

The Reactivity of *O*-Acylglycosyl Halides. Part X.¹ Exchange and Hydrolysis Reactions of 1,2-*trans*-*O*-Acetylglucosyl Chlorides in Acetone

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The hydrolysis and halogen exchange of three 1,2-*trans*-acetylglucosyl chlorides in acetone have been investigated. The rate data illustrate the influence of structural and environmental factors on observed kinetic behaviour.

THE exchange between acetylglucosyl bromides and lithium bromide in anhydrous acetone is of the second order and the relative rates of exchange of the 1,2-*cis*-

¹ Part IX, M. J. Duffy, M. Jefferies, G. Pass, and G. O. Phillips, *J.C.S. Perkin II*, 1972, 821.

compounds have been explained in terms of steric effects on the formation of a partly planar intermediate.² For the exchange of the 1,2-*trans*-compound the re-

² M. J. Duffy, G. Pass, and G. O. Phillips, *J. Chem. Soc. (B)*, 1971, 785.

action was also of the second order, but the group at C(2) exerted a significant accelerating effect on the reaction rate. In the hydrolysis reactions of acetyl-glycosyl bromides in acetone under nonsolvolytic conditions, only the 1,2-*trans*-compound was hydrolysed at a measurable rate. The rate of hydrolysis showed an apparent first-order dependence on the concentration of water over a 100-fold range. Addition of alkali-metal halides increased the hydrolysis rate of the 1,2-*cis*-compounds, but had little effect on the 1,2-*trans*-compound. The role of the alkali-metal halide is to anomerise³⁻⁵ the 1,2-*cis*-compound to the 1,2-*trans*-compound, which can then rapidly hydrolyse.⁶

The solvolysis of the acetyl-glycosyl halides, an S_N1 process, shows similar behaviour in that the 1,2-*cis*-anomer reacts more slowly than the 1,2-*trans*-anomer.⁷ This is explained in terms of the neighbouring group at C(2) in the 1,2-*trans*-compounds facilitating the formation of an intermediate carbonium ion.⁶ The formation of a cyclic carbonium ion by 1,2-*trans*-acetyl-glycosyl halides on alcoholysis yields alkyl 1,2-ortho-acetates.⁸ The nature of the group at C(2) apparently governs the formation of this cyclic ion and 1,2-ortho-esters are not formed during the solvolysis of the 2-trichloroacetyl *trans*-halide.⁹ Solvolysis of 3,4,6-tri-*O*-acetyl-β-D-glucosyl chloride is 60 times faster than that of 3,4,6-tri-*O*-acetyl-2-trichloroacetyl-β-D-glucosyl chloride, which along with different proportions of α- and β-glucosides in the products demonstrates the steric hindrance of a group at C(2) *trans* to the halogen.⁹

The exchange between chloride ion and tetra-*O*-acetylglucosyl chloride in acetonitrile⁴ is of the second order, and here also reaction occurs more rapidly with the 1,2-*trans*-anomer than with the 1,2-*cis*-anomer. There is some evidence that the 1,2-*trans*-anomer can undergo reaction both by an S_N2 mechanism and through dissociation into the acetoxonium ion. On the other hand, the reaction of tetra-*O*-methylglucosyl chloride¹⁰ and tetra-*O*-acetylglucosyl bromide with the thiophenoxide ion is of the second order, but the reaction of the corresponding mannosyl compound is not, pointing again to the anomalous behaviour of 1,2-*trans*-halides.

Here we investigate the kinetics of halide exchange and hydrolysis of a series of 1,2-*trans*-acetylglucosyl chlorides in acetone to clarify the role of the group at C(2) in chloride substitutions.

EXPERIMENTAL

Anhydrous acetone was prepared by distillation of AnalaR acetone three times over phosphoric oxide and the fraction boiling at 56° and 760 mmHg was collected.

Tetra-*O*-acetyl-β-D-glucopyranosyl chloride, m.p. 93—95 °C, α_D - 6.5° (*c* 3.6 in chloroform); 2-trichloroacetyl-

³ L. R. Schroeder, J. W. Green, and D. C. Johnson, *J. Chem. Soc. (B)*, 1966, 447.

⁴ R. U. Lemieux and J. Hayami, *Canad. J. Chem.*, 1965, **43**, 2162.

⁵ R. U. Lemieux and A. R. Morgan, *J. Amer. Chem. Soc.*, 1963, **85**, 1889.

⁶ G. L. Mattok and G. O. Phillips, *J. Chem. Soc.*, 1957, 258.

⁷ B. Capon, P. M. Collins, A. A. Levy, and W. G. Overend, *J. Chem. Soc.*, 1964, 3242.

3,4,6-triacetyl-β-D-glucopyranosyl chloride, m.p. 139—142 °C, α_D + 3.6° (*c* 7.4 in benzene); and 3,4,6 triacetyl-β-D-glucopyranosyl chloride, m.p. 152—154 °C, α_D + 31° (*c* 1 in chloroform), were prepared as previously described.¹¹ Lithium [³⁶Cl]chloride was prepared by diluting an aqueous solution of hydrogen [³⁶Cl]chloride of 100 μCi activity with dilute hydrochloric acid (8 ml). Lithium hydroxide (1.0 g) was added to the solution and the mixture was slowly evaporated to dryness. The dry residue was dissolved in anhydrous acetone and lithium chloride added to give the approximate molarity required. The solution was standardised against silver nitrate solution (0.1M) with Fluorescein as indicator.

Exchange Rates.—Measurements were made using the method and rate expression previously described.² Thus $k_1 t = [2.303 \log (1 - x/c)]/a$, where a is the concentration of β-RCI and x/c is the activity of the glucosyl chloride/the total activity. A plot of $\log (1 - x/c)$ against t should give a straight line with slope = $-k_1 a/2.303$. The results from the exchange between lithium [³⁶Cl]chloride (0.05M) and tetra-*O*-acetyl-β-D-glucosyl chloride (0.05M) at 25° are given as an example of a standard set of results.

100 x/c (%)	0.0	0.26	0.68	1.21	1.76	2.30	3.4
t /min	0	22	60	120	180	225	330

Hydrolysis Rates.—The acid produced during hydrolysis was determined with lacmoid indicator in ethanol, and a cooled aliquot portion of the reaction mixture was titrated against 0.002M-potassium hydroxide in ethanol. A plot of acid concentration against time gave a straight line from which the initial rate was calculated.

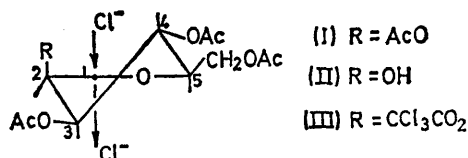
RESULTS AND DISCUSSION

The exchange between lithium chloride and the acetylglucosyl chloride is always second order (Table 1),

TABLE 1

Second-order rate constants for halogen exchange showing dependence on initial concentration of reactants at 25 °C

[LiCl]/M		0.1	0.05	0.025	0.0125
		10 ⁵ k ₂ /l mol ⁻¹ s ⁻¹			
Tetra- <i>O</i> -acetyl-β-D-glucosyl chloride (I)	0.05M	3.1	3.4	3.6	
	0.025M	3.07	3.2	3.0	
2-Trichloroacetyl-3,4,6-triacetyl-β-D-glucosyl chloride (III)	0.10M		1.1	0.96	
	0.05M		1.0	1.1	
3,4,6-Triacetyl-β-D-glucosyl chloride (II)	0.025M			4400	4400
	0.0125M			4450	4450



and is consistent with a bimolecular mechanism for the exchange process operating through a partly

⁸ R. U. Lemieux and A. R. Morgan, *Canad. J. Chem.*, 1965, **43**, 2199.

⁹ F. H. Newth and G. O. Phillips, *J. Chem. Soc.*, 1953, 2904.
¹⁰ A. J. Rhind-Tutt and C. A. Vernon, *J. Chem. Soc.*, 1960, 4637.

¹¹ R. L. Whistler and M. L. Wolfrom, 'Methods in Carbohydrate Chemistry,' Academic Press, New York, 1963, vol. II, pp. 224, 400.

planar transition state.^{1,2} The increasing order of the rates of exchange (III) < (I) < (II) would be anticipated on the basis of the decreased order of steric hindrance of group R.¹ A similar steric effect would arise if the chloride ion attacked a previously formed ion pair.¹² Such ion-pair formation is indeed probable,

in polar solvents is unimolecular. The greater reactivity of 1,2-*trans*-halides has been accounted for by anchimeric assistance from the neighbouring acetyl group at C(2), forming a cyclic carbonium ion.^{3,7} Such participation from the C(2) acetyl group would be anticipated for chloride (I). Hydrolysis then occurs

TABLE 2
Rate constants for chloride ion exchange with acetylglucosyl chlorides in anhydrous acetone

	<i>T</i> /°C	$10^5 k$ l mol ⁻¹ s ⁻¹	<i>E</i>	ΔG		ΔS cal mol ⁻¹ k ⁻¹
				kcal mol ⁻¹		
Tetra- <i>O</i> -acetyl- β -D-glucosyl chloride (0.05M); LiCl (0.05M)	20	1.9	19.5	23.5	19.0	-15.0
	25	3.4				
	30	6.1				
	35	10.0				
	25	1.0				
2-Trichloroacetyl-3,4,6-triacetyl- β -D-glucosyl chloride (0.05M); LiCl (0.05M)	30	1.5	21.5	24.0	21.0	-10.0
	35	2.5				
	0	600				
	5	950				
3,4,6-Triacetyl- β -D-glucosyl chloride (0.025M); LiCl (0.025M)	15	2100	13.0	19.5	12.5	-23.5
	25	4400				

in view of the decreased exchange rate with chloride (I) on lowering the dielectric constant of the medium.⁴

The nonsolvolytic hydrolysis of chloride (II) is first order with respect to chloride (II), but is greater than first order with respect to water (Table 3). Comparable

TABLE 3

The effect of initial concentration of triacetylglucosyl chloride and water on the rate of hydrolysis at 25 °C

[Triacetylglucosyl chloride]/M	0.025	0.025	0.025	0.05	0.05	0.075
[Water]/M	1	2	3	1	2	1
10 ⁸ Initial rate/mol l ⁻¹ s ⁻¹	4.2	18.3	50.0	8.4	35.0	12.5
10 ⁶ k ₁ /s ⁻¹	1.7	7.5	20.0	1.7	7.0	1.7

TABLE 4

The effect of initial concentration of tetra-acetylglucosyl chloride and water on the rate of hydrolysis at 25 °C

[Tetra-acetylglucosyl chloride]/M	0.025	0.025	0.025	0.05	0.05	0.05
[Water]/M	0.5	2	3	0.5	2	3
10 ⁷ Initial rate/mol l ⁻¹ s ⁻¹	3.9	15	23	7.5	31	45.5
10 ⁵ k ₂ /l mol ⁻¹ s ⁻¹	3.1	3.0	3.1	3.0	3.1	3.0

behaviour is found in the unimolecular solvolysis of acetylglucosyl halides, where the variation of rate with water concentration is attributed to a solvent-effect.^{9,13,14} The nonsolvolytic hydrolysis of chloride (I) is first order with respect to water and chloride (I) (Table 4), and so differs from the solvolytic reaction. The comparable hydrolysis of chloride (III) is so slow, even at 35 °C, that no satisfactory results could be obtained to elucidate the effects of water concentration and temperature. The increase in the rates of nonsolvolytic hydrolysis (I) > (II) > (III), however, is in the same sequence as found for the first-order solvolyses.^{6,9}

Generally the solvolysis of acetylglucosyl halides

¹² R. A. Sneen and J. W. Larsen, *J. Amer. Chem. Soc.*, 1969, **91**, 362.

¹³ F. H. Newth and G. O. Phillips, *J. Chem. Soc.*, 1953, 2896.

¹⁴ G. L. Mattok and G. O. Phillips, *J. Chem. Soc.*, 1956, 1836.

by attack of water on the cyclic carbonium ion,⁸ which rapidly yields the α -glucoside in acid solution.¹⁵ Identical behaviour was previously encountered with another 1,2-*trans*-halide, namely tetra-*O*-acetyl- α -D-mannosyl bromide.¹

No such cyclic ion formation is possible with chloride (II) because of the absence of the C(2) acetyl group. A similar conclusion was drawn from the acetolysis of chloride (II) in acetic acid.¹⁶ Due to the absence of neighbouring group participation chloride (II) hydrolyses more slowly than chloride (I). Chloride (III) hydrolyses even slower since the inductive effect of the halogen atoms prevents the trichloroacetyl group from forming a cyclic ion intermediate.⁹ Compared to chloride (II), therefore, the bulky C(2) group leads to a slower hydrolysis rate.

The addition of lithium chloride had no effect on the hydrolysis of chloride (III) (Table 5). This is in marked

TABLE 5

Initial rate of hydrolysis of 2-trichloroacetyl-3,4,6-triacetylglucosyl chloride

[Acetylglucosyl chloride]/M	0.1	0.1 (+ 0.025M-LiCl)
[Water]/M	2	2
10 ⁸ Initial rate/mol l ⁻¹ s ⁻¹	1.5	1.5

contrast to the effect of added lithium bromide on the hydrolysis of the 1,2-*cis*-acetylglucosyl bromides, and supports the postulate that the rate increase produced by lithium bromide¹ is due to anomerisation and not to a salt effect.

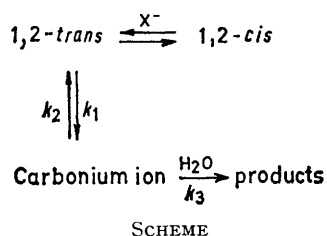
The main point of difference between solvolysis and nonsolvolytic hydrolysis is that under the latter conditions the reaction is of the second order for certain acetylglucosyl halides.

A possible reaction mechanism for hydrolysis and

¹⁵ R. U. Lemieux and A. R. Morgan, *Canad. J. Chem.*, 1965, **43**, 2214.

¹⁶ R. U. Lemieux and G. Huber, *Canad. J. Chem.*, 1955, **33**, 129.

exchange is shown in the Scheme. The rate of formation of acid = $k_3[\text{carbonium ion}][\text{H}_2\text{O}]$. Assuming that



[carbonium ion] reaches a stationary state then $k_1[1,2\text{-trans}] = k_2[\text{carbonium ion}] + k_3[\text{carbonium ion}][\text{H}_2\text{O}]$

For chloride (II), the absence of the C(2) acetyl group prevents formation of a cyclic carbonium ion. However the minimal steric hindrance and more localised charge⁷ on the carbonium ion will be factors favouring attack by the water molecule, increasing k_3 . There is then an approach to the limiting condition $k_2 < k_3[\text{H}_2\text{O}]$ and the reaction is of the first order. Since the rate-determining step is now the same for solvolysis and nonsolvolytic hydrolysis, the similar dependence on water concentration under both sets of conditions is to be expected.

Our results suggest that where anchimeric assistance occurs the rate-determining step for nonsolvolytic

TABLE 6
Effect of temperature on the rate constants for the reaction of acetylglucosyl chlorides (0.05M) with water (2M) in acetone

	$T/^\circ\text{C}$	$10^5 k_2$ $1 \text{ mol}^{-1} \text{ s}^{-1}$	E	ΔG kcal mol^{-1}	ΔH	ΔS $\text{cal mol}^{-1} \text{ K}^{-1}$
Tetra- <i>O</i> -acetylglucosyl	20	1.7	18.0	23.5	17.5	-20
	25	2.9				
	30	4.8				
	35	7.8				
Tri- <i>O</i> -acetylglucosyl		$10^6 k_1/\text{s}^{-1}$	17.5	24.5	17.0	-25
	25	7.0				
	30	11.5				
	35	18.0				

and $[\text{carbonium ion}] = k_1[1,2\text{-trans}]/(k_2 + k_3[\text{H}_2\text{O}])$. Therefore, the rate of formation of acid = $k_1 k_3 [1,2\text{-trans}][\text{H}_2\text{O}]/(k_2 + k_3[\text{H}_2\text{O}])$. The observed order of the reaction, therefore, depends on the relative values of k_2 and $k_3[\text{H}_2\text{O}]$. Solvolysis corresponds to the limiting condition that $k_2 \ll k_3[\text{H}_2\text{O}]$. Thus, under solvolytic conditions $d[\text{acid}]/dt = k_1[1,2\text{-trans}]$. However, under the nonsolvolytic conditions used in the present hydrolysis work, $[\text{H}_2\text{O}]$ is small and the ionising strength of the solvent is low. Thus there is an approach to the other limiting condition $k_2 \gg k_3[\text{H}_2\text{O}]$, when $d[\text{acid}]/dt = k_1 k_3 [1,2\text{-trans}][\text{H}_2\text{O}]/k_2$. No consideration has been taken of a possible solvent effect depending on $[\text{H}_2\text{O}]$; hence the Scheme explains the observed kinetic behaviour for the solvolysis and hydrolysis of the chloride (I) and of tetra-*O*-acetyl- α -D-mannosyl bromide,¹ where there is no experimental evidence of any solvent effect at low concentrations of water.

hydrolysis is the attack by water on the cyclic carbonium ion. In the absence of anchimeric assistance the formation of the carbonium ion is rate determining. A comparison of our exchange and hydrolysis results also indicates that anchimeric assistance exerts more influence on hydrolysis than on exchange. This accords with the observations that for an anomeric pair of acetylglucosyl chlorides, the rates of solvolysis⁶ differ by a factor of 10^3 but the rates of exchange⁴ by a factor of 16.

Therefore in broad mechanistic terms halogen-halogen exchange in acetone can be considered to operate *via* an S_N2 mechanism and hydrolysis *via* an S_N1 mechanism. The mechanism we have suggested demonstrates how structural and environmental factors can appreciably influence the observed kinetic behaviour.

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