The Influence of Cation Binding on the Kinetics of the Hydrolysis of Crown Ether Acetals

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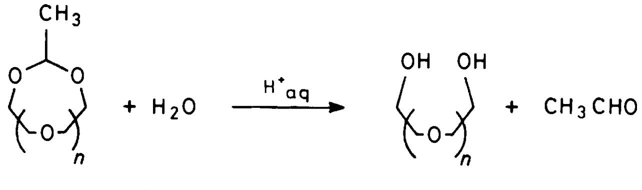
The rate of hydrogen ion-catalysed hydrolysis of crown ether acetals in 60 : 40 (v/v) dioxan–water is found to be strongly decreased by the addition of alkali and alkaline earth metal chlorides having cations of appropriate size to be complexed by the substrate ring. The compounds studied are the monoacetals $CH_3\overline{CH(OCH_2CH_2)_xO}$ with x = 1—8. The dependence of the initial rate of formation of acetaldehyde on metal-ion concentration is expressed in terms of (i) the equilibrium constant for complex formation, (ii) the influence of the bound cation on the rate constant, and (iii) an electrolyte effect. A curve-fitting procedure is used to derive the parameters governing the first two of these effects. The equilibrium constants are large and cannot be evaluated with any precision, but a fair estimate of the influence of the guest cation on the rate can be obtained. This effect is explicable by the electrostatic repulsion between the cationic charges of the metal ion and the proton added to the acetal in the first step of the hydrolysis. The size of the effect requires the values of the effective relative permittivity of the space between the charges to be close to that of the bulk solvent.



(I; n = 0−7) (1)

$$R^1CH(OR^2)_2 + H_{aq}{}^+ \underset{-1}{\overset{1}{\rightleftharpoons}} R^1CH(OR^2)_2H^+ \quad (2)$$

$$R^1CH(\overset{|}{O}R^2)_2H^+ + H_2O \xrightarrow{2} R^1CHO + HOR^2R^2OH + H^+{}_{aq} \quad (3)$$

The acid-catalysed hydrolysis (1) of crown ether acetals of the series (I) is expected to be strongly influenced by the presence of a bound metal cation, though the direction of the effect is not completely self-evident. The influence might be in the direction of additional catalysis by the metal ion. This possibility would be based on the grounds that a bound cation should have a similar effect to the proton bound in the pre-equilibrium (2) (where HOR^2R^2OH is the diol formed on hydrolysis) which precedes the rate-limiting step (3) according to the most commonly accepted mechanism for the hydrolysis of simple acetals.[1] Alternatively, the position of a bound metal cation might be unsuitable for facilitating the equivalent of step (3). In that case, the complexed crown ether acetal would be expected to be protonated in pre-equilibrium (2) to a smaller extent than is the free crown ether acetal, because of the basicity-lowering electrostatic influence of the bound metal ion. This would result in a reduction of the rate of the observed acid-catalysed hydrolysis. In fact, the cation-binding properties of these compounds were searched for and detected in a preliminary study of the effect of a series of metal chlorides on their rate of hydrolysis.[2] A rate reduction for the formation of acetaldehyde was observed for suitable combinations of ing size and metal-ion radius. The result clearly points to the basicity-lowering effect as being at least predominant. In those experiments a fixed and relatively large concentration of alkali-metal chlorides (0.25M) was used and the rate comparisons were made by fitting the data points of individual runs to a first-order rate equation. In the present full report the kinetics of some of these reactions and the role of metal ions have been analysed more completely for a range of concentrations of added metal chloride.

We assume that the following reactions are to be considered when the hydrolysis occurs in the presence of a metal ion that is able to form a 1 : 1 complex with the substrate R. The complexing reaction (4) is assumed to be a rapid process in either direction, as seems to be well established for other reactions of this general type,[3] and to be characterised by an (association) equilibrium constant K. Similarly, the product glycol G (like the corresponding glyme [4]) may undergo some rapid and less extensive interaction with metal ions but, since only the appearance of acetaldehyde is spectrophotometrically monitored as a function of time, this does not affect the observed kinetics. Acetaldehyde is produced in two concurrent reactions, (5) and (6), from free and complexed substrate, characterised by the respective second-order rate coefficients k_f and k_c.

$$R + M^{m+} \rightleftharpoons RM^{m+} \quad (4)$$

$$R + H_2O \xrightarrow[k_f]{H^+{}_{aq}} G + CH_3CHO \quad (5)$$

$$RM^{m+} + H_2O \xrightarrow[k_c]{H^+{}_{aq}} G + CH_3CHO + M^{m+} \quad (6)$$

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

Hydrogen ions are not consumed in the reaction, and the formation of acetaldehyde will follow first-order kinetics if (but only if) the ratio of the concentrations of R and RM^{m+} stays constant throughout the reaction. This obviously applies if no metal ions are present at all. It may also be a good approximation if they are added in such large excess that the percentage increase in free metal ion concentration during the course of a run is negligible. At intermediate concentrations, the concentration of free metal ion will significantly change during the course of a run and simple first-order kinetics are not observed. In fact, the concentration of free metal ion is controlled not only by the overall concentrations of R and M^{m+} and the value of K, but will also to some extent be influenced by the concentration of the glycol produced and its association constant for reaction with metal ions. Because of the uncertain role of the glycol the kinetic data were analysed in all cases so as to yield initial second-order rate coefficients, *i.e.* those applicable at the initial concentrations of substrate and free metal ions in the system. The values thus obtained are functions of k_f, k_c, and K and can be interpreted without reference to the possible complication caused by the complexing of metal ions by the glycol.

The stoicheiometric concentration (subscript st) of substrate in the system at any time t is given by equation (8). According to equations (5) and (6), its rate of decrease (which

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

is equal to the rate of increase of concentration of acetaldehyde) is expressed by equation (9) where the concentrations

$$-d[R_{st}]/dt = (k_f[R] + k_c[RM^{m+}])[H^+{}_{aq}] \qquad (9)$$

[R] and [RM^{m+}] are related through the equilibrium constant of reaction (4).

If free and crown ether acetal-complexed metal ions are the only metal species present in the system, and this will be true at the start of the reaction (although the inclusion of ion pairing, noted below, requires a slight modification), we can write equation (10) where the subscript zero denotes zero time of reaction. The equilibrium constant for reaction (4) may therefore be written as (11), the solution of which (12) allows

$$[M^{m+}{}_{st}]_0 = [M^{m+}]_0 + [RM^{m+}]_0 \qquad (10)$$

$$K = \frac{[RM^{m+}]_0}{([R_{st}]_0 - [RM^{m+}]_0)([M^{m+}{}_{st}]_0 - [RM^{m+}]_0)} \qquad (11)$$

$$[RM^{m+}]_0 = [-P - (P^2 - 4KQ)^{1/2}]/2K \qquad (12)$$

all concentrations at zero time to be expressed in terms of K and the initial stoicheiometric composition of the reaction medium, where $P = -K([R_{st}]_0 + [M^{m+}{}_{st}]_0) + 1$ and $Q = -K[R_{st}]_0[M^{m+}{}_{st}]_0$. Restricting equation (9) to the initial rate of reaction, we have equation (13) or (14)

$$\left(\frac{d[CH_3CHO]}{dt}\right)_{t\to 0} = (k_f[R]_0 + k_c[RM^{m+}]_0)[H^+{}_{aq}] \qquad (13)$$

$$(k_\psi)_{t\to 0} = \frac{1}{[R_{st}]_0}\left(\frac{d[CH_3CHO]}{dt}\right)_{t\to 0} = (k_f[R]_0 + k_c[RM^{m+}]_0)[H^+{}_{aq}]/[R_{st}]_0 \qquad (14)$$

with the condition (15). From equations (8), (10), and (12) the

$$(k_2)_{t\to 0} = (k_\psi)_{t\to 0}/[H^+{}_{aq}] \qquad (15)$$

concentrations required in equation (14) can be written in terms of the known initial stoicheiometric concentrations and the (unknown) constant K.

In equation (14) the rate coefficient k_f is known from the reaction rate in the absence of added metal ion, and the dependence of the initial pseudo-first-order rate coefficient on the stoicheiometric concentration of metal chloride should involve two adjustable parameters whose values are, in principle at least, deducible by matching calculated and experimental initial rate coefficients.

The situation is actually more complicated because k_c, relating to a reaction in which the transition state is formed (*via* a pre-equilibrium) from two positive ions, must be subject to a primary kinetic electrolyte effect in solutions of finite ionic strength, *i.e.* it will be a function of the concentration of the added metal chloride. Furthermore, at high salt concentrations, specific electrolyte effects on both k_f and k_c assume importance. This is explicitly considered in the Discussion section where we examine the evaluation of k_c and K from rate measurements for the hydrolysis in 60 : 40 (v/v) dioxan–water mixture at 25 °C.

The term ' free ' crown ether acetal throughout this paper is intended to include not only completely uncomplexed substrate but also any forms of the acetal that involve reversible binding of solvent molecules. Provided such equilibria are established rapidly, they will have no detectable effect on the kinetic course of the hydrolysis. For example, if, by analogy with the known complexing of water by crown ethers,[5,6] the crown ether acetals can bind a water molecule in a similar way as a metal ion, then the measured equilibrium constant K in equation (7) must receive a slightly more elaborate interpretation than the equation implies. The ratio of the water-complexed and uncomplexed forms of the substrate R (R_h and R_u, respectively) will be constant in a solvent containing a high and fixed proportion of water, according to the equilibrium constant K_h for hydration. The overall metal-binding

$$K_h = [R_h]/[R_u] \qquad (16)$$

$$[R] = [R_u] + [R_h] = [R_u](1 + K_h) \qquad (17)$$

$$K_u = [RM^{m+}]/[R_u][M^{m+}] \qquad (18)$$

$$= K/(1 + K_h) \qquad (19)$$

equilibrium (4) refers to all forms of ' free ' R, *i.e.* as given by equation (17). It follows that the equilibrium constant for metal-ion binding by the unhydrated substrate (K_u) will differ from the measured value of K [equation (7)], as expressed in equations (18) and (19). However, ratios of K values for the binding of different cations by the same substrate molecule are the same as ratios of K_u values, and the consideration of the role of water-complexing is not relevant to such comparisons. On the other hand, ratios of K for binding of the same metal ion to different crown ether acetals would not be the same as ratios of K_u if the value of K_h is both large and strongly dependent on ring size. For the analogous crown ethers it has been reported that K_h varies by less than a factor of ten on going from a 2-oxygen compound to a 7-oxygen compound.[5] If the crown ether acetals resemble the corresponding crown ethers in this respect, then large ratios of K values for different substrates will also reflect large ratios of values of K_u, but this does not apply to the interpretation of finer differences. Analogous considerations apply to the possible, though less probable, binding of dioxan by the crown ether acetal.

Nomenclature.—To avoid excessively cumbersome names for compounds (I) we have adapted Pedersen's abbreviated nomenclature system for crown ethers,[7] as previously explained.[2] In this system, compound (I) is called 2-methyl-($3n + 5$)-crown-($n + 2$), or ($3n + 5$)-C-($n + 2$) for short, the numeral preceding the word ' crown ' indicating total ring size and the second numeral the number of oxygen atoms in the ring.

Experimental

The purification of dioxan was based on a method due to Fagley and Oglukian.[8] All samples were tested for stability with acid (*i.e.* absence of acetal impurities) and gave a negative

Table 1. Solvent effect on HCl-catalysed hydrolysis at 25 °C

Dioxan % (v/v)		0	10	20	30	40	50	60	70
$\frac{k_2(\text{solvent})}{k_2(\text{water})}$	A	(1)	0.952	0.800	0.598	0.427	0.258	0.180	0.172
	B	(1)				0.314		0.142	

A 2-Methyl-5-crown-2, B 2-propyl-8-crown-3.

test for peroxides. They were stored in well sealed dark bottles in a refrigerator. Mixtures with water (triply distilled) were prepared by mixing appropriate volumes of solutions of reactants and solvents, 60 : 40 denoting a mixture of 60 volumes of dioxan with 40 volumes of water, both at room temperature. The concentration of metal chlorides (AnalaR) in stock solutions was checked by titration with silver nitrate. Hydrochloric acid solutions were prepared from standard volumetric solutions (B.D.H.).

Crown ether acetals were prepared and checked for purity as described previously.[9]

Two new members of the series, 23-C-8 (2-methyl-1,3,6,9,-12,15,18,21-octaoxatricosane), b.p.175 °C at 0.09 mmHg, and 26-C-9 (2-methyl-1,3,6,9,12,15,18,21,24-nonaoxahexacosane), b.p. 194 °C at 0.1 mmHg, were prepared in 16 and 11% yield, respectively, from acetaldehyde and the corresponding diol, by the procedure previously described.[9] The n.m.r. spectra of the compounds had the same features as for the other cyclic monoacetals reported. On hydrolysis the compounds yielded acetaldehyde in amounts representing 97 and 96% of the theoretical values. The requisite polyethyleneglycols were prepared according to Liu's method.[10]

The reaction mixtures for kinetic runs were prepared by mixing in the cuvette appropriate volumes of dioxan and of stock solutions of crown ether acetal in dioxan (or dioxan–water) and of metal halide in water. To start the reaction and to adjust the solvent composition, an appropriate volume of aqueous hydrochloric acid was added last. The progress of the formation of acetaldehyde was monitored spectrophotometrically (Gilford model 222–Pye Unicam SP500 combination, Zeiss M4Q3, or Pye Unicam SP8-100, with output accessories) at 280 nm.

For runs without added metal salt, the reactions obeyed first-order kinetics, and the rate coefficients were evaluated using a non-linear least-squares program based on DeTar's program LSG.[11]

For runs with added metal salt, various computational procedures were tried for the evaluation of initial first-order rate coefficients. It was found most convenient and reliable to fit the absorbance values at time t (A_t) to a power series of the form (20) where the negative of the second coefficient (C_1)

$$\ln (A - A_\infty) = C_0 + C_1 t + C_2 t^2 \ldots \qquad (20)$$

$$\left(\frac{\mathrm{d} \ln (A - A_\infty)}{\mathrm{d}t}\right)_{t \to 0} = C_1 = (-k_\psi)_{t \to 0} \qquad (21)$$

corresponds to the required rate coefficient. The number of powers of t to be included in the polynomial (20) (usually 3 or 2) was determined by use of Snedecor's F test.[12]

The choice of 60 : 40 (v/v) dioxan–water as the standard solvent in these experiments followed from (i) the very low solubility of the larger substrates in water, and (ii) the relatively low sensitivity shown by 2-methyl-5-crown-2 (2-methyldioxolan) to solvent composition between 60 and 70% (v/v) of dioxan (Table 1). For this substrate our results for second-order rate constants ($k_2 = k_\psi/[\mathrm{H^+_{aq}}]$) in aqueous hydrochloric acid solution (0.0131 dm^3 mol^{-1} s^{-1}) agreed well with most of the earlier measurements using various kinetic techniques (0.0130,[13] 0.0136,[14] 0.0141,[14] 0.0129,[15] 0.0135,[16] 0.0146 [17] dm^3 mol^{-1} s^{-1}).

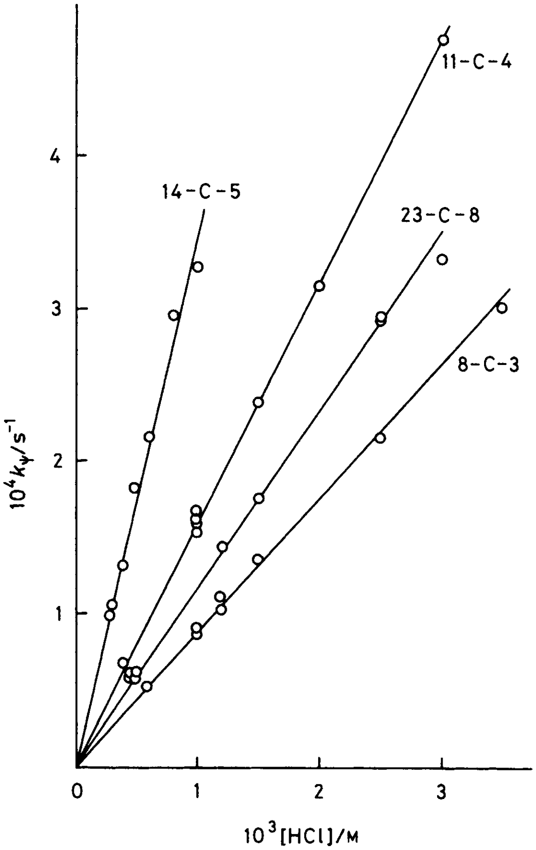


Figure 1. Illustrations of dependence of hydrolysis rate on concentration of hydrochloric acid

Table 2 lists values of the second-order rate constant for the substrate in the absence of metal ions (k_2^0). In all cases k_ψ was strictly proportional to the hydrogen ion concentration (at the low concentrations studied), as illustrated in Figure 1. This proportionality was also found in the presence of a constant concentration of the alkali-metal chlorides. There was no intercept, demonstrating that the metal ion was not itself a positive catalyst. For most of the substrate–metal chloride systems the reactions followed first-order kinetics, and the dependence of the second-order rate coefficients k_2 on ionic strength (I), corrected for ion association, as explained in the Discussion section, satisfied equation (22) where the superscript zero signifies zero ionic strength. Figure 2 gives some specimen

$$\lg k_2 = \lg k_2^0 + B'I \qquad (22)$$

Table 2. Second-order rate constants for hydrolysis of crown ether acetals in the absence of cation binding (group A)

Substrate	Metal ion *	$10^3k_2^0$/ dm^3 mol^{-1} s^{-1}	B'/ dm^3 mol^{-1}
5-C-2		2.31 ± 0.07	
	Li^+	2.39 ± 0.05	1.56 ± 0.02
	Na^+	2.0 ± 0.1	2.09 ± 0.09
	K^+	1.9 ± 0.1	1.91 ± 0.05
	Rb^+	2.39 ± 0.06	0.32 ± 0.09
	Mg^{2+}	2.31 ± 0.08	0.37 ± 0.08
	Ca^{2+}	2.26 ± 0.07	0.54 ± 0.07
	Sr^{2+}	2.17 ± 0.07	0.55 ± 0.06
	Ba^{2+}	2.32 ± 0.08	0.45 ± 0.05
	Weighted average:	2.28 ± 0.05	
8-C-3		87 ± 2	
	Li^+	94 ± 3	2.39 ± 0.09
	Na^+	83 ± 4	2.34 ± 0.09
	K^+	85 ± 2	2.75 ± 0.14
	Rb^+	85 ± 2	1.90 ± 0.09
	Cs^+	90 ± 3	1.49 ± 0.06
	Mg^{2+}	83 ± 2	1.40 ± 0.12
	Ca^{2+}	87 ± 2	1.05 ± 0.08
	Sr^{2+}	88 ± 2	1.65 ± 0.09
	Ba^{2+}	89 ± 3	1.27 ± 0.06
	Weighted average:	86.6 ± 0.9	
11-C-4		160 ± 5	
	K^+	160 ± 5	1.3 ± 0.1
	Rb^+	160 ± 10	1.38 ± 0.08
	Cs^+	150 ± 10	1.08 ± 0.07
	Mg^{2+}	160 ± 10	0.88 ± 0.05
	Ca^{2+}	150 ± 10	0.54 ± 0.03
	Sr^{2+}	160 ± 10	0.79 ± 0.06
	Ba^{2+}	160 ± 10	0.96 ± 0.08
	Weighted average:	158 ± 2	
14-C-5		348 ± 17	
	Li^+	320 ± 20	0.54 ± 0.04
	K^+	360 ± 10	0.44 ± 0.15
	Rb^+	360 ± 10	0.33 ± 0.36
	Cs^+	320 ± 20	0.54 ± 0.04
	Mg^{2+}	360 ± 10	0.78 ± 0.09
	Ca^{2+}	360 ± 10	0.57 ± 0.10
	Sr^{2+}	360 ± 20	0.59 ± 0.04
	Weighted average:	355 ± 5	
17-C-6		166 ± 5	
	Li^+	150 ± 10	2.56 ± 0.12
	Mg^{2+}	160 ± 10	0.88 ± 0.06
	Weighted average:	162 ± 4	
20-C-7		125 ± 11	
	Li^+	130 ± 10	4.8 ± 0.6
	Mg^{2+}	126 ± 8	0.59 ± 0.06
	Ca^{2+}	122 ± 8	0.86 ± 0.07
	Weighted average:	125 ± 2	
23-C-8		117 ± 3	
	Li^+	110 ± 7	1.9 ± 0.1
	Mg^{2+}	116 ± 2	0.17 ± 0.06
	Ca^{2+}	118 ± 7	0.43 ± 0.08
	Sr^{2+}	119 ± 5	0.21 ± 0.13
	Weighted average:	116 ± 1	
26-C-9		97 ± 1	

* Added as chloride.

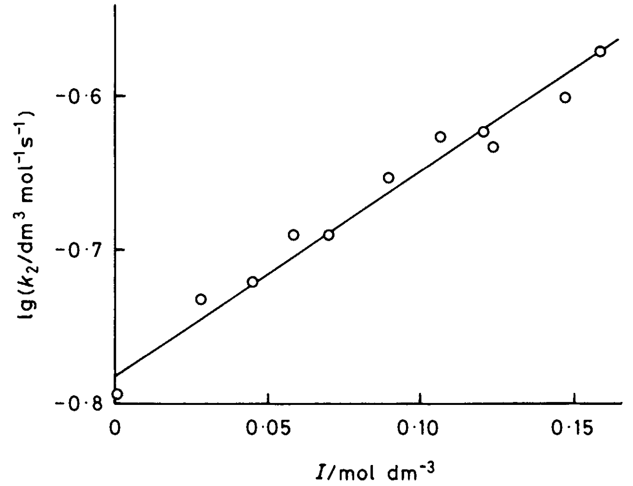


Figure 2. Illustration of electrolyte effect on hydrolysis rate in the absence of cation-binding (11-C-4 and KCl)

Table 3. Rate constants for hydrolysis of 17-C-6 in chloroacetic acid–chloroacetate buffers. $[17\text{-C-6}]_0$, 0.15M; $[CH_2ClCO_2H]/[CH_2ClCO_2Na]$, 1

10^3 $[CH_2ClCO_2H]$/M	5.0	10.0	15.0
10^4 k_ψ/s^{-1}	2.21 ± 0.10	2.17 ± 0.07	2.09 ± 0.08

results. This behaviour is taken to indicate absence of cation-binding. The value of k_2^0 therefore also corresponds to k_f in equation (9), so that Table 2 accordingly includes the computed ' best ' values of k_2^0 in those cases where equation (22) is

$$\lg k_f = \lg k^0_f + B'I \tag{23}$$

obeyed, together with the corresponding values of B'.

Discussion

It is well known from earlier studies [13–18] that the hydrolysis of 2-methyl-5-crown-2 is subject to specific catalysis by hydrogen ions and that catalysis by other Brønsted acids is not detectable. Experiments with a chloroacetic acid buffer and 2-methyl-17-crown-6 (Table 3) are consistent with the expectation that the same mechanism should apply throughout the series of crown ether acetals. Whilst we have not specifically tested this point, there do not seem to be any grounds for supposing that metal ion-complexed crown ether acetals would behave differently in this respect.

The hydrolysis rate of the crown ether acetals increases by a factor of nearly 140 from the 5-crown-2 to the 14-crown-5 compound, which is the most reactive member of the series, and then falls off to an almost constant value which is about one-third of the maximum. The largest rate difference occurs between the first two compounds.

The effect of adding chlorides of the alkali or alkaline earth metals on the rate of acid-catalysed hydrolysis is in some cases (group A) simply a linear increase [of the logarithm of the rate constant; equation (22)], as commonly observed for reactions involving one non-ionic reactant (Figure 2). In other cases (group B) the rate decreases for small additions to a minimum beyond which an increase in the metal-ion concentration results in a less steep increase in the rate. These **U**-shaped curves (an example is shown in Figure 3) were found with

Table 4. Occurrence of cation binding (group B behaviour)

Substrate (cavity diameter/pm) [a]	Metal (cation diameter/pm) Li (136)	Na (196)	K (266)	Rb (296)	Cs (334)	Mg (180)	Ca (188)	Sr (220)	Ba (268)
5-C-2 (50 ± 10)	—	—	—	—	—	—	—	—	—
8-C-3 (70 ± 10)	—	—	—	—	—	—	—	—	—
11-C-4 (110 ± 20)	+	0	—	—	—	—	—	—	—
14-C-5 (180 ± 20)	—	+	0	0	—	0	0	—	—
17-C-6 (260 ± 30)	—	+	+	+	+	—	+	—	
20-C-7 (350 ± 50)	—	+	+	+	+	—	—	+	+
23-C-8 (410 ± 50)	—		+	+	+	0	0	0	0
26-C-9 (430 ± 60)			0	+	+				

[a] Estimated from scale models.

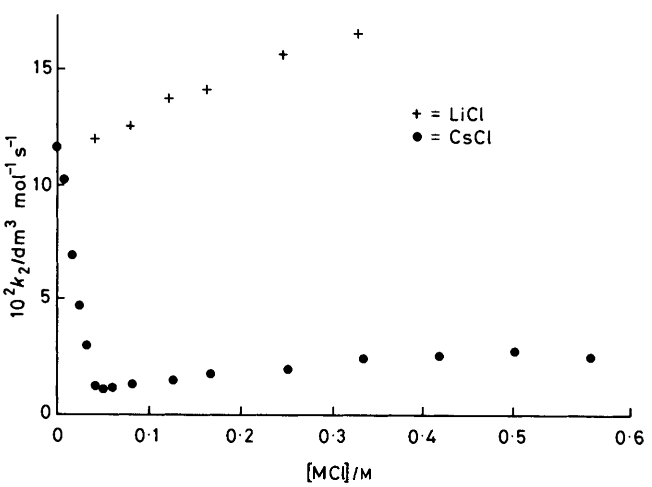


Figure 3. Experimental points for typical effects of alkali-metal chlorides on initial rate of hydrolysis (23-C-8 with LiCl and CsCl)

crown ether acetals having a ring of an appropriate size to accommodate the metal ion within the central cavity. Group B behaviour actually begins to be noticeable slightly before the inside radius of the annulus exceeds the cation radius. This suggests that cation binding can occur even when the metal ion cannot fit exactly inside the ring. Table 4 indicates by a + sign for which substrate–metal ion pairs this type of behaviour was observed, whereas a — sign indicates the observation of the linear electrolyte effect. Intermediate behaviour, *viz.* a flat or very shallow **U**-shaped curve, was observed in some cases, and is thought to indicate very weak cation-binding. This response is indicated in Table 4 by a zero. (A blank space denotes lack of data.) The pattern of the Table implies that cation-binding of the type established for crown ethers is responsible for the rate decrease, as was already concluded from our preliminary data.[2] In terms of the mechanism of equations (4)—(6), it also implies that k_c is smaller than k_f. The qualitative interpretation of the **U**-shaped curves is thus that addition of metal ions converts part of the substrate R into a less reactive metal-ion adduct, according to equation (4). The extent of this conversion is controlled by the equilibrium constant K (equation 7) and the concentration of metal ions. If the value of K is large, virtually all the substrate is complexed at high concentrations of metal ions, which must in all cases be greater than the substrate concentration. The rate constant for the reaction of uncomplexed substrate, k_f, is itself expected to depend on the concentration of added salts in a similar way as the reactions in group A.

Hydrolysis of metal-complexed acetal *via* reaction (6) should be subject to a primary kinetic electrolyte effect [equation (24)] where the activity coefficients y (on a concentration basis) relate to reactants RM^{m+} and H^+_{aq} of charge $+m$ and $+1$, respectively, and $y^\ddagger$ refers to a transition state of charge $+(m+1)$. If ionic activity coefficients are expressible in the form (25), equation (23) can be written as (26). The Debye–Hückel parameter A has the value 2.697 in

$$k_c = k_c^0 \,.\, y_{RM}y_H/y^\ddagger \qquad (24)$$

$$-\lg y_i = Az_i^2[I^{1/2}/(1+\rho I^{1/2})] \qquad (25)$$

$$\lg k_2 = \lg k_c = \lg k_c^0 + 2Az_{RM}[I^{1/2}/(1+\rho I^{1/2})] \qquad (26)$$

60 : 40 (v/v) dioxan water (ε_r 25.86).[19] An estimated average value of 1.4 for the parameter ρ has been used throughout.

Equation (25) is expected to be valid only at very low concentrations. Its range of validity can be extended by application of the ion-association concept (27),[20] as formulated by Fuoss,[21] who has provided conductometric values of ion-pair association constants (28) in dioxan–water mixtures

$$M^+ + Cl^- \rightleftharpoons (M^+Cl^-) \qquad (27)$$

$$K_{pair} = [(M^+Cl^-)]/[M^+][Cl^-] \qquad (28)$$

(LiCl, 37;[22] NaCl, 24;[23] KCl, 21;[24] RbCl, 20;[25] CsCl, 20 dm^3 mol^{-1} [26]). Accordingly we consider that alkali-metal ions are present in our solutions in three forms, *viz.* as free ions, as crown-complexed ions [equation (4)] and as ion pairs [equation (29)]. Ion pairing of crown-complexed cations [equation (30)] is taken to be negligible because of the large size of the cation. By use of the experimental values of K_{pair}[22-26] the correction of equation (25) can be performed without the introduction of adjustable parameters. This treatment is assumed to be adequate up to an ionic strength of 0.15 mol dm^{-3}.

$$[M^+_{st}] = [M^+] + [RM^+] + [(M^+Cl^-)] \qquad (29)$$

$$RM^+ + Cl^- \rightleftharpoons (RM^+\ Cl^-) \qquad (30)$$

Table 5. Effect of alkali-metal chlorides: equilibrium and rate constants (group B)

Crown ether acetal	Metal	$\lg(K/$ $\text{dm}^3\ \text{mol}^{-1})$	k_f/k_c^0
11-C-4	Li	1.8	10
14-C-5	Na	5.1	26
17-C-6	Na	2.5	49
	K	3.3	149
	Rb	3.0	47
	Cs	2.3	46
20-C-7	Na	4.4	28
	K	3.4	105
	Rb	4.9	122
	Cs	5.4	91
23-C-8	K	1.6	1 550
	Rb	3.8	52
	Cs	4.8	100
26-C-9	Rb	4.2	26
	Cs	2.1	83

The value of K_{pair} for hydrogen and chloride ions has been reported[27] to be about one-third of that for sodium chloride, and we have consistently used the value $K_{\text{pair}} = 7\ \text{dm}^3\ \text{mol}^{-1}$ in that case.

The occurrence of ion pairing reduces the concentration of free metal and hydrogen ions and also affects the value of the ionic strengths of the solution. Figure 2 and the values of the parameter B' in Table 2 refer to such corrected ionic strengths.

Our model for the **U**-shaped curves of group B accordingly assumes that the total initial rate is given by equation (14) in which the requisite initial concentrations of R and RM^{m+} are expressed by equations (12) and (8) and the dependence of k_c upon ionic strength is represented by equations (26) and (29). The resulting system of equations contains two unknown (or adjustable) parameters, K and k_c^0. The electrolyte effect on k_f, according to equation (23), is negligible since the contribution from the hydrolysis of uncomplexed R is most important when the concentration of salt is so low that k_f is not appreciably different from k_f^0. The value of k_f need not be taken as unknown in this modelling of the system, since it is obtainable from runs in the absence of metal chloride.

According to these principles, a program was devised to fit the course of the experimental values of $(k_2)_{t\rightarrow 0}$ as a function of metal chloride concentration by stepwise iterative adjustment of the above parameters so as to produce the best fit by the least-squares criterion. Given initial estimates of K, the initial concentrations of R, RM^{m+}, and M^{m+} were iteratively calculated from equations (10), (12), and (28). Having evaluated $[\text{RM}^{m+}]_0$ and $[(\text{M}^+\text{Cl}^-)]$, we know the initial concentration of metal ion $[\text{M}^{m+}]_0$ and we can write equations (31) and (32). From the values of K_{pair} and initial

$$[\text{R}]_0 = \frac{[\text{R}_{\text{st}}]_0}{1 + K\,[\text{M}^{m+}]_0} \tag{31}$$

$$[\text{RM}^{m+}]_0 = \frac{K[\text{R}_{\text{st}}]_0[\text{M}^{m+}]_0}{1 + K[\text{M}^{m+}]_0} \tag{32}$$

estimates of k_c^0 and K, values of k_c were calculated [equation (26)] and thus the simulated values of $(k_2)_{t\rightarrow 0}$ according to equations (14) and (15), *i.e.* equation (33).

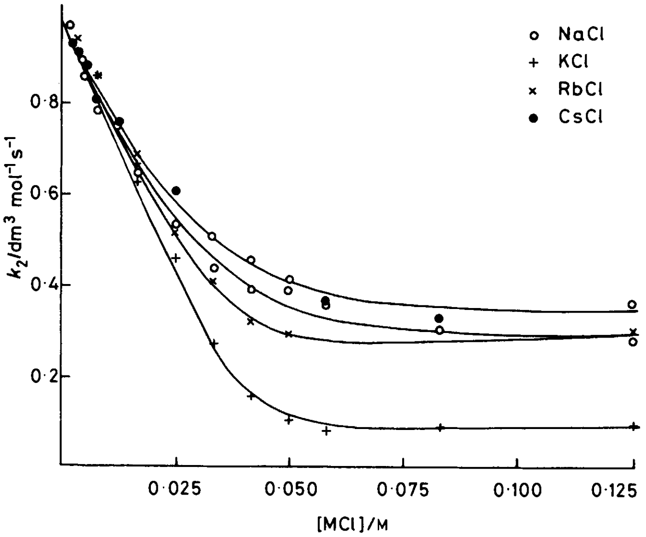


Figure 4. Experimental points and computer-simulated curves for effect of alkali-metal chlorides on initial rate of hydrolysis of 17-C-6

Table 6. Calculated optimum parameters k_c^0/k_f and K for the system 20-C-7 + RbCl for different values of K_{pair} and k_f

K_{pair}	$10^5\ k_f/$ $\text{dm}^3\ \text{mol}^{-1}$ s^{-1}	Residual	k_c^0/k_f	$10^{-3}\ K/$ $\text{dm}^3\ \text{mol}^{-1}$
0	12 500	6.9×10^6	0.0058	2.9
	13 750	0.52×10^6	0.0058	6.0 (a)
20	12 500	6.7×10^6	0.0101	162
	13 750	0.39×10^6	0.0081	78 (b)

$$(k_2)_{t\overset{\text{calc.}}{\longrightarrow}0} = (k_f + k_cK[\text{M}^{m+}]_0)/(1 + K[\text{M}^{m+}]_0) \tag{33}$$

The procedure then minimises the sum of the squares of the deviations between experimental and calculated values of $(k_2)_{t\rightarrow 0}$. Optimum values of the parameters K and k_c^0 are obtained from this analysis. These results are contained in columns 3 and 4 of Table 5 where one of the listed parameters is the ratio k_f/k_c^0. Figure 4 illustrates that the calculated curves provide a fair fit to the experimental rate constants. The calculations were generally repeated for other values of K_{pair}. It was found that Fuoss's values usually gave significantly better fits (according to the least-squares criterion) than could be obtained if ion pairing was assumed to be absent (*i.e.*, $K_{\text{pair}} = 0$), and generally appeared to be valid. For consistency we have therefore used Fuoss's constants[23-26] throughout.

Whilst the calculated curves provide a fit to the initial rate constants, it does not follow that the values of the parameters k_c^0 and K can be reliably deduced in all cases. It is evident from equation (33) that the value of K (in relation to $[\text{M}^+]$) governs the influence of K and k_c^0 on the magnitude of $(k_2)_{t\rightarrow 0}$ and hence determines whether reasonably reliable estimates of k_c^0 and K are obtainable by curve-fitting. The values listed in Table 5 should, for the most part, be taken as rough indications only. The dependence of these ' best ' parameters on the assumed values of some of the constants is illustrated in Table 6.

Table 7. Illustration of best fits obtainable for different assumed values of K_{pair} [data in lines (a) and (b) of Table 6]

10^3 [RbCl]/M	10^4 k_2(obs)	10^4 k_2(calc) [a]	10^4 k_2(calc) [b]	$10^4\Delta_a$ [c]	$10^4\Delta_b$ [d]
0	1 353	1 375	1 375	−22	−22
1.67	1 343	1 318	1 319	25	24
5.00	1 213	1 206	1 206	7	7
8.33	1 100	1 094	1 095	6	5
16.7	800	818	821	−18	−21
25.0	569	547	553	22	16
33.3	301	290	290	11	11
41.7	89	111	95	−22	−6
50.0	96	79	91	17	5
58.3	100	78	95	22	5
125	123	135	132	−12	−9

(Values in columns 2—6 are expressed as multiples of dm^3 mol^{-1} s^{-1})

[a] Calc. with the parameters in line (a) of Table 6. [b] Calc. with the parameters in line (b) of Table 6. [c] Difference between values in columns 2 and 3. [d] Difference between values in columns 2 and 4.

Whereas the order of magnitude of the ratio k_c^0/k_f is fairly well established, the (large) values of K are seen to be strongly dependent on the assumption of the ion-pair association constant. The derived values of k_c^0/k_f and K are much less dependent on the assumed precise value of the constant k_f, although the fit is much worse (and hence the residual is considerably increased) when an inappropriate value of k_f is taken (because there are now large deviations at low salt concentration).

The relatively small effect exerted by the value of K_{pair} on the best fit obtainable is further illustrated in Table 7. The value of K_{pair} nevertheless has a very large effect on the best value of K required to obtain this fit. It follows conversely that, in the absence of totally certain values of K_{pair}, reliable values of K are not obtainable by curve-fitting.

In Table 5 all the values of K for potassium chloride seem to be somewhat out of line, being smaller than expected in relation to the other salts. This inconsistency is possibly attributable to an inappropriate value of K_{pair}.

The difference between the rate constants k_f and k_c^0, defined in equations (5) and (6) and expressed by their ratio, arises from the electrostatic effect of the complexed cation. Values of this ratio are large, mostly between 40 and 120, which explains why preliminary conclusions on cation binding, drawn on the assumption that k_c is negligibly small,[2] are qualitatively correct. The reaction mechanism for the hydrolysis in the absence of metal ion, as expressed in equations (2) and (3), implies that k_f is the product of the rate coefficient for the second step and the equilibrium constant of the pre-equilibrium {equation (34) where $K_{RH} = [H^+_{aq}][R]/[RH^+] = k_{-1}/k_1$}. Applying the same mechanism to the hydrolysis of the

$$k_f = k_2/K_{RH} \qquad (34)$$

complexed acetal [equations (35) and (36)], we obtain the

$$RM^{m+} + H^+_{aq} \underset{-1M}{\overset{1M}{\rightleftharpoons}} RMH^{(m+1)+} \qquad (35)$$

$$RMH^{(m+1)+} + H_2O \xrightarrow{2M} CH_3CHO + G + H^+_{aq} + M^{m+} \qquad (36)$$

$$k_c = k_{2M}/K_{RMH} \qquad (37)$$

Table 8. Application of electrostatic model: evaluation of effective relative permittivity

Crown ether acetal	Metal	$\ln(k_f/k_c^0)$	r/pm	ε_r
11-C-4	Li	2.33	368	65
14-C-5	Na	3.27	460	37
17-C-6	Na	3.89	503	29
	K	5.00	501	22
	Rb	3.84	488	30
	Cs	3.82	478	31
20-C-7	Na	3.32	623	27
	K	4.62	626	19
	Rb	4.60	633	19
	Cs	4.23	638	21
23-C-8	K	7.34	711	11
	Rb	3.95	711	20
	Cs	4.61	716	17
26-C-9	K	2.88	726	27
	Rb	3.25	726	24
	Cs	4.42	731	17
			Mean:	23.4

corresponding equation (37) where $K_{RMH} = [H^+][RM^{m+}]/[RMH^{(m+1)+}] = k_{-1M}/k_{1M}$ and hence equation (38). The

$$k_f/k_c^0 = k_2^0K^0_{RMH}/k^0_{2M}K^0_{RH} \qquad (38)$$

presence of the cationic change is expected to lead to a large value for the ratio K^0_{RMH}/K^0_{RH}. By comparison, the ratio k^0_{2M}/k^0_2 is expected to differ much less from unity. Accordingly, we shall elaborate the simplified form (39) of equation (38). Following Bjerrum,[28] this effect of electric charge on the

$$k_f/k_c^0 = K^0_{RMH}/K^0_{RH} \qquad (39)$$

dissociation constant of an acid is given by (40) where, in our

$$K^0_{RMH}/K^0_{RH} = \exp(me_0^2/kT\varepsilon_r r) \qquad (40)$$

case, r is the distance between the acid proton and the centre of the metal ion of charge $m+$. Combination of equations (39) and (40) then leads to equation (41).

$$\ln(k_f/k_c^0) = me_0^2/kT\varepsilon_r r \qquad (41)$$

The approach is reasonably successful when applied to the dissociation constants of long-chain dicarboxylic acids. Its inadequacy in other cases is signalled by the fact that agreement between experiment and calculation is obtained only if the relative permittivity ε_r is assigned a much lower value (*ca.* 2) than the value for the bulk solvent.[29,30] In effect, ε_r has to be taken as an empirical parameter, and this is true even in more satisfactory elaborations of the electrostatic model.[31] In the crown complexes of the present work the role of the solvent is somewhat different from that in those applications since the transmission of the electrostatic effect does not at all involve interactions through covalent bonds. We have examined this question by using our data to solve equation (41) for ε_r.

Estimates of the distance r (Table 8) were obtained by measurements on space-filling scale molecular models of crown ether acetal–metal ion adducts with the additional assumption that the O–H distance in the protonated acetal is

Table 9. Results for alkaline earth chlorides

Substrate	Metal	lg(K/dm^3 mol^{-1})	k_f/k_c^0	r/pm	ε_r
17-C-6	Ca	2.4	16.5	483	41
20-C-7	Sr	1.6	31	626	26
	Ba	4.1	255	621	16

one-half of the average crystallographic distance between hydrogen-bonded oxygen atoms in hydrated oxonium ions. The tabulated distances represent the approximate average model centre-to-centre distances between the added proton and the metal ion for different conformations of the ring consistent with keeping the metal ion within it or (for systems in which the metal ion was too large for this to be achievable) as close as possible to the centre of the ring.

The values of ε_r obtained by solution of equation (41) are given in the last column of Table 8. Although they are not constant (and absolute constancy cannot be expected in view of the uncertainties inherent both in the experimental rate ratio k_f/k_c^0 and in the model distances r), the values are mostly in the range 15—30, with an average $\varepsilon_r = 23$. This value is sufficiently close to the relative permittivity of the bulk solvent (25.9) for the conclusion that the electrostatic repulsion between the two positive charges in the transition state (or conjugate acid of the acetal) is attenuated roughly to the extent required by the bulk permittivity. It appears that the repulsion between the surface of the metal ion (a 'conducting sphere') and the proton is propagated through the solvent and not across the periphery of the ring. In view of the fact that most of the distance between the two centres of charge in the dication of the crown ether acetal is contributed by the size of the ion, the agreement is remarkable and its explanation is likely to be less facile than that given here.

The chlorides of the alkaline earth metals are strongly associated in dioxan–water mixtures. The available experimental data cover only a range of mixtures containing higher proportion of water than our solvent.[32] The theoretical equation (42), derived by Fuoss[21] and Hemmes[33] (where Z_ie_0 is the algebraic charge of the ion i, and a is the centre-to-

$$K_{\text{pair}} = \frac{4\pi N_A a^3}{3000} \exp\left(-Z_M Z_x e_0^2/\varepsilon_r a k T\right) \qquad (42)$$

centre distance of the ions in the pair) can be used as an extrapolation function to obtain estimates of the degree of ion association in 60 : 40 dioxan–water. It is thus found that even the pair of ions showing the weakest association (Ba^{2+} and Cl^-) is 99% associated into $BaCl^+$ at a concentration of 6×10^{-3}M. We assume that (MCl^+) ion pairs effectively behave as large univalent cations, so that further association to $M^{2+}Cl_2^{2-}$ is negligible. On this basis, the solutions of the divalent chlorides are treated as uni-univalent electrolytes (MCl^+, Cl^-) without further association. The experimental results and derived parameters are given in Table 9. The effective relative permittivities evaluated in this way seem to fit into the general pattern shown by the alkali-metal chlorides and support the approximate validity of the approach used.

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