The Reactivity of *O*-Acylglycosyl Halides. Part XI.[1] Exchange and Hydrolysis Reactions of *O*-Benzoylglycosyl Bromides

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Bromide exchange reactions and the hydrolyses of a series of benzoylglycosyl bromides in acetone have been investigated. The exchange reactions are second order and occur with inversion of configuration. Only the benzoylmannosyl bromide hydrolyses at a measurable rate, but addition of lithium bromide catalyses the hydrolysis of 1,2-*cis*-benzoylglycosyl bromides.

THE halogen exchange reactions between lithium bromide and *O*-acylglycosyl bromides in anhydrous acetone are second order.[2] Steric effects give the same sequence of reaction rates as found for the S_N1 solvolyses of these compounds.[3] Steric effects might be expected [4] to give a slower exchange rate for the acetylmannosyl bromide compared with the acetylglycosyl bromide. That a faster exchange rate is in fact observed suggests possible anchimeric assistance in exchange reactions of 1,2-*trans*-acetylglycosyl halides. However, for a series of 1,2-*trans*-acetylglucosyl chlorides steric factors are of greater significance than anchimeric assistance.[1]

Hydrolysis of *O*-acylglycosyl bromides in acetone is appreciable only with the 1,2-*trans*-compound.[5] This is comparable with the observation that solvolysis of 1,2-*trans*-compounds is more rapid than solvolysis of corresponding *cis*-compounds.[6] Moreover the rate of hydrolysis of the 1,2-*trans*-compounds has a significant dependence on the ability of the group at C(2) to form a cyclic carbonium ion.[1,7] Addition of alkali-metal halides results in anomerisation of the 1,2-*cis*-compounds, with a consequent rapid hydrolysis of the 1,2-*trans*-compound.[8,9]

We have now investigated the halide exchange and hydrolysis reactions of a series of *O*-benzoylglycosyl bromides in acetone. In particular we wish to compare the effect of replacing acetyl with benzoyl in the exchange reaction, where steric effects are predominant, with the effect on the hydrolysis reaction where formation of a carbonium ion is of major significance.

EXPERIMENTAL

Anhydrous acetone was prepared by distillation of AnalaR acetone three times over phosphorus pentaoxide; the fraction, b.p. 56° at 760 mmHg, was collected.

Tetra-*O*-benzoyl-α-D-glucopyranosyl bromide had m.p. 130°, $[\alpha]_D$ +124°; tetra-*O*-benzoyl-α-D-mannopyranosyl bromide had $[\alpha]_D$ +11·7°; tri-*O*-benzoyl-β-L-arabinopyranosyl bromide had m.p. 144°, $[\alpha]_D$ +201°; and tri-*O*-benzoyl-α-D-xylopyranosyl bromide had m.p. 137°, $[\alpha]_D$ +118°; all were prepared as described.[10,11] Standard solutions of lithium $[^{82}\mathrm{Br}]$bromide were prepared as previously described.[2]

Exchange Rates.—Measurements were made using the method and rate expression already described.[2] Thus $k_1t = [2{\cdot}303 \log (1 - x/c)]/a$ where a is the initial concentration of glycosyl bromide and x/c is (the activity of the glycosyl bromide)/(the total activity). A plot of $\log (1 - x/c)$ against t should give a straight line with slope $-k_1a/2{\cdot}303$. The results from the exchange between lithium $[^{82}\mathrm{Br}]$-bromide (0·05M) and tetra-*O*-benzoyl-α-D-glucosyl bromide (0·05M) at 25° are given as an example of a standard set of results:

100x/c (%)	0	9·3	16·6	22·2	27·9	30·4
t/min	0	20	40	60	80	100

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. A plot of acid concentration against time gave a straight line from which the initial rate and hence the rate constants were calculated.

RESULTS AND DISCUSSION

For the rate of exchange of bromide ion with acetylglycosyl bromides the rate increases in the order glucosyl < mannosyl < arabinosyl < xylosyl.[2] For the exchange of bromide ion with benzoylglycosyl bromides the same sequence is observed as shown in Table 1. From the effect of changes in the concentrations of lithium bromide and benzoylglycosyl bromide (Table 2) it is evident that the reaction is first order in both reactants. The slight decrease in rate constant with increasing lithium bromide concentration could be due to decreased dissociation of the lithium bromide.[12] Thus the exchange reaction shows characteristics of the classical S_N2 process, as previously found for the exchange reaction of acetylglycosyl bromides.[2] It was suggested that the bimolecular reaction involves the formation of a partly planar conformation of the acetylglycosyl bromide, and for different acetylglycosyl bromides the variation in exchange rates is due to steric effects for the acetyl substituents. A similar explanation would account for the S_N2 reaction rates of the *O*-benzoylglycosyl halides examined here.

The same overall sequence of rates is observed for the acetyl- and benzoyl-glycosyl bromides. We find, however, that the ratio $k_{\mathrm{benzoyl}}/k_{\mathrm{acetyl}}$ is glucosyl, *ca.* 8; man-

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TABLE 1

Rate constants for bromide ion exchange in anhydrous acetone

Bromide	T/°C	10^5k_2/ l mol^{-1} s^{-1}	E_a (kJ mol^{-1})	$\Delta G^{\ddagger}$ (kJ mol^{-1})	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (J K^{-1} mol^{-1})
Tetra-*O*-benzoyl-α-D-glucosyl	5	9				
	19	50				
	25	153	34·0	89·0	81·5	−25
	30	186				
	35	320				
Tetra-*O*-benzoyl-α-D-mannosyl	13	142				
	17	350				
	19	512	47·0	85·5	44·5	−137
	25	660				
	30	890				
Tri-*O*-benzoyl-β-L-arabinosyl	0	85				
	17	656	66·0	84·5	63·0	−72
	25	997				
	32	1786				
Tri-*O*-acetyl-β-L-arabinosyl	16	240				
	20	425	75·0	85·5	72·5	−44
	25	650				
	35	1055				
Tri-*O*-benzoyl-α-D-xylosyl	25	1550				

TABLE 2

Second-order rate constants (10^5 l mol^{-1} s^{-1}) for bromide exchange showing dependence on initial concentration of reactants.

[LiBr]/M		0·025	0·05	0·10
Tetra-*O*-benzoyl-α-D-glucosyl bromide	0·05M	160	155	145
	0·025M		150	
Tri-*O*-benzoyl-β-L-arabinosyl bromide	0·05M	1050	995	1035
	0·025M		1010	

nosyl, *ca.* 10; arabinosyl, *ca.* 2; and xylosyl, *ca.* 2. Having regard to the S_N2 character of the reactions this difference in the benzoyl/acetyl increments between the hexose and pentose derivatives is understandable. Removal of the C(5) group would be accompanied by a large decrease in steric hindrance. Subsequent accommodation of a less or more favourable steric grouping would have a less pronounced effect than it would have done in the more highly 'bunched' hexose transiton state. When the CH_2OAc group at C(5) is removed, a greatly increased exchange rate is found for the arabinose and xylose compounds compared with their hexose equivalents.[2] Surprisingly, removal of a CH_2OBz group at C(5) produces a smaller increase in exchange rate than removal of a CH_2OAc group, which points to less steric hindrance in the bimolecular transition state of the benzoyl derivatives. Indeed, exchange is always faster for the benzoyl than the corresponding acetyl compound. Despite their larger overall size, it is clear that the benzoyl groups can be more favourably intercalated into the partly planar intermediate than the acetyl groups.

When a small quantity of water is added to the acetone, only the benzoylmannosyl bromide hydrolyses at a significant rate; no reaction is observed with the corresponding glucosyl or arabinosyl bromide. Measurable hydrolysis of the glycosyl and arabinosyl bromides occurs in the presence of lithium bromide. A similar effect has been observed with the acetylglucosyl bromides.[3] However, the behaviour of the benzoylglycosyl bromides exhibits several points of difference from the acetylglycosyl bromides. The hydrolysis of the benzoylmannosyl bromide is greater than first order in water and the rate is considerably reduced by the addition of lithium bromide (Table 3), whereas the hydrolysis of acetylmannosyl bromide is first order in water and is not significantly affected by added lithium bromide. Although the addition of lithium bromide results in measurable hydrolysis of the benzoylglucosyl and benzoylarabinose bromides, the rate is appreciably slower than the exchange rate (Table 4), there is no first-order dependence on the concentration of lithium bromide and the reaction is greater than first order in water (Table 5).

TABLE 3

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

[Water]/M	0·5	0·5	1·0	1·0	2·0
[LiBr]/M		0·05		0·05	
10^6k_1/s^{-1}	1·2	0	3·2	0·5	12·5

TABLE 4

Exchange and hydrolysis rates of *O*-acylglycosyl bromides (0·05M) in the presence of lithium bromide (0·05M) in acetone at 25°

	Exchange		Hydrolysis (0·5M-H_2O)	
	Initial rate × 10^7/ mol l^{-1} s^{-1}		Initial rate × 10^7/ mol l^{-1} s^{-1}	
Bromide	Benzoyl	Acetyl	Benzoyl	Acetyl
O-Acylglucosyl	38	5	3	6
O-Acylmannosyl	165	17	0 (0·5 when [LiBr] = 0)	10
O-Acylarabinosyl	250	163	6	31
O-Acylxylosyl	387	190		95

TABLE 5

First-order rate constants for the hydrolysis of tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (0·05M) in the presence of lithium bromide in acetone at 25°

[LiBr]/M	0·05	0·05	0	0·05
[Water]/M	0·1	0·3	0·5	0·8
10^6k_1/s^{-1}	1·6	6·5	0	10·2

This is a marked difference in behaviour compared with the acetylglycosyl bromides where the catalysed hydrolysis is first order in lithium bromide and independent of the concentration of water.[5]

The faster rate of hydrolysis of the 1,2-*trans*-compound compared with the 1,2-*cis*-compound has been attributed to a neighbouring group effect.[5] This effect has also been invoked to explain the faster solvolysis rates of 1,2-*trans*-compounds compared with those of the 1,2-*cis*.[7,13] Where the group at C(2) provides no anchimeric assistance, the *O*-methylmannosyl and *O*-methylglucosyl chlorides solvolyse at similar rates.[4] The methanolysis of 1,2-*trans*-*O*-benzoylglycosyl halides gives a methylglycoside of retained configuration, whereas 1,2-*cis*-*O*-benzoylglycosyl halides have methylglycosides with inverted configuration.[10,14] It is found in the present work that

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the hydrolysis of *O*-benzoylmannosyl bromide is slower than hydrolysis of *O*-acetylmannosyl bromide, whereas the opposite is true for the exchange reaction (Table 4). These observations suggest that the hydrolysis reaction involves anchimeric assistance, and that the reaction mechanism differs from the mechanism of the exchange reaction.

The different rates of hydrolysis then arise from properties of the carbonium ions. The kinetics of hydrolyses of a series of 1,2-*trans*-*O*-acetylglucosyl chlorides have been rationalised in terms of a two step process, involving formation of a carbonium ion, followed by nucleophilic attack of water on this ion.[1] This suggestion compares with the hypothesis that substitution at a saturated carbon atom always involves the formation of an ion pair intermediate.[15] When the hydrolysis is greater than first order in water, as we find for the *O*-benzoylmannosyl bromides, this implies that the rate-determining step is formation of the carbonium ion, and the rate increase is due to a solvent effect on this unimolecular step.[3,13] The effect of lithium bromide is also consistent with rate-determining formation of the carbonium ion, where the mass action effect of the bromide ion inhibits the dissociation of the glycosyl-bromide.

On the other hand, the rate of hydrolysis of 1,2-*cis*-*O*-benzoylglycosyl bromides is increased by the addition of lithium bromide, and the rate of this catalysed hydrolysis is greater than first order in water (Table 5). The rate of this catalysed hydrolysis is faster than the uncatalysed hydrolysis of the *O*-benzoylmannosyl bromide (Table 4).

As previously demonstrated for the hydrolysis of the acetylglycosyl bromides [5] we suggest that this is due not to a salt effect but to anomerisation arising from halide exchange, a reaction which is of the first order in lithium bromide, and is faster than the hydrolysis reaction (Table 4). The 1,2-*trans*-compound so formed hydrolyses rapidly, according to the mechanism proposed for the hydrolysis of *O*-benzoylmannosyl bromide. This is supported by the much greater rate of solvolysis of 1,2-*trans*-*O*-acylglucosyl halide compared with 1,2-*trans*-*O*-acylmannosyl halide.[7] However, lithium bromide will also be expected, in view of its effect on the hydrolysis of *O*-benzoylmannosyl bromide, to have an inhibiting effect on the hydrolysis reaction. This inhibiting effect is not of the first order in lithium bromide. The net result of these two effects is a marked increase in hydrolysis of the 1,2-*cis*-compounds on the addition of lithium bromide, but the overall reaction is not of the first order in lithium bromide and the rate of hydrolysis is appreciably lower than the rate of exchange. The observed greater than first-order dependence on water concentration then arises from a solvent effect on the rate-determining unimolecular dissociation of the 1,2-*trans*-compound.

Thus by reference to our present results with benzoyl derivatives it is possible to retain the broad distinction between S_N2 bimolecular exchange reactions and hydrolysis reactions proceeding *via* carbonium ions. Consideration must be given, however, to the relative rates of formation of the carbonium ion and its subsequent fate to explain the overall kinetics which are observed. As in our previous work we can conclude that anchimeric assistance is of more importance in the hydrolysis reaction than in the exchange reaction. The changes produced when acetyl is replaced by benzoyl in the acylglycosyl bromides confirm this view, with a benzoyl group at C(2) inhibiting the formation of the cyclic carbonium ion, but producing lower steric hindrance in the S_N2 reaction.

[4/248 *Received, 8th February,* 1974]

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