The Reactivity of *O*-Acylglycosyl Halides. Part IX.[1] Reaction between Alkali-metal Halides and Tetra-*O*-acetylglycosyl Bromides

By **M. J. Duffy, M. Jeffries, G. Pass,** and **G. O. Phillips,*** Department of Chemistry and Applied Chemistry, University of Salford, Salford M5 4WT

The mechanism of hydrolysis and halogen-exchange reactions of a series of acetylglycosyl bromides in acetone has been investigated. Under the non-solvolytic conditions used. only acetylmannosyl bromide hydrolyses at a measurable rate when alkali-metal halides are absent. In the presence of lithium bromide. the 1.2-*cis*-glycosyl halides hydrolyse at rates which are identical with the rates of bromide exchange for these halides. Similar results were obtained with sodium iodide.

From the kinetics and the effects of temperature when alkali-metal halide is present bimolecular halogen exchange appears to be the rate-determining step which occurs before rapid hydrolysis.

THE solvolyses of the acetylglycosyl halides are considered to follow a unimolecular dissociation mechanism. The rate-determining step is the formation of a carbonium ion, which is facilitated by donation of electrons from the lactol oxygen.[2-4] When the acetylglycosyl halide has an acetoxy-group at C(2) *trans* to the halide at C(1), formation of a cyclic ion can occur, leading to an increase in reactivity.[5] The solvolysis of substituted glycosyl halides is always accompanied by inversion when the group C(2) is *cis* to the halide.[3,4,6-8] When a substituent at C(2) is *trans* to the halide, inversion generally occurs in solvolysis,[3,5,9] but exceptions have been observed.[7,9,10]

During solvolyses in aqueous acetone the 1,2-*cis*-halide reacts at a slower rate than the corresponding 1,2-*trans*-halide.[3] Moreover, it was also noted that the rate of solvolysis of the 1,2-*cis*-compounds increases with time and with the addition of sodium bromide. On the other hand, the solvolysis of the 1,2-*trans*-compound does not change with time, and there is no dependence on added sodium bromide. These observations were all rationalised in terms of an S_N1 mechanism. During the alcoholysis of tetra-*O*-acetyl-α-D-glucosyl bromide, formation of the α-glucopyranoside was attributed to an S_N2 reaction between the glucosyl bromide and bromide ions liberated during solvolysis.[4] The product from this exchange would be the β-glucosyl bromide, which could react *via* the 1,2-acetoxonium ion.[9]

In the corresponding unimolecular reactions of aryl halides the rate is independent of the concentration of the added nucleophile at low concentrations of added nucleophile,[11] although it is dependent on the nature of the nucleophile. This behaviour was rationalised in terms of a quadrupole intermediate.

A limited number of substitutions of glycosyl halides have been studied in which the concentration of added nucleophile is of the same order as the concentration of glycosyl halide.[1,7,9,12] Here the rate is of the first order in added nucleophile, with the exception of 2,3,4,6-tetra-*O*-methyl-α-D-mannosyl chloride, where there was no evidence for an S_N2 reaction.[7] Substitution is accompanied by inversion of configuration. Exceptions were noted for 1,2-*trans*-glycosyl compounds, where the greater rate of substitution than of inversion was attributed to a simultaneous unimolecular dissociation, with retention of configuration.[9,10] Previously we showed that the halogen exchange between lithium bromide and acetylglycosyl bromides is of the second order and leads to anomerisation.[1,5,13] We now examine the hydrolysis of these same glycosyl halides in acetone, under non-solvolytic conditions, and investigate the effect of adding alkali metal halides, in order to establish the nature of the catalysis induced by halide ions on the anomerisation and hydrolysis reactions.

EXPERIMENTAL

Anhydrous acetone was prepared by distillation of AnalaR acetone three times over phosphoric oxide and the fraction boiling at 56°/760 mmHg was collected. Anhydrous methanol was prepared by distillation of AnalaR methanol over magnesium turnings and iodine. The fraction boiling at 65°/760 mmHg was collected.

Tetra-*O*-acetyl-α-D-glucopyranosyl bromide, m.p. 88 °C, $\alpha_D + 186°$; tetra-*O*-acetyl-α-D-galactopyranosyl bromide, m.p. 83—85 °C, $\alpha_D + 205°$; tetra-*O*-acetyl-α-D-mannopyranosyl bromide, m.p. 53—54 °C $\alpha_D + 123°$; and tri-*O*-acetyl-α-D-xylopyranosyl bromide, m.p. 101—102 °C, $\alpha_D + 212°$ were prepared as previously described.[2,5] Sodium [^{131}I]iodide was prepared by diluting a solution of sodium [^{131}I]iodide of 2 mCi activity in dilute sodium hydroxide (0·05 ml) with dry acetone (2 ml) and adding this solution to dry sodium iodide (7·5 g). The mixture was dried on a hot plate at 110 °C for 3—4 h. The dry sodium iodide was dissolved in dry acetone and made up to 250 ml to give 0·2M-sodium [^{131}I]iodide.

Exchange Rates.—Solutions of acetylglucosyl bromide

---

[1] Part VIII, M. J. Duffy, G. Pass, and G. O. Phillips, *J. Chem. Soc.* (*B*), 1971, 785.

[2] F. H. Newth and G. O. Phillips, *J. Chem. Soc.*, 1953, 2896, 2900, 2904.

[3] B. Capon, P. M. Collins, A. A. Levy, and W. G. Overend, *J. Chem. Soc.*, 1964, 3242.

[4] L. R. Schroeder, J. W. Green, and D. C. Johnson, *J. Chem. Soc.* (*B*), 1966, 447.

[5] G. L. Mattok and G. O. Phillips, *J. Chem. Soc.*, 1957, 268.

[6] R. U. Lemieux and G. Huber, *Canad. J. Chem.*, 1955, **33**, 128.

[7] A. J. Rhind-Tutt and C. A. Vernon, *J. Chem. Soc.*, 1960, 4637.

[8] G. L. Mattok and G. O. Phillips, *J. Chem. Soc.*, 1956, 1836.

[9] R. U. Lemieux and J. Hayami, *Canad. J. Chem.*, 1965, **43**, 2162.

[10] W. A. Bonner, *J. Amer. Chem. Soc.*, 1961, **83**, 962.

[11] E. D. Hughes *et al.*, *J. Chem. Soc.*, 1957, 1206—1278.

[12] N. B. Chapman and W. E. Laird, *Chem. and Ind.*, 1954, 20.

[13] R. U. Lemieux and A. R. Morgan, *J. Amer. Chem. Soc.*, 1963, **85**, 1889.

and sodium [^{131}I]iodide in anhydrous acetone were prepared in separate sealed vessels. These were thermostatted and after reaching the required temperature were mixed in a sealed reaction vessel. An aliquot portion (5 ml) of the solution was immediately taken and pipetted into chloroform (10 ml) and water (10 ml) containing a small amount of lithium chloride to assist phase separation. The mixture was well stirred and the phases allowed to separate. The organic and aqueous layers were separated and a 5 ml aliquot portion of each was counted in a liquid-type Geiger–Müller tube. This procedure was repeated at regular intervals. The concentration of labelled sugar (acetylglucosyl iodide), x, was calculated from the expression (1). A plot of x against t gives a straight line,

$$x = c \times \%\ \text{activity in } CHCl_3 \text{ layer} \times 10^{-2}\ \text{mol l}^{-1} \qquad (1)$$

from which the initial rate of reaction can be calculated. The results from the exchange between sodium [^{131}I]iodide (0·025M) and tetra-*O*-acetyl-α-D-glucosyl bromide (0·05M) at 25 °C are given in Table 1 as an example of a standard set of results.

TABLE 1

x	0·24	0·72	1·06	1·31	1·60	1·97	2·18	2·53	3·30
t/min	0	32	64	92	112	146	166	199	258

Hydrolysis Rates.—The acid produced during hydrolysis was determined with lacmoid indicator in ethanol, and the cooled aliquot portion of reaction mixture titrated against 0·002M-potassium hydroxide in ethanol.

For the hydrolysis (2) of the 1,2 trans halides in the absence of alkali halide the rates were calculated by use

$$RBr + H_2O \longrightarrow ROH + HBr \qquad (2)$$

of the standard second-order expression (3) for dissimilar initial concentrations where a = the initial concentration

$$\log_{10}\frac{b(a-x)}{a(b-x)} = \frac{k_2t(a-b)}{2\cdot303} \qquad (3)$$

of RBr, b = the initial concentration of water, and x = the concentration of HBr at time t. A plot of $\log_{10}[(a-x)/(b-x)]$ against t gives a straight line with slope $k_2(a-b)/2\cdot303$. For calculation of the rate of hydrolysis of the 1,2-*cis*-compounds, when LiBr is present the reactions considered were (4) and (5). During exchange, the concentration of LiBr remains constant, hence we obtain equations (6) and (7), where now b = the initial con-

$$\alpha\text{-RBr} + LiBr \xrightarrow{\text{slow}} \beta\text{-RBr} + LiBr \qquad (4)$$

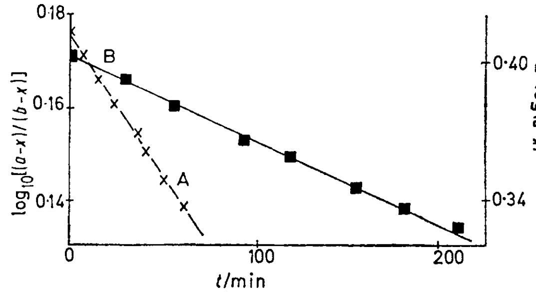
$$\beta\text{-RBr} + H_2O \xrightarrow{\text{fast}} ROH + HBr \qquad (5)$$

$$\frac{dx}{dt} = k_2b(a-x) \qquad (6)$$

$$\log_{10}\frac{a}{a-x} = \frac{k_2bt}{2\cdot303} \qquad (7)$$

centration of LiBr. A plot of $\log_{10}(a-x)$ against t gives a straight line with slope $= -k_2b/2\cdot303$. The Figure shows the results from the hydrolysis of tetra-*O*-acetyl-α-D-mannosyl bromide at 32 °C plotted as $\log_{10}[(a-x)/(b-x)]$ against t, and the results from the hydrolysis of tetra-*O*-acetyl-α-D-glucosyl bromide in the presence of lithium bromide at 25 °C, plotted as $\log_{10}(a-x)$ against t.

When reactions were studied with added sodium iodide a deep iodine colour developed during hydrolysis. The concentration of iodine was determined by titration against 0·002M-sodium thiosulphate or by optical density measurements. It was found by carrying out the hydrolysis under air or carbon dioxide to minimise iodine formation, that although the amounts of iodine or acid varied, the sum of iodine plus acid was constant. A plot of (iodine + acid) against time gave a straight line from which the initial rate was calculated. The results from the sodium iodide (0·05M)-catalysed hydrolysis of tetra-*O*-acetyl-α-D-glucosyl bromide at 25 °C are given in Table 2 as standard sets of results, to indicate the effect of an inert atmosphere.



A, Hydrolysis of tetra-*O*-acetyl-α-D-mannosyl bromide (0·05M), H_2O (0·33M) at 32 °C. B, Hydrolysis of tetra-*O*-acetyl-α-D-glucosyl bromide (0·025M) in the presence of LiBr (0·05M) at 25 °C

TABLE 2

Air							
10^3 × Acid equiv./l^{-1}	0	0·48	0·80	1·36	1·64	1·80	1·84
Iodine	0	0·25	0·44	0·90	1·28	1·72	2·18
Total	0	0·73	1·24	2·26	2·92	3·52	4·02
t/min	0	50	75	120	150	180	210
Carbon dioxide							
10^3 × Acid equiv./l^{-1}	0	0·24	0·72	1·28	1·90	2·54	
Iodine	0	0·10	0·22	0·34	0·44	0·50	
Total	0	0·34	0·94	1·62	2·34	3·04	
t/min	0	30	60	90	120	150	

Methanolysis Rates.—The acid produced was determined by titration as already described and rates were also determined polarometrically by use of thermostatted polarimeter tubes (2 dm).

RESULTS AND DISCUSSION

Previously[1] we found that the rates of exchange of bromide ion with acetylglycosyl bromides increase in the order glucosyl < galactosyl < mannosyl < xylosyl, and could be interpreted in terms of a bimolecular nucleophilic attack by the bromide ion on the acetylglycosyl bromide. Our results indicate that when a small quantity of water is added to the acetone, two effects are observed. First, lithium bromide added to aqueous acetone increases the rate of hydrolysis of glucosyl, galactosyl, and xylosyl bromides, but has no effect on the rate of hydrolysis of the mannosyl bromide. Secondly, only the acetylmannosyl bromide hydrolyses at a significant rate in the absence of lithium bromide. These results are shown in Table 3. The effect of temperature on the apparent second-order rate constant is given in Table 4. The results in Table 5 show the effect of adding lithium bromide to 1,2-*cis*-compounds in aqueous acetone, where previously in the absence of lithium bromide the rate of hydrolysis could not be measured. When lithium bromide is present, the rate of hydrolysis is independent of the water concentration and of the first order in acetylglycosyl bromide and lithium bromide (Table 6). Significantly, the rate constants and thermodynamic data in Table 5 for hydrolysis are in good agreement with the corresponding values for the second-order halogen exchange reaction when no significant amount of water is present.[1]

TABLE 3

Second-order rate constants for the hydrolysis of tetra-*O*-acetyl-α-D-mannosyl bromide (0·05M) in acetone at 25 °C

Water/M	0·1	0·3	0·5	1·0	0·1	0·5
LiBr/M					0·05	0·05
10^5k_2/l mol^{-1} s^{-1}	3·8	4·0	3·9	3·7	3·9	4·0

TABLE 4

Effect of temperature on the second-order rate constants for the reaction of tetra-*O*-acetyl-α-D-mannosyl bromide (0·05M) with water (0·3M) in acetone

T/°C	10^5k_2 / l mol^{-1} s^{-1}	E / kcal mol^{-1}	$\Delta G^\ddagger$ / kcal mol^{-1}	$\Delta H^\ddagger$ / kcal mol^{-1}	$\Delta S^\ddagger$ / cal mol^{-1} K^{-1}
20	2·5				
25	4·0	16·0	23·5	15·5	−27
32	7·6				
40	15·5				

TABLE 5

Second order rate constants for hydrolysis of acetylglycosyl bromide (0·05M) in acetone; {H_2O} 0·1M; {LiBr} 0·05M

T/°C	10^5k / l mol^{-1} s^{-1}	E / kcal mol^{-1}	$\Delta G\ddagger$ / kcal mol^{-1}	$\Delta H\ddagger$ / kcal mol^{-1}	$\Delta S\ddagger$ / cal mol^{-1} K^{-1}
Tetra-*O*-acetylglucosyl					
17	11·1				
25	25·1				
30	43·7	19·0	22·0	18·5	−12
35·5	76·0	(22) *	(22·5)	(21·5)	(−3)
Tetra-*O*-acetylgalactosyl					
14·5	8·3				
20	16·4				
25	25·3	19·0	22·0	20·5	−12
30	46·0	(22·5)	(22)	(22)	(0)
35	79·5				
Tri-*O*-acetylxylosyl					
0	30				
15	139				
20	236	16·5	20·5	16·0	−15
25	381	(19)	(20)	(18·5)	(−5)

* Values given in parentheses correspond to those for equivalent reaction involving only bromide–bromide exchange in the absence of water.

TABLE 6

Effect of acetylglucosyl bromide, lithium bromide, and water concentrations on the second-order rate constants for hydrolysis

Acetylglucosyl bromide/M	Lithium bromide/M	Water/M 0·1	Water/M 0·3	Water/M 0·5
		10^5k_2/l mol^{-1} s^{-1}		
0·05	0·05	25·1	26·1	24·5
0·025	0·05	24·6	24·8	
0·025	0·025	24·6		25·2
0·05	0·05 (+0·05M-$LiClO_4$)		22·0	

In order to establish whether such agreement is general, we have quantitatively compared the non-solvolytic hydrolysis of acetylglucosyl bromide in acetone in the presence of sodium iodide and the exchange with sodium iodide when no significant amount of water is present. Table 7 shows the results for halogen exchange, indicating that the reaction is of the first order in glucosyl bromide and sodium iodide. From the variation of the second-order rate constant with temperature, the thermodynamic constants for the exchange reaction were obtained (Table 8). The hydrolysis, when sodium iodide is present, is also of the first order in glucosyl bromide and sodium iodide (Table 9), and the thermodynamic parameters were similarly calculated from the effect of temperature on the reaction rates (Table 10). It is again significant that the rate constants for hydrolysis and halogen exchange, and the associated thermodynamic parameters are comparable. It seems reasonable, therefore, to suggest that the rate-determining step is the same in both

TABLE 7

The effect of initial concentration of glucosyl bromide and sodium iodide on the rate of exchange at 25 °C

Acetylglucosyl bromide/M	0·025	0·025	0·05	0·1	0·1
Sodium iodide/M	0·025	0·05	0·025	0·025	0·1
10^7 × Initial rate/mol l^{-1} s^{-1}	1·1	2·25	2·15	4·4	18·0
10^5k_2/l mol^{-1} s^{-1}	17·7	18·0	17·2	17·6	18·0

TABLE 8

Rate constants for iodide ion exchange with acetylglucosyl bromide in anhydrous acetone

T/°C	10^5k / l mol^{-1} s^{-1}	E / kcal mol^{-1}	$\Delta G^\ddagger$ / kcal mol^{-1}	$\Delta H^\ddagger$ / kcal mol^{-1}	$\Delta S^\ddagger$ / cal mol^{-1} K^{-1}
0	1·1				
15	6·2				
25	17·7	18	22·5	17·5	−16·5
35	50·3				

TABLE 9

The effect of initial concentration of acetylglucosyl bromide and sodium iodide on the rate of hydrolysis at 25 °C (0·1M-water)

Acetylglucosyl bromide/M	0·025	0·05	0·1	0·1
Sodium iodide/M	0·025	0·05	0·05	0·1
10^7 × Initial rate/mol l^{-1} s^{-1}	1·0	4·1	8·1	16·0
10^5k_2/l mol^{-1} s^{-1}	16·0	16·4	16·2	16·0

TABLE 10

Rate constants for sodium iodide catalysed hydrolysis of acetylglucosyl bromide (0·1M-water)

T/°C	10^5k_2 / l mol^{-1} s^{-1}	E / kcal mol^{-1}	$\Delta G^\ddagger$ / kcal mol^{-1}	$\Delta H^\ddagger$ / kcal mol^{-1}	$\Delta S^\ddagger$ / cal mol^{-1} K^{-1}
0	1·0				
15	5·8				
25	16·2	18	22·5	17·5	−16·5
35	4·5				

reactions. Bimolecular halogen exchange is followed by rapid hydrolysis of the halide anomeric with the original acetylglycosyl halide. The product isolated from the reaction between sodium iodide and the 1,2-*cis*-acetylglucosyl bromide in acetone is the 1,2-*cis*-acetylglucosyl iodide. Thus, although equilibrium is rapidly established between the 1,2-*cis*- and the 1,2-*trans*-iodides in acetone, the equilibrium is well over to the 1,2-*cis*-glucosyl iodide.[9] Precipitation of sodium bromide occurs when $<1\%$ of the acetylglucosyl bromide has reacted. However, since hydrolysis and exchange reactions proceed in a parallel manner, as with lithium bromide where no precipitation occurs, the presence of precipitate does not appear to influence the rates of reaction. The rate constants for the exchange of sodium iodide and lithium bromide with acetylglucosyl bromide are $17{\cdot}7 \times 10^{-5}$ and $19{\cdot}3 \times 10^{-5}$ l mol^{-1} s^{-1}, respectively. Sodium iodide is highly dissociated in acetone, whereas lithium bromide is weakly dissociated,[14] and therefore, for equimolar solutions the iodide-ion concentration is greater than the bromide-ion concentration. The results indicate that bromide ion is a stronger nucleophile than iodide in acetone, which is in agreement with previous observations of the relative nucleophilic strengths of bromide and iodide ions in non-hydroxylic solvents.[9,15]

No such catalysis of the hydrolysis was found, however, when lithium bromide was added to the 1,2-*trans*-halide, acetylmannosyl bromide. It is apparent that we are not simply encountering a salt effect, which accelerates the S_N1 hydrolysis of the sugar halide. Thus, the addition of lithium perchlorate has no significant effect (Table 6). Further, if such a salt effect were the explanation this should be equally or even more pronounced for the acetylmannosyl bromide, which is hydrolysed by a well established S_N1 reaction. Moreover, the observed hydrolysis of this 1,2-*trans*-halide in the absence of lithium bromide, which does not occur with the 1,2-*cis*-halides, is further confirmation that anchimeric assistance by the neighbouring C(2) acetyl group is the dominating factor controlling the S_N1 hydrolysis of this halide. Finally, additional evidence that we are not dealing with acceleration due to salt effects comes from the observation that changing the lithium bromide concentration influences the rate almost identically in aqueous and anhydrous acetone. Ionic-strength effects are normally more important in the presence of small quantities of water. Therefore, we discount the possibility that we are dealing with a salt effect, particularly since lithium bromide and sodium iodide show the same behaviour.

We consider, therefore, that the observations on halide–halide exchange, halide-ion-catalysed hydrolysis, and uncatalysed hydrolysis reactions can be explained in terms of the known anomerisation reaction[4,9,13] and the more rapid solvolysis of the 1,2-*trans*-compound than of the 1,2-*cis*-compound.[5] Reaction (8) is of the

$$\text{1,2-}cis \underset{(8)}{\overset{X^-}{\rightleftharpoons}} \text{1,2-}trans \xrightarrow[(9)]{H_2O} \text{products}$$

first order in halide and of the first order in acetylglycosyl halide,[9,13] would occur with inversion, and is the rate-determining step in the hydrolysis of the 1,2-*cis*-compounds. Our results do not allow us to decide whether attack of halide ion occurs as in a conventional S_N2 reaction or on a previously formed ion pair.[16] The accelerating effect of the *trans*-C(2)-acetoxy-group, even in such bimolecular reactions, may be an indication that the latter process is more probable. Steric factors will have a similar effect on the rate in either case.[17,18] The hydrolysis step (9) must be considerably faster than the exchange step, for the latter to be so unequivocally rate-determining. For this reason the hydrolysis of the 1,2-*trans*-anomer of the acetylglucosyl bromide will have a rate constant $\gg 25 \times 10^{-5}$ l mol^{-1} s^{-1}, which is greater than our measured rate constant for the hydrolysis of the acetylmannosyl bromide, $3{\cdot}8 \times 10^{-5}$ l mol^{-1} s^{-1}. This is in accordance with previous observations[8] where the rates of solvolysis of the 1,2-*trans*-acetylglucosyl halide and 1,2-*trans*-acetylmannosyl halide were in the ratio 380 : 1.

There is considerable evidence that reaction (9) proceeds by an S_N1 mechanism.[2,3,5,8] There are features, however, which are not characteristically associated with this mechanism. First is the steric course of the reaction which leads almost completely to inversion of configuration. Owing to mutarotation of the hydrolysis products catalysed by acid, polarimetric measurements cannot be used in aqueous acetone to follow the course of the reaction. No such complication arises during methanolysis. Comparison of the course of methanolysis of acetylmannosyl bromide by use of polarimetry and titrimetry (Table 11) indicates that almost complete inversion accompanies methanolysis. For the 1,2-*cis*-acetylglycosyl bromides on the

TABLE 11

Comparison of percentage reaction from titrimetric and polarimetric measurements for the reaction between acetylmannosyl bromide (0·05M) and methanol (2M) at 25 °C

t/min	α_{obs}	Reaction (%)		
		(a)	(b)	(c)
25	3·48	4	3·5	9·0
35	3·43	4·5	4·5	12·0
50	3·34	5·5	6·0	15·0
65	3·26	7	7·5	19·0
75	3·20	8	8·5	22·0
100	3·09	10·5	10·5	27·0

(a) Calculated from methanolysis rate. (b) Calculated assuming product is β-anomer. (c) Calculated assuming product is α-anomer.

---

[14] C. C. Evans and S. Sugden, *J. Chem. Soc.*, 1949, 270.

[15] S. Winstein, L. G. Savedoff, S. Smith, I. D. R. Stevens, and J. S. Gall, *Tetrahedron Letters*, 1960, No. 9, 24.

[16] R. A. Sneen and J. W. Larsen, *J. Amer. Chem. Soc.*, 1969, **91**, 362.

[17] J. T. Edward, *Chem. and Ind.*, 1955, 1102.

[18] G. L. Mattok and G. O. Phillips, *J. Chem. Soc.*, 1958, 130.

other hand, no methanolysis is detectable in methanolic acetone alone. As in the hydrolyses, anchimeric assistance by the C(2) acetoxy-group in the ionization process accounts for the reactivity of the 1,2-*trans*-halide, and provides further support for the S_N1 character of the reaction. Secondly, water exerts an accelerating effect on the hydrolysis which is reasonably of the first order over the range 0·1—1·0M-water (Table 3). If it is assumed such a dependence is maintained to 25% (w/w) aqueous acetone, and $k_1 = k_2[H_2O]$ then the expected first-order constant would be $31 \times 10^{-6} \times 11{\cdot}6 = 36 \times 10^{-5}$ s^{-1}. This compares with the published value[3] of 39×10^{-5} s^{-1}. Such a regular dependence on water concentration over a 100-fold range points to an unusually strong medium effect and might be indicative of some participation of water in the transition state[19] for the solvent system of low polarity.

We have two indications that consideration of the reactions of the 1,2-*trans*-halide in terms of classical S_N1 or S_N2 mechanisms may be an oversimplification. Participation by the C(2) acetyl enhances the rate of the bimolecular halogen exchange[1] and the participating nucleophile water exerts an unusually direct influence on the reaction rate of the unimolecular reactions. Neither is characteristic of the two classical nucleophilic substitution mechanisms, and might be indicative of a more complex intermediate.

[1/1713 *Received, 20th September*, 1971]

---

[19] R. H. Boyd, R. W. Taft, A. P. Wolf, and D. R. Christman, *J. Amer. Chem. Soc.*, 1960, **82**, 4729.