

## The Reactivity of *O*-Acylglycosyl Halides. Part XII.<sup>1</sup> Solvent Effects on Exchange and Hydrolysis Reactions

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Bromide exchange reactions and hydrolysis reactions of a series of acetylglucosyl halides in a selection of solvents have been investigated. The 1,2-*trans*-glycosyl halides show a greater variation in reaction rate than 1,2-*cis*-glycosyl halides with change of solvent.

THE solvolysis of acetylglucosyl halides proceeds by an S<sub>N</sub>1 mechanism; compounds with the 1,2-*trans*-configuration react appreciably faster than the corresponding 1,2-*cis*-compounds.<sup>2-4</sup> This increase in rate is attributed to a neighbouring group effect.<sup>5</sup> Investigation of the hydrolysis reactions in acetone has also shown the significant effect of anchimeric assistance on the reaction rate,<sup>6,7</sup> although the hydrolysis reaction is of the second order.

The rate of the S<sub>N</sub>1 alcoholyses of tetra-*O*-acetyl- $\alpha$ -D-glucosyl bromide decreases with decreasing solvent polarity.<sup>4</sup> Similarly in acetone-water or methanol-water solvents the rate of S<sub>N</sub>1 solvolysis of acylglycosyl halides decreases with decreasing solvent polarity.<sup>2,8</sup> The effect is more pronounced for compounds with the 1,2-*cis*- than with the corresponding 1,2-*trans*-configuration.<sup>3,5</sup>

There are few S<sub>N</sub>2 reactions involving acylglycosyl halides and little investigation of solvent effects on these reactions. Certain acylglycosyl halides which react by an S<sub>N</sub>2 mechanism in solvents of low ionizing power react by an S<sub>N</sub>1 mechanism in solvents of higher ionizing power.<sup>9,10</sup>

We have now investigated the exchange and hydrolysis reactions of a series of acylglycosyl halides in different solvents, in an attempt to clarify the role of the neighbouring group in these reactions.

<sup>1</sup> Part XI, M. J. Duffy, G. Pass, and G. O. Phillips, *J.C.S. Perkin II*, 1974, 1466.

<sup>2</sup> F. H. Newth and G. O. Phillips, *J. Chem. Soc.*, 1953, 2896, 2900, 2904.

<sup>3</sup> B. Capon, P. M. Collins, A. A. Levy, and W. G. Overend, *J. Chem. Soc.*, 1964, 3242.

<sup>4</sup> L. R. Schroeder, J. W. Green, and D. C. Johnson, *J. Chem. Soc. (B)*, 1966, 447.

<sup>5</sup> G. L. Mattok and G. O. Phillips, *J. Chem. Soc.*, 1957, 268.

<sup>6</sup> M. J. Duffy, M. Jefferies, G. Pass, and G. O. Phillips, *J.C.S. Perkin II*, 1972, 821.

<sup>7</sup> G. Pass, G. O. Phillips, and A. Samee, *J.C.S. Perkin II*, 1973, 932.

<sup>8</sup> G. L. Mattok and G. O. Phillips, *J. Chem. Soc.*, 1956, 1836.

### 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. AnalaR glacial acetic acid was used without further purification. Anhydrous acetonitrile was prepared by distilling general purposes reagent grade acetonitrile three times over phosphoric oxide and finally over anhydrous potassium carbonate. The fraction boiling at 78° and 760 mmHg was collected. Anhydrous 1,4-dioxan was prepared by drying general purposes reagent grade 1,4-dioxan over magnesium sulphate, then sodium wire, and the fraction boiling at 101° and 760 mmHg was collected.

Tetra-*O*-acetyl- $\beta$ -D-glucopyranosyl chloride, m.p. 93—95°,  $\alpha_D$  -65°; 2-trichloroacetyl-3,4,6-triacetyl- $\beta$ -D-glucopyranosyl chloride, m.p. 139—142°,  $\alpha_D$  +3.6°; 3,4,6-triacetyl- $\beta$ -D-glucopyranosyl chloride, m.p. 152—154°,  $\alpha_D$  +31°; tetra-*O*-acetyl- $\alpha$ -D-glucopyranosyl bromide, m.p. 88°,  $\alpha_D$  +186°; tetra-*O*-acetyl- $\alpha$ -D-mannopyranosyl bromide, m.p. 53—54°,  $\alpha_D$  +123°; and tri-*O*-acetyl- $\alpha$ -D-xylopyranosyl bromide, m.p. 101—102°,  $\alpha_D$  +212°, were prepared as previously described.<sup>2,11,12</sup> Lithium [<sup>82</sup>Br]-bromide was prepared as described.<sup>13</sup>

**Exchange Rates.**—Measurements were made using the method and rate expression already described.<sup>13</sup> Thus  $kt = [2.303 \log(1 - x/c)]/a$  where  $a$  is the initial concentration of glycosyl halide and  $x/c$  is the activity of the glycosyl halide/the total activity. A plot of  $\log(1 - x/c)$  against  $t$  should give a straight line with slope =  $-ka/2.303$ .

**Hydrolysis Rates.**—The acid produced during hydrolysis was determined with lacmoid indicator, and the cooled aliquot portion of reaction mixture titrated against 0.002M-potassium hydroxide in ethanol. A plot of acid concen-

<sup>9</sup> A. J. Rhind-Tutt and C. A. Vernon, *J. Chem. Soc.*, 1960, 4637.

<sup>10</sup> R. U. Lemieux and J. Hayami, *Canad. J. Chem.*, 1965, **43**, 2162.

<sup>11</sup> G. L. Mattok and G. O. Phillips, *J. Chem. Soc.*, 1959, 2244.

<sup>12</sup> R. L. Whistler and M. L. Wolfrom, 'Methods in Carbohydrate Chemistry,' Academic Press, New York, 1963, vol. II, pp. 224, 400.

<sup>13</sup> M. J. Duffy, G. Pass, and G. O. Phillips, *J. Chem. Soc. (B)*, 1971, 785.

tration against time gave a straight line from which the initial rate, and hence the rate constants were calculated.

#### RESULTS AND DISCUSSION

The results in Table 1 show that in acetic acid the rates of exchange of the 1,2-*cis*-compounds are both reduced by *ca.* 10-fold compared with the corresponding

TABLE 1

Second-order rate constants for the exchange between lithium [<sup>82</sup>Br]bromide and *O*-acetylglycosyl bromides in acetic acid at 25°

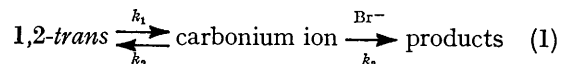
Glycosyl bromide	<i>t</i> /°C	10 <sup>5</sup> <i>k</i> <sub>2</sub> /l mol <sup>-1</sup> s <sup>-1</sup>	<i>E</i>	$\Delta G^\ddagger$	$\Delta H^\ddagger$	$\frac{\Delta S^\ddagger}{J K^{-1} mol^{-1}}$
			kJ mol <sup>-1</sup>			
Tetra- <i>O</i> -acetyl- $\alpha$ -D-glucosyl	25	1.92 (19.3) *				
Tri- <i>O</i> -acetyl- $\alpha$ -D-xylosyl	16	34.5	62	91	59.5	-104
	20	50.7				
	25	69.1 (760) *				
	31	121				
Tetra- <i>O</i> -acetyl- $\alpha$ -D-mannosyl	17	71.7				
	25	115 (69) *				
	31	336	67	89	64.5	-82
	40	597				

\* Figures in parentheses are exchange rates in acetone.

exchange rates in acetone, but the exchange rate of the 1,2-*trans*-compound is increased slightly. Although tetra-*O*-acetyl- $\alpha$ -D-glucosyl bromide and tri-*O*-acetyl- $\alpha$ -D-xylosyl bromide will have different steric properties in the activated complex, in neither case is there any possibility of anchimeric assistance. The neighbouring group at C(2) does exert an effect in the exchange reactions of tetra-*O*-acetyl- $\alpha$ -D-mannosyl bromide.<sup>13</sup>

Lower dissociation of lithium bromide occurs in glacial acetic acid than in acetone, and there is an increased tendency for ion pairs to be formed.<sup>14</sup> A reduction in the effective bromide ion concentration would explain the reduction in the exchange rates of the

reaction rate in acetic acid might be expected if dissociation of the glycosyl bromide contributes to the overall mechanism. However the bromide exchange reaction is second-order, which means that if the solvent is to exert any effect on a dissociative step it does so in a non-rate-determining step. The preliminary formation (1) of a carbonium ion is one possibility,<sup>7,16</sup> with bromide



ion attack on this species as the rate-determining step. The rate of bromide ion exchange =  $k_1 k_3 [1,2\text{-trans}] [\text{Br}^-] / (k_2 + k_3 [\text{Br}^-])$  and for the limiting case  $k_2 \gg k_3 [\text{Br}^-]$ , that is when recombination occurs appreciably faster than exchange, then the bromide exchange reaction will be second order and the rate increases with increasing values of  $k_1/k_2$ . The solvent effects described above will increase  $k_1/k_2$ .

The exchange results in acetic acid are consistent with a greater solvent effect on the 1,2-*trans*-compound than on the 1,2-*cis*. However the extent of lithium bromide dissociation also depends on the solvent, so that a change of solvent alters the concentration of bromide ion. The observed change in reaction rate with change of solvent is thus the net effect of two, possibly opposing trends. A lower bromide concentration in acetic acid tends to obscure the effect of the solvent on the acetylglycosyl halide. To study the effects due to solvent changes on the acetylglycosyl halide alone we have investigated the hydrolysis reactions in dioxan and acetonitrile, where the effective concentration of the added water does not depend on the ionizing power of the solvent.

The results in Table 2 show that hydrolysis of tetra-*O*-acetyl- $\beta$ -D-glucosyl chloride in acetonitrile is of the second order, as previously found for hydrolysis in acetone.<sup>7</sup> In dioxan the rate of hydrolysis is decreased

TABLE 2

The effect of initial concentration of tetra-*O*-acetyl- $\beta$ -D-glucosyl chloride and water on the rate of hydrolysis at 25° in acetonitrile and 1,4-dioxan

Acetonitrile	[Glucosyl chloride]/M	0.025	0.025	0.025	0.05	0.05	0.05	0.1
	[Water]/M	1.0	2.0	3.0	1.0	2.0	3.0	1.0
	10 <sup>7</sup> Initial rate/mol l <sup>-1</sup> s <sup>-1</sup>	42.8	84.1	125	89.2	170	250	16.8
	10 <sup>5</sup> <i>k</i> <sub>2</sub> /l mol <sup>-1</sup> s <sup>-1</sup>	17.1	16.8	16.7	17.8	17.0	16.7	16.8
Dioxan	[Glucosyl chloride]/M	0.025	0.025	0.025	0.05	0.05	0.05	0.1
	[Water]/M	1.0	2.0	3.0	1.0	2.0	3.0	1.0
	10 <sup>7</sup> Initial rate/mol l <sup>-1</sup> s <sup>-1</sup>	2.5	6.1	11.3	5.1	13.1	22.8	12.0
	10 <sup>5</sup> <i>k</i> <sub>2</sub> /l mol <sup>-1</sup> s <sup>-1</sup>	1.0	1.2	1.5	1.0	1.3	1.5	1.2

1,2-*cis*-compounds. The different behaviour of the 1,2-*trans*-compound suggests that it may arise from anchimeric assistance, which requires a dissociative step. For the unimolecular solvolysis of *t*-butyl halides comparison of the reaction rates in various solvents at 25° with the rate of solvolysis in 80% ethanol-water shows a smaller decrease in rate in acetic acid than in acetone-water.<sup>15</sup> Thus comparing the bromide exchange reactions in acetic acid and acetone a faster

<sup>14</sup> A. K. Holliday and A. G. Massey, 'Inorganic Chemistry in Non-Aqueous Solvents,' Pergamon, Oxford, 1965, p. 72.

and the reaction is now slightly greater than first order in water. The hydrolysis of trichloroacetyl-3,4,6-tri-acetyl- $\beta$ -D-glucosyl chloride, which was too slow in acetone to allow the order of the reaction to be established, we now find in acetonitrile to be of the second order (Table 3). However the hydrolysis of tri-*O*-acetyl- $\beta$ -D-glucosyl chloride in acetonitrile and dioxan

<sup>15</sup> E Grunwald and S. Winstein, *J. Amer. Chem. Soc.*, 1948, **70**, 846.

<sup>16</sup> C. G. Swain and E. E. Pegues, *J. Amer. Chem. Soc.*, 1958, **80**, 812.

although first order in glucosyl chloride is of higher order in water (Tables 4 and 5), as previously found for

TABLE 3

The effect of initial concentration of 2-trichloroacetyl-3,4,6-triacetyl- $\beta$ -D-glucosyl chloride and water on the rate of hydrolysis in acetonitrile at 35°

[Glucosyl chloride]/ M	0.05	0.05	0.05	0.1	0.1	0.1
[Water]/M	1.0	2.0	3.0	1.0	2.0	5.0
$10^8$ Initial rate/ mol l <sup>-1</sup> s <sup>-1</sup>	7.3	15.0	22.2	16.2	30.4	83.0
$10^7 k_2$ /l mol <sup>-1</sup> s <sup>-1</sup>	14.7	15.0	14.8	16.2	15.2	16.6

the reaction in acetone.<sup>7</sup> In the three solvents the rate of hydrolysis of triacetylglucosyl chloride is always of

common mechanism which involves the intermediate formation of a configurationally stable ion pair.<sup>17</sup> The first-order behaviour of triacetylglucosyl chloride may then be attributed to rate-determining formation of the carbonium ion, and hence the observed activation energy varies considerably with change of solvent (Table 6). For the tetra-acetylglucosyl chloride, the acetyl group at C(2) assists in the formation of the carbonium ion, and attack of water on the carbonium ion is now rate determining. Thus a change of solvent has a much smaller effect on the activation energy (Table 6). The slightly greater than first order dependence on water for hydrolysis in dioxan represents borderline behaviour between the traditional S<sub>N</sub>I and

TABLE 4

The effect of initial concentration of tri-*O*-acetyl- $\beta$ -D-glucosyl chloride and water on the rate of hydrolysis at 25° in acetonitrile and 1,4-dioxan

Acetonitrile	[Glucosyl chloride]/M	0.025	0.025	0.025	0.05	0.05	0.05	0.1
	[Water]/M	1.0	2.0	3.0	1.0	2.0	3.0	2.0
	$10^7$ Initial rate/mol l <sup>-1</sup> s <sup>-1</sup>	0.6	3.1	7.0	1.3	6.25	13.7	12.25
	$10^6 k_1$ /s <sup>-1</sup>	2.5	12.5	28.0	2.6	12.5	27.4	12.25
Dioxan	[Glucosyl chloride]/M	0.025	0.05	0.05	0.05	0.1		
	[Water]/M	2.0	1.0	2.0	3.0	2.0		
	$10^7$ Initial rate/mol l <sup>-1</sup> s <sup>-1</sup>	1.27	0.66	2.67	6.7	4.4		
	$10^6 k_1$ /s <sup>-1</sup>	5.1	1.3	5.0	13.8	4.4		

high order in water, a characteristic of a solvent effect in a unimolecular solvolysis.<sup>2,8</sup> The reaction of tetra-

TABLE 5

Effect of solvent on the order in water ( $[H_2O]^n$ ) of the hydrolysis reaction of acetylglucosyl chlorides

	Dioxan	Acetone	Acetonitrile
Tetra- <i>O</i> -acetyl	1.3	1.0	1.0
Tri- <i>O</i> -acetyl	2.2	2.2	2.2
2-Trichloroacetyl			1.0

acetylglucosyl chloride is first order in water in solvents of high ionizing power and only begins to show any

S<sub>N</sub>2 mechanisms. This suggests that in a solvent of very low ionizing power, the rate of ion pair formation now approaches the rate of attack of water on the ion pair. Hydrolysis of 2-trichloroacetyl-3,4,6-tri-*O*-acetylglucosyl chloride in acetonitrile is of the second order (Table 4) which suggests that the trichloroacetyl group at C(2) may be able to exert a neighbouring group effect. The increased steric hindrance due to the bulky trichloroacetyl group slows the rate-determining attack by the water.

The results in Table 7 indicate that a reaction involving anchimeric assistance is affected to a greater

TABLE 6

Effect of temperature on the rate constants for the reaction of acetylglucosyl chlorides (0.05M) with water (2.0M) in dioxan and acetonitrile

Solvent	Acetylglucosyl chloride	<i>t</i> /°C	$10^5 k_2$ l mol <sup>-1</sup> s <sup>-1</sup>	$E$		$\Delta S^\ddagger$	
				kJ mol <sup>-1</sup>		J K <sup>-1</sup> mol <sup>-1</sup>	
Dioxan	Tetra- <i>O</i> -acetyl- $\beta$ -D-	20	0.75				
		25	1.3	71.0	97.0	69.0	-96.5
		35	3.2	(75.5) *	(98.5)	(73.5)	(-84)
		44	6.9				
Acetonitrile	Tetra- <i>O</i> -acetyl- $\beta$ -D-	0	1.3				
		20	10.0	70.5	96.5	68.5	-96.5
		25	17.0				
		35	36.1				
Acetonitrile	Tri- <i>O</i> -acetyl- $\beta$ -D-		$10^6 k_1$ /s <sup>-1</sup>				
		25	12.5				
		30	17.3	57.5	102.0	55.5	-160
		35	23.8	(73.5) *	(103.0)	(71.5)	(-105)
		40	39.3				

\* Values in parentheses are for the reaction in acetone.<sup>7</sup>

change from this behaviour in dioxan, a solvent of low ionizing power (Table 6). The marked difference in the hydrolysis behaviour of triacetyl- and tetra-acetylglucosyl chloride may represent the two extremes of a

extent by change of solvent than a reaction without anchimeric assistance. This is comparable to the

<sup>17</sup> R. A. Sneen and J. W. Larsen, *J. Amer. Chem. Soc.*, 1969, **91**, 362, 6031.

TABLE 7

The effect of change of solvent on the initial rate  $\times 10^7$  for the hydrolysis of acetylglucosyl chlorides (0.05M) in the presence of water (2.0M) at 25°

	Acetonitrile ( $\epsilon \sim 40$ )	Acetone ( $\epsilon \sim 20$ )	Dioxan ( $\epsilon \sim 2$ )
2,3,4,6-Tetra- <i>O</i> -acetyl- $\beta$ -D-	170	29	13
2-Trichloroacetyl-3,4,6-triacetyl- $\beta$ -D-	1.4	0.15	
3,4,6-Tri- <i>O</i> -acetyl- $\beta$ -D-	6.3	3.5	2.3

behaviour observed for the exchange reaction (Table 1) but differs from reported behaviour of the  $S_N1$  solvolysis reactions.<sup>3,5</sup> However in these reported solvolysis reactions the overall ionizing power of the solvent is altered by incremental addition of water. As we have seen the hydrolysis of acylglycosyl halides where there is anchimeric assistance is of lower order with respect to water than hydrolysis of acylglycosyl halides in the absence of anchimeric assistance. If this behaviour also holds true at higher water concentrations<sup>6</sup> then reactions without anchimeric assistance will increase in rate more rapidly with increasing water concentration than reactions with anchimeric assistance. No conclusion as to charge separation in the transition state can be drawn in this event, since two different rate-determining steps are operating. Where water concentration is held constant and solvent polarity altered by changing the solvent then the greater effect of solvent on the hydrolysis of tetra-*O*-acetylglucosyl chloride than

on the hydrolysis of tri-*O*-acetylglucosyl chloride, suggests there is more overall charge separation with the formation of a cyclic carbonium ion than with the formation of an 'open' carbonium ion.

We conclude that both the hydrolysis and exchange reactions of the 1,2-*trans*-acylglycosyl halides involve a two-step process, with formation of carbonium ions. Whether carbonium ion formation is the rate-determining step or not controls the observed order of the hydrolysis and exchange reactions. This would be in agreement with the proposal for a unifying mechanism for  $S_N1$  and  $S_N2$  reactions.<sup>18</sup> However with the acetylglucosyl halides there is as yet no conclusive evidence that the same intermediate is involved in both the exchange and hydrolysis reactions. There is no consistent pattern of variation of hydrolysis rates compared with exchange rates, as the substituent at C(2) is changed.<sup>1</sup>

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