579. *The Reactivity of the* O-*Acylglycosyl Halides. Part I. The Solvolytic Reactions of Tetra*-O-*acetyl*-α-D-*glucopyranosyl* 1-*Bromide.*

By F. H. Newth and G. O. Phillips.

Solvolytic reactions of tetra-*O*-acetyl-α-D-glucopyranosyl 1-bromide have been examined kinetically. The first-order rate constants are greater in the more polar solvents, and in the presence of alkali the rate is unaffected. Racemization has been observed in aqueous-acetone solution. These results show that the nucleophilic substitution is unimolecular.

The series of sugar derivatives which possess a halogen atom at the potential reducing group in the molecule, the *O*-acyl-glycosyl 1-halides, is well established. The halogen is reactive and with nucleophilic reagents substitution occurs readily. Until 1924 it was believed that the stable form of tetra-*O*-acetyl-D-glucosyl 1-bromide (acetobromoglucose) was a β-derivative. The evidence for this classification lay solely in the fact that it yields acetylated β-glucosides or the β-penta-*O*-acetate when the halogen is replaced (Koenigs and Knorr, *Ber.*, 1901, **34**, 95). Hudson, however, revised the classification of the acetylhalogeno-derivatives of the sugars as α- or β-forms on the basis of their optical rotatory powers (*J. Amer. Chem. Soc.*, 1924, **46**, 462; Phelps and Hudson, *ibid.*, p. 2591) and the common tetra-*O*-acetyl-D-glycosyl 1-bromide and 1-chloride were shown to be α-derivatives. It follows that inversion occurs in the replacement reactions of the halogen atom. The

Koenigs–Knorr reaction of tetra-*O*-acetyl-α-D-glucosyl 1-bromide leads to the corresponding tetra-*O*-acetyl-β-D-glucoside and in this reaction inversion is complete and the yield almost quantitative.

It has been pointed out by Frush and Isbell (*J. Res. Nat. Bur. Standards*, 1941, **27**, 412) that this is the normal course of the reaction when the acetyl group at $C_{(2)}$ in the sugar molecule is *cis* to the halogen atom. When the halogen atom and the neighbouring acetyl group are *trans* to one another, however, the reaction with methanol in the presence of silver carbonate or quinoline leads to the formation of a methyl 1 : 2-orthoacetate together with the anomeric α- and β-glycosides. In the analogous reaction with water, a tetra-acetate is produced which has the same configuration as the parent halide. Fresh evidence has been adduced recently by Fletcher and Hudson (*J. Amer. Chem. Soc.*, 1950, **72**, 4173) and Ness, Fletcher, and Hudson (*ibid.*, 1951, **73**, 296, 959) who have examined the reactions of the *O*-benzoyl 1-halides of several sugars and confirm the importance of the acyl group at $C_{(2)}$. These authors showed that the halides gave first-order rate constants in methanol–dioxan (9 : 1). Kinetic order is, however, not diagnostic of mechanism and a particular technique is necessary for its determination (Hughes, *Trans. Faraday Soc.*, 1941, **37**, 611).

Although the reaction of the *O*-acylglycosyl 1-halides with alcohols is normally carried out in the presence of an acid acceptor, it is known that complicated kinetic results are obtained in the presence of silver salts. An examination of the reaction of tetra-*O*-acetyl-α-D-glucosyl 1-bromide has been made, therefore, with hydroxylic solvents alone. Two methods were used : one was to follow the change of optical rotation, and the other was to measure the acid liberated during the reaction by titration with standard alkali. The two methods gave good agreement, $10^5k^{21\cdot2}$ being 2·83 and 2·80 (sec.$^{-1}$) respectively in 100% methanol. Koenigs and Knorr (*loc. cit.*) found that deacetylation occurred during the methanolysis when the concentration of tetra-*O*-acetyl-α-D-glucosyl 1-bromide was *ca.* 0·5M, and methyl β-D-glucoside was formed. Ness, Fletcher, and Hudson (*loc. cit.*) also reported partial deacetylation during methanolysis of 1·0M-tri-*O*-acetyl-α-L-rhamnosyl 1-bromide, but deacetylation was not observed with the tri-*O*-benzoate. In the present work, 0·02—0·06M-solutions have been used and deacetylation by liberated hydrogen ions was only detected when the reaction was slow and at an elevated temperature. The titrimetric method had the advantage that the amount of alkali required to neutralise the liberated acid could be calculated and compared with the final, experimental value. In the polarimetric experiments, occurrence of deacetylation could be inferred only from the final value of the optical rotation.

Catalysis by liberated hydrobromic acid was observed and Fig. 1 shows that this was negligible during the first 70% (240 min.) of the solvolysis of tetra-*O*-acetyl-α-D-glucosyl 1-bromide in 100% methanol but becomes significant at higher concentrations of hydrogen bromide. Thus after 160 min. it is just evident when the initial concentration of added hydrogen bromide is 0·003M and marked when it is 0·023M. The initial values of $10^5k^{21\cdot2}$ were 2·80, 2·81, and 4·48 (sec.$^{-1}$) respectively in simultaneous runs. A similar behaviour observed with unimolecular reactions and called the " salt effect " (Bateman, Hughes, and Ingold, *J.*, 1940, 960; Bell, " Acid–Base Catalysis," Oxford Univ. Press, 1941, p. 11) is attributed to the accumulation of ions in the reaction medium as the reaction proceeds, which increases the ionizing properties of the medium and facilitates the ionization of the C–Hal bond. A mass-law influence is also believed to be superimposed on this by the anions produced but this would be negligible compared with the effect of the increase in ionic strength. In the presence of a neutral bromide a slight increase in rate was observed. Simultaneous polarimetric measurements gave values of 2·03 (sec.$^{-1}$) in methanol alone and 2·14 (sec.$^{-1}$) in methanol containing 0·04M-lithium bromide for 10^5k^{18}. With tetra-*O*-acetyl-α-D-glucosyl 1-bromide and other *O*-acetylglycosyl 1-halides studied later the effect of acceleration by liberated acid has been avoided by considering only the first 50% of the reaction for rate-measurement purposes.

The effect of the addition of various concentrations of sodium hydroxide on the rate of reaction of tetra-*O*-acetyl-α-D-glucosyl 1-bromide in 60% aqueous acetone is summarised in Table 1. The rate is obviously independent of the concentration of hydroxyl ions. Since such a powerful nucleophilic reagent does not alter the rate of reaction at all, it indicates strongly that the solvent does not take part in the rate-determining stage. The possibility of a bimolecular mechanism occurring in the 60% aqueous acetone is thus eliminated. (Aqueous acetone was chosen as the medium in which to investigate the effect of alkali on the reaction because deacetylation by the hydroxyl ion is very slow. In absolute alcoholic alkali, deacetylation would have been an important side reaction.)

TABLE 1. *Rate of reaction of tetra-*O*-acetyl-α-*D*-glucosyl* 1*-bromide in* 60% *aqueous acetone in the presence of sodium hydroxide.* [Halide] ≈ 0·05M.

[NaOH] (N)	—	0·025	0·075
$10^5 k^{21·2}$ (sec.$^{-1}$)	5·09	5·03	5·03

The effect of solvent changes on the reaction rate gives auxiliary evidence of reaction mechanism (Hughes, *loc. cit.*). In a more ionizing solvent, both S_N1 and S_N2 mechanisms should be facilitated, but the S_N1 mechanism is affected more strongly by solvation factors. In Table 2 are shown the first-order rate constants for the reaction of tetra-*O*-acetyl-α-D-glucosyl 1-bromide with hydroxylic media. It can be seen that the rate increases when the amount of water in aqueous methanol is increased. Similarly the rate increases with the amount of water in aqueous acetone and is decreased by addition of acetone to methanol. The observed increase in rate is less than that which has been determined for the unimolecular solvolysis of *neo*pentyl or *iso*propyl bromide (Dostrovsky, Hughes, and Ingold, *J.*, 1946, 173), but comparison of a cyclic with an acyclic halide is not strictly valid.

FIG. 1.

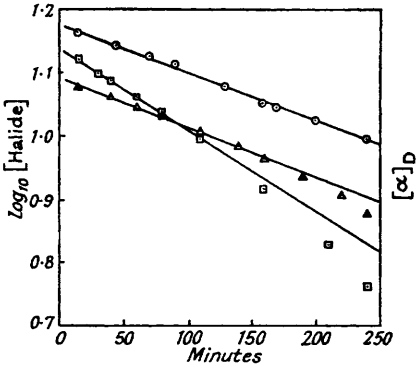

FIG. 2.

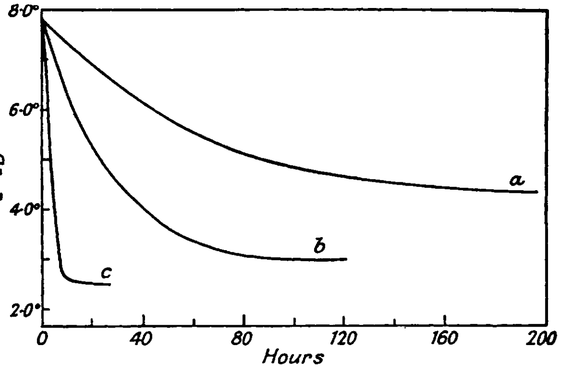

FIG. 1. *Effect of acid on the reaction of tetra-*O*-acetyl-α-*D*-glucosyl* 1*-bromide with methanol at* 21·2°.
○ *Methanol alone.* △ *Methanol initially* 0·003N *with respect to* HBr.
□ *Methanol initially* 0·023N *with respect to* HBr.

FIG. 2. *Effect of aqueous-acetone media on the hydrolysis of tetra-*O*-acetyl-α-*D*-glucosyl* 1*-bromide.*
(*a*) 87·6%, (*b*) 76·9%, (*c*) 60% *Aqueous acetone* (*c* = 1; *l* = 4).

TABLE 2. *The effect of solvent variation on the rate of solvolysis of tetra-*O*-acetyl-α-*D*-glucosyl* 1*-bromide at* 21·2°. [Halide] = 0·05M.

Medium	$10^5 k$ (sec.$^{-1}$)	Medium	$10^5 k$ (sec.$^{-1}$)
100% Methanol	2·80	90% Aq. acetone	0·14
,, ,,	2·83 *	80% ,,	0·50
90% Aq. methanol	5·80	70% ,,	1·78
87·4% ,,	6·33 *	60% ,,	4·89
80% ,,	11·12	90% Methanol–acetone	1·19
70% ,,	22·7	70% ,,	0·82
60% ,,	36·1 *	50% ,,	0·35

* Polarimetric method.

Bimolecular substitution at an asymmetric carbon atom invariably leads to inversion, whereas a unimolecular mechanism permits either retention or inversion. The hydrolysis of tetra-*O*-acetyl-α-D-glucosyl 1-bromide in aqueous acetone was examined polarimetrically and Fig. 2 shows the rate of change of rotation in 60%, 76·9%, and 87·6% aqueous acetone. As the ionizing power of the medium increases the rate shows a marked increase (values for *k* in similar media are given in Table 2), and the final value of the rotation depends upon the medium. Tetra-*O*-acetyl-D-glucose is the sole product of the reaction, and a higher final value for α_D in the medium containing the more inert solvent must represent an increase in the amount of the (+)-α-form in the product. This racemization can only be explained if the unimolecular mechanism is operating. This conclusion was supported by a qualitative examination of the reaction of tetra-*O*-acetyl-α-D-glucosyl 1-bromide with sodium iodide in acetone. The reaction at 20° was too fast to measure, and after 10 min. tetra-*O*-acetyl-α-D-glucosyl 1-iodide was isolated in 76% yield. The significant feature, in addition to the velocity, is the almost complete retention of configuration under conditions which are most conducive to operation of the bimolecular mechanism.

EXPERIMENTAL

Purification of Solvents.—Methanol. Acetone and formaldehyde were detected by the method of Hartley and Raikes (*J.*, 1925, **127**, 524) and were removed by the hypoiodite method of Bates, Mullaly, and Hartley (*J.*, 1923, **123**, 401). After boiling with calcium oxide the methanol was dried over magnesium and fractionally distilled through a Fenske-packed column. The fraction, n_D^{20} 1·3288, boiling at 64·7°/760 mm. was collected. The water content was less than 0·02% (Karl Fischer).

Acetone. "AnalaR" solvent was dried over calcium chloride and distilled. The fraction boiling at 56°/760 mm. was collected.

The term *x*% aqueous methanol or aqueous acetone used in this work refers to a medium obtained by mixing at room temperature *x* volumes of dry solvent with (100 − *x*) volumes of distilled water. Similarly, *x*% methanol–acetone refers to a mixture of *x* volumes of methanol with (100 − *x*) volumes of acetone.

*Tetra-*O*-acetyl-α-D-glucosyl 1-Bromide.*—This was prepared from either α- or β-penta-*O*-acetylglucose by treatment with hydrogen bromide in glacial acetic acid. The crystalline product was recrystallised from dry ether until the m. p. was 88—89°.

Rate Measurements.—(a) *Titrimetric method.* In each experiment a weighed quantity of the halide was dissolved in the required medium in a 50-ml. standard flask to give an approx. 0·05M-solution. Both halide and solvent were kept at the temperature of the thermostat (21·2° ± 0·05°) before mixing. Zero time was taken when half the solvent had been added. At known intervals 5-ml. aliquots were withdrawn and run into 50 ml. of absolute ethanol which had been cooled in acetone–carbon dioxide. The solution was titrated with standard alcoholic potassium hydroxide (*ca.* 0·02N), with lacmoid as indicator. The initial concentration of halide was given by the titre at infinite time. Log$_{10}$ [Halide] was plotted against time, *t*, and the first-order rate constant given by $k = -2·303 \times$ slope of line (sec.$^{-1}$). The rate constants are listed in Table 2, and some individual runs are illustrated below :

Concentrations of halide are expressed in equivalent ml. of standard alkali per 5 ml. of solution. *k* is in sec.$^{-1}$.

90% *Aqueous methanol.*

t (min.)	0	30	45	60	75	105	120	150	180	225	250
[Halide]	8·09	7·26	6·89	6·56	6·20	5·59	5·30	4·79	4·32	3·72	3·39

[Halide] = 0·0486M by wt. [KOH] = 0·030N.
Slope of line : $-1·51 \times 10^{-3}$ min.$^{-1}$. $10^5k = 5·80$.

70% *Methanol–acetone.*

t (min.)	0	20	40	60	90	120	150	200	250	300
[Halide]	9·78	9·68	9·57	9·46	9·37	9·18	9·02	8·78	8·53	8·32

[Halide] = 0·0491M by wt. [KOH] = 0·0251N.
Slope of line : $-2·084 \times 10^{-4}$ min.$^{-1}$. $10^5k = 0·82$.

70% *Aqueous acetone.*

t (hr.)	0	1	2	3	5	6	8·5	10
[Halide]	8·71	8·19	7·63	7·19	6·31	5·92	5·04	4·58

[Halide] = 0·0487M by wt. [KOH] = 0·0270N.
Slope of line : $-2·786 \times 10^{-2}$ hr.$^{-1}$. $10^5k = 1·78$.

(b) *Polarimetric method.* A known amount of the halide was dissolved in the appropriate medium ($c \sim 1$) and put into a polarimeter tube (2 or 4 dm.). The first-order rate constant was calculated from the slope of the line obtained by plotting $\log_{10} (\alpha_t - \alpha_\infty)$ against time where α_t is the optical rotation at time, t, and α_∞ that at infinite time. The rate constants are listed in Tables 1 and 2 and an individual run is illustrated below.

100% *Methanol.* 21·2°.

t (min.) ...	10	25	50	85	100	120	135	150	175	200	225	300	∞
α_D	8·34°	8·16°	7·82°	7·45°	7·09°	6·97°	6·79°	6·60°	6·36°	6·10°	5·84°	4·92°	—02·1

c, 2·165; l, 2. Slope: $-7{\cdot}37 \times 10^{-4}$ min.$^{-1}$. $10^5k = 2{\cdot}83$ (sec.$^{-1}$).

*Reaction of Tetra-*O*-acetyl-α-*D*-glucosyl* 1-*Bromide with Sodium Iodide in Acetone.*—The bromide (5 g.) was dissolved in dry acetone (20 ml.) and a solution of sodium iodide (2·5 g.) in acetone (20 ml.) rapidly added at room temperature (20°) with shaking (cf. Helferich and Gootz, *Ber.*, 1929, **62**, 2791). After 10 min. the reaction was stopped by adding water and tetra-*O*-acetyl-α-D-glucosyl 1-iodide (5·34 g.) was isolated, having m. p. 108—109° (Helferich and Gootz give m. p. 109—110°).

The authors thank Professor S. Peat, F.R.S., for his interest in the work described in this and the following two papers, and the Department of Scientific and Industrial Research for a maintenance grant (to G. O. P.).

UNIVERSITY COLLEGE OF NORTH WALES, BANGOR.

[*Received, March 27th,* 1953.]