation complex reaches a limiting concentration as the concentration of salt is increased, and because the value of k_c decreases as the ionic strength of the solution increases. Although the values of k in Fig. 1 approach a limiting value at a concentration of NaCl of *ca.* 0.25 mol dm^{-3}, the crown ester is not fully complexed at this concentration. Further increase in the concentration of salt brings about a decrease in k because of the effect of ionic strength on the value of k_c. Studies at concentrations of salt greater than 0.25 mol dm^{-3} were not carried out because of the uncertainties in the Debye–Hückel theory in this region.

Although good fits to the experimental data are obtained with the mechanism in eqns. (2)–(4), owing to the assumptions involved in the application of eqn. (8), and in particular the limited validity of the Debye–Hückel law at concentrations as high as 0.25 mol dm^{-3}, the derived values of k^0_c and K are subject to a large uncertainty. The breakdown of the Debye–Hückel law is the most serious source of uncertainty in the values of k^0_c and K and ion-pairing in these solutions does not have a large effect. If ion-pairing is neglected good fits to the experimental data are generated and the values of k^0_c and K that are obtained do not differ greatly from those given in Table 1.

The absence of binding by Li^+ and the relative values of the equilibrium constants for binding of the other cations is compatible with the estimated[2] diameter (170–220 pm) of the cavity of benzo-15-crown-5 and the cation diameters (pm) of Li^+ (136), Na^+ (196), K^+ (266), Rb^+ (296) and Cs^+ (334).[2] The highly-solvated lithium ion is too small to interact simultaneously with all of the crown ether oxygens and binds to a negligible extent. The binding of Na^+, K^+, Rb^+ and Cs^+ and the absence of binding of Li^+ is typical of the behaviour for crown ether rings of this size.

The derived values of K for binding of Na^+, K^+ and Rb^+ (see Table 1) are smaller than the corresponding values measured for benzo-15-crown-5 and these cations in methanol–water mixtures[6] at a constant ionic strength of 0.1 mol dm^{-3}. In 20% and 40% (w/w) methanol–water mixtures, for which the relative permittivity (ε_r) is 70 and 61, respectively, the equilibrium constant for binding of Na^+ to benzo-15-crown-5 has values of 5.2 ± 0.4 and 15 ± 5, respectively. In 70% methanol–water (ε_r 47) the value of K is 98 ± 25. For binding of K^+, Rb^+ and Cs^+, respectively, to benzo-15-crown-5 in 70% methanol–water the following values of K were obtained: 32 ± 20, 63 ± 40 and 50 ± 1. One reason for the values of the cation-binding constants of 4′-(4-nitrophenoxycarbonyl)benzo-15-crown-5 in ethanol–water being smaller than those for benzo-15-crown-5 in methanol–water is the electron-withdrawing effect of the 4-nitrophenoxycarbonyl group. For example, it has been shown[13] that the equilibrium constant for binding of Na^+ to 4′-methoxycarbonylbenzo-15-crown-5 in acetone is three times lower than that for binding of Na^+ to benzo-15-crown-5. The effect of a 4-nitrophenoxycarbonyl substituent in the 4′ position is likely to be similar.

The rate coefficients for hydrolysis of the crown ester/cation complexes (k^0_c) are seven to twelve times greater than the rate coefficient for hydrolysis of the uncomplexed crown ester (see Table 1). It is likely that this is due to a stabilisation of the transition state for the hydrolysis by the positive charge of the bound cation close to the reaction centre.

Kinetic data for the hydrolysis in the presence of KCl were also obtained in 49%, and 39% (w/w) ethanol–water. In calculating the corrections for the change in ionic strength by the Debye–Hückel theory, the following values were used for the relative permittivity in eqn. (11): 54% ethanol–water (ε_r 46.8), 49% (ε_r 49.8), 39% (ε_r 55.6). The experimental data were fitted by the values of k^0_c and K given in Table 1. The decrease in the value of K as the relative permittivity of the solvent increases (ε_r 46.8, K 4.5; ε_r 49.8, K 4.0; ε_r 55.6, K 2.5) is compatible with greater stabilisation of the free cation (due to solvation) on going to a more polar solvent. A similar trend was reported for the binding of Na^+ to benzo-15-crown-5 in methanol–water mixtures.[6] The decrease in the value of k^0_c as the relative permittivity of the solvent increases is in the direction expected for a diminution of the electrostatic interaction between the complexed cation and the carbonyl group. This suggests that the effective relative permittivity of this space increases as the permittivity of the bulk solvent increases.

In the present work the increases in reactivity brought about by metal ion binding are smaller than those observed for the hydrolysis of crown ether acetals[4] and crown malonates,[5] where the reactive site is in the crown ether ring. In these latter examples, the bound cation is much closer to the reaction centre and consequently the effect of the charge is much greater. The magnitude of the present effects are similar to those observed[14] for the reaction of a substituted benzo-18-crown-6 compound with 1-benzyl-1,4-dihydronicotinamide in 70% (w/w) methanol–water (ε_r 47). In the presence of 0.2 mol dm^{-3} of the cations NH_4^+, K^+, Rb^+ or Cs^+ the rate coefficient is increased *ca.* 2-fold compared with the rate coefficient in the absence of cations, and in the presence of Na^+ the increase is 1.4-fold. As with the reaction of 4′-(4-nitrophenoxycarbonyl)benzo-15-crown-5 the reaction is taking place at an atom attached to the 4-position of a benzo crown ether.

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