The Influence of Cation Binding on the Kinetics of the Hydrolysis of a Crown Ether-like Cyclic Ester

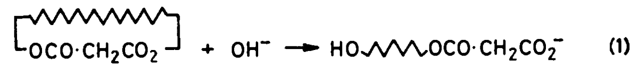
David S. Baker and Victor Gold *
Department of Chemistry, King's College London, Strand, London WC2R 2LS

The initial rate of the reaction in 60:40 (v/v) dioxan–water between hydroxide ion and the cyclic diester (1,5,8,11,14,17-hexaoxanonadecane-2,4-dione formed from malonic acid and pentaethylene glycol (3,6,9,12-tetraoxatetradecane-1,14-diol) to give the acyclic half ester is found to be strongly increased by the addition of sodium chloride, potassium chloride, rubidium chloride, and caesium chloride in low concentration. The effect is analysed in terms of complex formation between substrate and metal ion, the complexed form having a higher reactivity. Approximate values of the equilibrium constant and rate constant involved are derived by a curve-fitting procedure. The ratio of the initial rate constants for reaction of complexed and uncomplexed ester is in accordance with the electrostatic attraction between the bound metal ion and the negative charge introduced by the attack of the hydroxide ion, provided the effective relative permittivity of the space between the two charges is taken to have a value close to the relative permittivity of the bulk solvent.

In the hydrolysis of crown ether acetals, catalysed by hydrogen ions, metal ions of a size appropriate for guest–host interaction decrease the rate of reaction.[1,2] The effect is interpreted as arising from the electrostatic repulsion between the metal cation bound inside the crown ether-like ring and the site of protonation on one of the acetal oxygen atoms. Its size is fairly well predicted by straightforward electrostatic calculations.

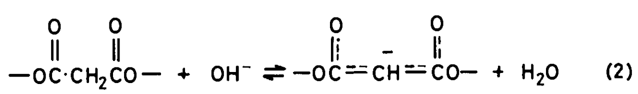
The present work attempts to test and extend this approach by examining the corresponding effect of metal ions on the rate of hydrolysis of an ester of similar structure. Ester hydrolysis involves reaction between hydroxide ions and the substrate. If the conclusions drawn from the acetal hydrolyses are correct, the electrostatic interaction between a bound metal ion and the approaching hydroxide ion should in this case lead to a semi-quantitatively predictable increase in the rate of reaction.

The substrate chosen for this study was the malonate diester (I) of pentaethylene glycol (3,6,9,12-tetraoxatetradecane-1,14-diol). The compound (1,5,8,11,14,17-hexaoxanonadecane-2,4-dione, or 19-crown-6 malonate for short) had previously been prepared and shown to bond some metal ions, though the association constants are smaller than for crown ethers of similar ring size.[3,4] The hydrolysis was studied at 25 °C in dioxan–water (60:40, v/v), the same conditions as for the earlier study of crown ether acetals.[2] The kinetics of hydrolysis of diesters is generally complicated because the two ester groups as a rule react at different, but not vastly different, rates.[5] Our study has therefore concentrated on the rate of the first step (1). The rate of this



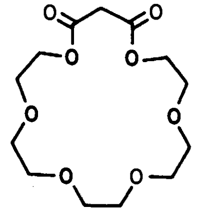
$$\text{OCO}\cdot CH_2CO_2 + OH^- \longrightarrow HO\text{∿∿}OCO\cdot CH_2CO_2^- \qquad (1)$$

process can be monitored spectrophotometrically because the malonic acid diester is in rapid equilibrium with its enolate ion [equation (2)]. Although this ion is present in very low



$$-O\overset{\overset{O}{\|}}{C}\cdot CH_2\overset{\overset{O}{\|}}{C}O- + OH^- \rightleftharpoons -O\overset{\overset{O}{\vdots}}{C}\!=\!\overset{-}{CH}\!=\!\overset{\overset{O}{\vdots}}{C}O- + H_2O \qquad (2)$$

concentrations (and therefore does not appreciably affect the concentration of the ester and its rate of reaction), it has an intense absorption at 262 nm (compared with 260 nm for the anion of diethyl malonate [6]). The hydrolysis products, the malonate ion and the monoester anion, are considerably less acidic than diesters of malonic acid and consequently do not exhibit this absorption in alkaline solution. To check the validity of this kinetic method, the hydrolysis of diethyl malonate was similarly monitored spectrophotometrically. The value of the second-order rate constant for the hydrolytic loss of one ethoxide group ($k_{t \to 0}$ 1.19 dm^3 mol^{-1} s^{-1}) was in exact agreement with the results from titrimetric studies.[5]



(I)

The concentration of the absorbing enolate ion is controlled by equilibrium (2) and is therefore not directly proportional to the concentration of either of the reactants (ester or hydroxide ion) unless that reactant is present in much lower concentration than the other one. In the present study such grossly unequal concentrations were not entirely achieved in practice. The use of a five-fold excess of ester over hydroxide ion means that the reaction is performed under conditions where the decrease in absorbances is only approximately proportional to the decrease in concentration of hydroxide ion. We therefore use the approximation (3), where D is the

$$[OH^-]_t = [OH^-]_0 \frac{D_t - D_\infty}{D_0 - D_\infty} \qquad (3)$$

absorbance at the time indicated as subscript, noting that the expression approaches exactness as $t \longrightarrow 0$, and that its validity is not altered even if the malonate ester is partly complexed by metal ions [provided the complexation equilibrium (4) is rapidly established].

When the reaction is carried out in the presence of cations that can form a 1 : 1 complex with the substrate, the disappearance of the diester is the sum of two processes, the hydrolysis of uncomplexed ester (R) and the hydrolysis of complexed ester (RM$^+$), as summarised in equations (4)—(6).

$$\mathrm{R} + \mathrm{M}^+ \rightleftharpoons \mathrm{RM}^+ \qquad (4)$$

$$\mathrm{R} + \mathrm{OH}^- \xrightarrow{k_f} \text{Monoester anion} \qquad (5)$$

$$\mathrm{RM}^+ + \mathrm{OH}^- \xrightarrow{k_c} \text{Monoester anion} + \mathrm{M}^+ \qquad (6)$$

Equilibrium (4) is assumed to be rapidly established, compared with the rates of the subsequent reactions, which seems justifiable by analogy with similar processes.[7] The equilibrium constant K [equation (7)] and the rate constant k_c are unknown

$$K = [\mathrm{RM}^+]/[\mathrm{R}][\mathrm{M}^+] \qquad (7)$$

in the analysis of rate data. The rate constant k_f can be evaluated separately, provided it is possible to carry out the reaction in the presence of a non-complexing hydroxide base. Under conditions of complexing the stoicheiometric concentration of substrate $[\mathrm{R_{st}}]$ and the rate of its disappearance are given by equations (8) and (9). The integrated rate equation

$$[\mathrm{R_{st}}] = [\mathrm{R}] + [\mathrm{RM}^+] \qquad (8)$$

$$-\frac{d[\mathrm{R_{st}}]}{dt} = -\left(\frac{d[\mathrm{R}]}{dt} + \frac{d[\mathrm{RM}^+]}{dt}\right) \qquad (9)$$

for the second-order reaction (2) (where $[\mathrm{R_{st}}]_0 > [\mathrm{OH}^-]_0$), can be written in the form (10) where k is the second-order

$$\ln\left(1 + \frac{\Delta}{[\mathrm{OH}^-]_t}\right) = \ln\left(\frac{[\mathrm{R_{st}}]_0}{[\mathrm{OH}^-]_0}\right) + \Delta kt \qquad (10)$$

rate coefficient and $\Delta = [\mathrm{R_{st}}] - [\mathrm{OH}^-]$.[8] If the hydrolysis were an uncomplicated ester hydrolysis, the difference Δ would be constant throughout the course of the reaction. In the hydrolysis of diesters it progressively increases from its initial value as the hydrolysis of the monoester takes place. Equation (10) is accordingly a limiting equation that approaches exactness as $t \longrightarrow 0$. We have already noted that equation (3) which is used to deduce the concentration of $[\mathrm{OH}^-]_t$, required in equation (10), is a similarly limiting equation. There is the additional complication that weak association may also occur between metal ions and hydrolysis products, in which case the assumption (11) will progressively become less valid as the reaction proceeds. Accordingly, the

$$[\mathrm{M}^+{}_{\mathrm{st}}] = [\mathrm{M}^+] + [\mathrm{RM}^+] \qquad (11)$$

concentration $[\mathrm{RM}^+]$ can be exactly expressed in terms of K and initial concentrations at zero time [see equation (11) of ref. 2], but not at later stages of the reaction.

For these various reasons we have treated the kinetic data so as to obtain the initial value ($t \longrightarrow 0$) of the second-order rate constant k in equation (10). To this end, values of ln $(1 + \Delta_0/[\mathrm{OH}^-]_t)$ were fitted to a polynomial function of time (12) by the method of least squares. The requisite number of statistically significant terms (usually 2 or 3) was decided on the basis of Snedecor's F test.[9] The required initial second-order rate coefficient $k_{t\rightarrow 0}$ is accordingly given by

$$\ln(1 + \Delta_0/[\mathrm{OH}^-]_t) = a_0 + a_1t + a_2t^2 + \ldots \qquad (12)$$

$$k_{t\rightarrow 0} = a_1/\Delta_0 \qquad (13)$$

equation 13. The variance of a_1 was taken as a measure of the standard deviation of $k_{t\rightarrow 0}$. From equations (5), (6), and (9) the rate constant $k_{t\rightarrow 0}$ is interpreted as the sum (14).

$$k_{t\rightarrow 0} = (k_f[\mathrm{R}]_0 + k_c[\mathrm{RM}^+]_0)/[\mathrm{R_{st}}]_0 \qquad (14)$$

Combining equations (7) and (14) we obtain (15), which is identical in form with the rate equation used in the treatment of crown ether acetal hydrolysis.

$$k_{t\rightarrow 0} = (k_f + k_cK[\mathrm{M}^+]_0)/(1 + K[\mathrm{M}^+]_0) \qquad (15)$$

Reaction (6) involves two oppositely charged ions. It is accordingly subject to a primary kinetic electrolyte effect which we express in a form (16) that is analogous to the equation used in connection with the hydrolysis of crown ether acetals,[2] except that the second term on the right-hand side is opposite in sign because of the different charge type of the reaction. The possible involvement of ion-pairing between

$$\lg k_c = \lg k_c{}^0 - 2A[I^{\frac{1}{2}}/(1 + \rho I^{\frac{1}{2}})] \qquad (16)$$

metal ions and chloride ions was included as before,[2] again using the ion-pair formation constants for alkali-metal chlorides deduced by Fuoss and his collaborators from conductivity measurements.[10] On the basis of our experience with crown ether acetals, the measurements in the present work have focussed on low concentrations of added salt (up to an ionic strength of 0.018M). For this reason the Debye–Hückel law, on which equation (16) is based, is more adequate in the present study. The correction for departures from it, which we have treated in terms of ion-pairing, is accordingly less important and has a much reduced effect on the values of the parameters derived from the analysis of the data.

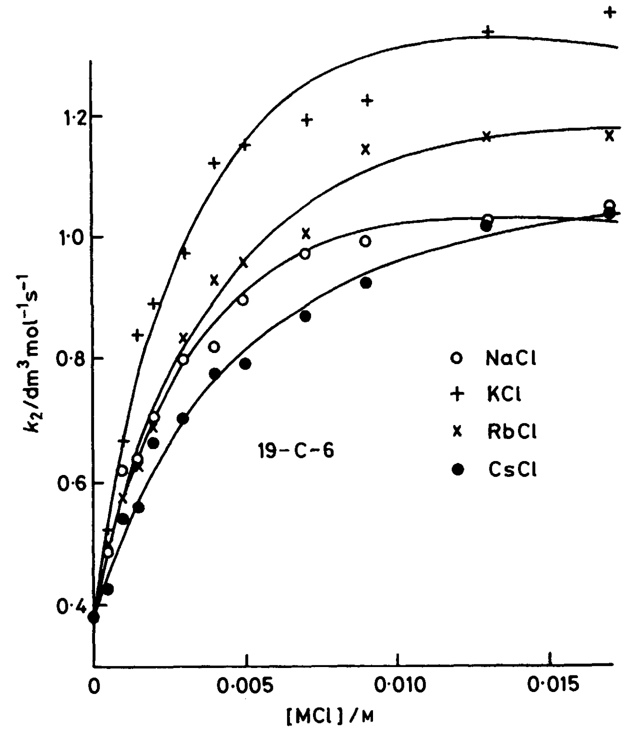
The routine for evaluating K and $k_c{}^0$ from $k_{t\rightarrow 0}$ was exactly the same as that described for the hydrolysis of crown ether acetals.[2]

Because of the low concentration of hydroxide ion in the system, ion association between alkali-metal cations and hydroxide ions is relatively unimportant. As we were unable to find experimental information concerning this, we have consistently used for $\mathrm{M^+\,OH^-}$ the same value of K_{pair} as for $\mathrm{M^+\,Cl^-}$. This estimate was based on the similar size of the two anions.

It should, however, be noted that variation of this parameter between values of 0 and 50 mol^{-1} dm^3 caused a maximum change of only *ca.* 4% in the best-fit values of $k_c{}^0/k_f$ and K. There was no significant change in the fit of theoretically computed curves to the experimental rate constants.

Since ion-pairing becomes significant only at the higher concentrations, ion-pairing of the lithium ion (present at a constant concentration of 10^{-3}M) was neglected throughout.

The Figure summarises the results of the study. The experimental points, showing a large increase in the rate of hydrolysis at quite low salt concentrations for all four alkali-metal chlorides studied, confirm the expectation that metal halides with cations of appropriate size should stabilize a transition state involving the attack on the ester by an anion. The base used in all these experiments was added as lithium hydroxide, and the second-order rate constant 'in the absence of added metal cation' ($k_{t\rightarrow 0}$ 0.38 dm^3 mol^{-1} s^{-1}) actually relates to a 10^{-3}M solution of lithium hydroxide. It is possible that there is some binding of the lithium ion by the substrate but the extent is expected to be slight. In this context two points are to be noted. First, the sequence of the curves in the Figure, with the effect of cations indicating the order $\mathrm{K^+ > Rb^+ > Na^+ > Cs^+}$, is the same as for the acid-catalysed hydrolysis of the crown ether acetal (2-methyl-17-crown-6) containing the same number of ether oxygen atoms in the crown ring (see Figure 4 of ref. 2). It was shown previously that for this acetal lithium ions gave no indication of cation



Experimental points and computer-simulated curves for effect of alkali-metal chlorides on initial rate of hydrolysis

binding. By analogy, the effect of 10^{-3}M-lithium ion is expected to be exceedingly small. A change in the concentration of lithium hydroxide from 1×10^{-3} to 1.66×10^{-3}M causes no significant change in the second-order rate constant.

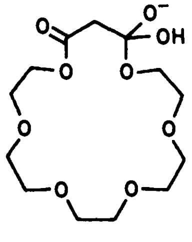
Second, because the reaction rate increases with added salt, the parameters derived from a computer simulation of the dependence of $k_{t\to 0}$ on salt concentration according to equation (5) are not sensitive to the precise value assumed for k_f. The full curves drawn in the Figure are the ' best ' computed curves, and the corresponding values of K and k_c^0/k_f are given in the Table. Comparison of values of K with corresponding ones for the crown ether acetals with the same number of ring oxygen atoms similarly shows potassium ions to be most strongly bound,[2] but the values of the equilibrium constant (for complex formation) are smaller in the case of the crown ether malonate. The comparatively weak cation-binding ability of crown ether esters had previously been recognised.[4]

The effect of the bound cation on the rate constant of the reaction (expressed in this case as the ratio k_c^0/k_f, whereas values of the inverse ratio were listed for the crown ether acetals) is of similar size as for the corresponding crown ether acetals. As before, we have sought to relate the effect to the distance between the two centres of charge in the transition state. The Table lists values of this distance, measured from space-filling scale models on the assumption that the transition state is geometrically similar to the tetrahedral intermediate (II), and that the pseudo-equilibrium between ester and transition state (which governs the reaction rate) can be approximated by an equilibrium between (I) and (II). The Bjerrum model used in the description of the cation effect on acetal hydrolysis was again applied so as to yield values of the effective relative permittivity by solution of equation (17).

$$\varepsilon_r = e_0^2/kTr \ln (k_c^0/k_f) \qquad (17)$$

Parameters relating to cation-binding derived from hydrolysis rate constants and equations (14) and (16)

Metal	lg(K/ dm^3 mol^{-1})	k_c^0/k_f	r/pm	ε_r
Na	1.7	25	625	28
K	1.8	31	623	26
Rb	1.4	41	610	25
Cs	1.0	66	600	22
			Mean:	25.3



(II)

These are given in the last column of the Table. The average value of the relative permittivity is found to be 25.3. Again, this is quite close to the value for the solvent alone. The fact that the same value is deduced from two sets of experiments in which the added cations have the opposite effect makes it improbable that the result arises from the introduction of some fortuitous erroneous factor in the analysis of the data by a least-squares curve-fitting procedure. Accordingly, we infer that the Bjerrum model[11] for the effect of distant charges on ionisation equilibria may perhaps more generally be applied to the effect of guest metal ions on ionic reactions of a crown ether-like host molecule, and, somewhat surprisingly, that it is the bulk relative permittivity that attenuates the electrostatic interaction of the charges.

These semi-quantitative conclusions reached may have wider applications than in the context of the family of compounds reported on in this and the preceding paper. The modification of reactivity brought about by the charge of a bound cation elsewhere within the guest molecule may be an important factor in controlling the chemistry and hence physiological activity of substances such as ionophoric antibiotics and enzymes. Our work provides some guidance for predicting the size of such effects.

Experimental

The substrate, 19-crown-6 malonate, was prepared according to the procedure described by Izatt *et al.*[4] The m.p., 65—66 °C, and ^{1}H n.m.r. spectrum confirmed the identity of the product. The purification of dioxan and preparation of reactant solutions, and spectrophotometry followed the general procedures previously described. A wavelength of 262 nm was used to monitor the change of concentration of the enolate ion of the malonic acid ester (from which the rate of reaction was calculated by the computational procedure described above). All rate measurements refer to 25 °C and 60 : 40 (v/v) dioxan–water as solvent. Values of $k_{t\to 0}$ without added alkali chloride were in 10^{-3}M-LiOH: 0.391, 0.380; in 1.67×10^{-3}M-LiOH; 0.386 dm^3 mol^{-1} s^{-1}.

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