# The Effect of Bound Metal Ions on the Reactivity of Crown Ether-like Substrates with Hydrolysable Rings

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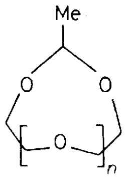
The rate of hydrogen ion-catalysed hydrolysis of crown ether acetals (**1**) is decreased on complexing of alkali metal cations, whereas a rate increase is correspondingly observed for the reaction of a crown ether ester (**2**) with hydroxide ions; both effects are semi-quantitatively intelligible on a simple electrostatic model and require the relative permittivity relevant to the interaction of the charges to be that of the bulk solvent.

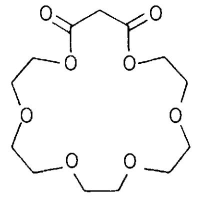
A metal ion complexed within a crown ether-like host molecule is expected to modify the reactivity of functional groups located on the periphery of the host. It has previously been reported[1] that alkali metal cations of appropriate size to be complexed by macrocyclic acetals of the general formula (**1**) reduce the rate of their hydrogen ion-catalysed hydrolysis. A more detailed study of the effect of varying the concentration of added alkali metal chlorides upon the initial rate of this reaction in 60:40 (v/v) dioxan–water mixture at 25 °C now shows that the decrease is qualitatively consistent with the picture that there is an equilibrium between complexed and uncomplexed forms of the substrate, ($RM^+$ and R), the former having a much smaller rate constant for reaction with hydrogen ions. This interpretation leads to equation (1) where

$$k_{t,0} = (k_f + k_c K[M^+]_0)/(1 + K[M^+]_0) \qquad (1)$$

$K = [RM^+]_0/[R]_0[M^+]_0$; $[M^+]_0$ signifies the concentrations of uncomplexed metal ion at zero time, and $k_f$ and $k_c$ are the second-order rate coefficients for R and $RM^+$, respectively. The quantitative formulation of the rate depression requires explicit recognition of the primary kinetic electrolyte effect for a reaction between ions of like charge, including an allowance for the inapplicability of the Debye–Hückel limiting law at the higher concentrations by the inclusion of values derived from Fuoss's measurements[2] for the ion-pair formation constants of the chlorides. The effect is illustrated in Figure 1(a) for the hydrolysis of (**1**) ($n$ = 4) in the presence of sodium chloride, one of the sixteen crown ether acetal–alkali metal cation combinations that we have found to show pronounced behaviour of this type. The solid curve represents the fit provided by equation (1) with appropriate values of the parameters involved. By contrast, substrate–ion pairs in which ring size and cation size are very different show only a weak electrolyte effect which increases the rate. The obvious explanation of the observed rate depression ($k_c/k_f << 1$) lies in the electrostatic repulsion between the metal ion and the positive charge incorporated into the transition state by the hydrogen ion. It then follows that for a reaction involving the attack of hydroxide ion on a cation-binding substrate there should be a rate increase ($k_c/k_f >> 1$) upon addition of a metal ion of suitable size. Such behaviour is indeed observed for the hydrolysis of the macrocyclic ester (**2**) (effected by hydroxide-ion attack). This ester, for which the results are shown in Figure 1(b), has



(**1**) ($n$ = 2–7)



(**2**)

**Table 1.** Results for crown derivatives containing six ring oxygen atoms.

| | (1) ($n$ = 4) | | | | (2) | | | |
|---|---|---|---|---|---|---|---|---|
| Salt | $\lg(K/\mathrm{dm^3mol^{-1}})$ | $k_f/k_c$ | $r$/pm | $\epsilon_r$ | $\lg(K/\mathrm{dm^3mol^{-1}})$ | $k_f/k_c$ | $r$/pm | $\epsilon_r$ |
| NaCl | 5.2 | 49 | 503 | 29 | 1.7 | 0.040 | 625 | 28 |
| KCl | 3.3 | 149 | 501 | 22 | 1.8 | 0.032 | 623 | 26 |
| RbCl | 3.0 | 47 | 488 | 30 | 1.4 | 0.025 | 610 | 25 |
| CsCl | 2.3 | 46 | 478 | 31 | 1.0 | 0.015 | 600 | 22 |

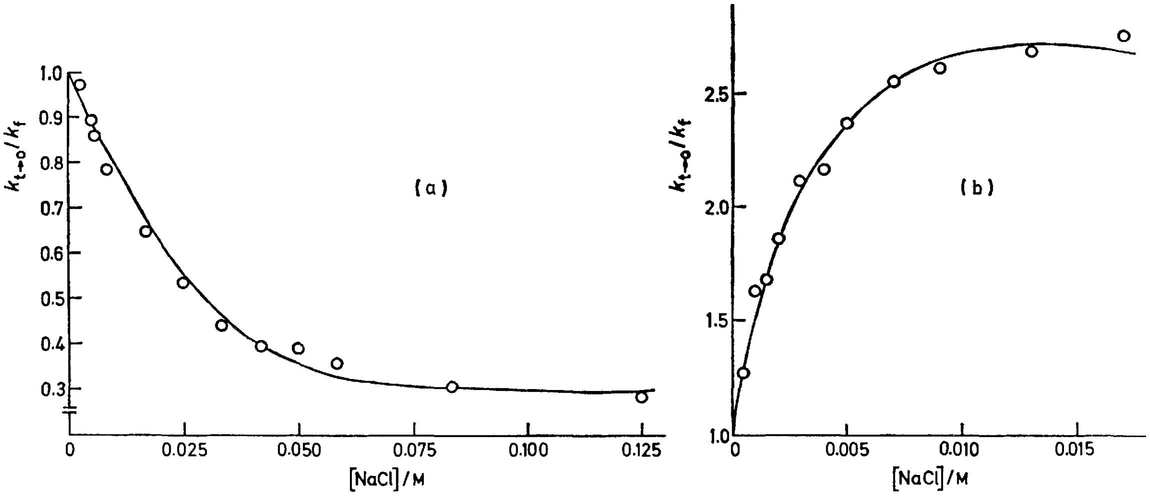


**Figure 1.** Plots of $k_{t\to o}/k_f$ (equation 1) *vs.* [NaCl] for (a) hydrolysis of (**1**; $n = 4$); (b) hydrolysis of (**2**).

the same number of ring oxygen atoms as the acetal, the results for which are illustrated in Figure 1(a). Again, the solid curve gives a computed fit based on equation (1) with inclusion of ordinary electrolyte effects. The values of the parameters $k_c/k_f$ and $K$ that give closest agreement according to the least-squares criterion between experimental points and calculated curves are given in Table 1 for the effect of four alkali metal chlorides on the two substrates included in Figure 1. The large values of $K$ are very approximate only because widely differing values of $K$ allow almost equally good fits to the experimental data.

According to the electrostatic model proposed by Bjerrum,[3] in the first instance to account for the ratio of the dissociation constants of dibasic acids, the relative stability of the transition states for hydrolyses of complexed and uncomplexed substrates should be expressed by equation (2), where $m$ is the

$$\ln(k_f/k_c) = me^2/kT\epsilon_r r \qquad (2)$$

product of the algebraic values of the charges on the metal ion (expressed as multiples of the electronic charge $e$) and $r$ is the centre-to-centre distance between the charges, which can be estimated from scale models. In the present work, as in later elaborations of Bjerrum's theory,[4] the problem with equation (2) lies in the choice of the value of $\epsilon_r$, the effective relative permittivity relevant to the interaction between the charges. Using the ratios $k_f/k_c$ derived from the curve-fitting procedure, we have solved equation (2) for $\epsilon_r$, with the results shown in the Table 1, and including the results for all the acetal runs we obtain an average value of 23; the corresponding average value for the ester runs is 25.3. The bulk value for the relative permittivity of the solvent[5] is 25.9. The agreement between the results for two systems of different charge types thus indicates that the Bjerrum model is applicable if the appropriate value of the relative permittivity is that appertaining to the bulk solvent, in spite of the fact that most of the space between the two charges is taken up by the metal ion and the crown ring. This is unexpected because in systems where the charge propagation includes intervening bonds the appropriate value of $\epsilon_r$ is very much lower.[4] The conclusions from the present work may be important in considerations of the effect of bound cations on the reactivity of guest molecules for other systems, such as cell membranes, ionophoric antibiotics, and enzymes.

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