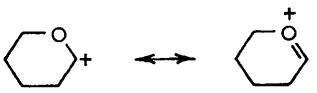
617. *Reactions at Position 1 of Carbohydrates. Part V.*[1] *Nucleophilic Displacement Reactions of Acetylglycosyl Halides.*

By B. Capon, P. M. Collins, A. A. Levy, and W. G. Overend.

Measurements have been made of the rates of (i) solvolysis of a range of acetylglycosyl halides in aqueous acetone, and (ii) reaction of the halides with lithium phenyl sulphide. It is concluded that (i) the solvolyses of those halides in which the acetoxyl group at C-2 and the halogen at C-1 are *cis* proceed by an S_N1 mechanism, (ii) if there is a *trans* arrangement of these groups the solvolysis involves neighbouring-group participation, (iii) an S_N2 mechanism operates in the reactions of the glycosyl halides with lithium phenyl sulphide. The effect, on the reactivities, of variation of substituents, and of their configuration in the sugars, is discussed.

The kinetics of displacement reactions of *O*-acetyl- and *O*-benzoyl-glycosyl halides have been studied by several workers.[2-6] Newth and Phillips [3] showed convincingly that several 1,2-*cis*-*O*-acetylglycosyl halides undergo solvolysis in aqueous acetone by an S_N1 mechanism, and Lemieux and Huber [5] reached a similar conclusion for the acetolysis of 3,4,6-tri-*O*-acetyl-β-D-glucosyl chloride. This behaviour is readily rationalised as arising from stabilisation of the intermediate carbonium ion by mesomeric electron release from the ring oxygen.



With 1,2-*trans*-acetyl- or -benzoyl-glycosyl halides, neighbouring-group participation by the 2-acyloxy-group is possible and does in fact occur, as is shown by the isolation of products of retained configuration [2,5] in methanolyses and acetolyses, and by enhanced reaction rates [2,4,5] ascribable to anchimeric assistance. It appears, therefore, that the preferred mechanism for displacement of the halide in 1,2-*cis*-acetylglycosyl halides is S_N1, whereas for the *trans*-halides neighbouring-group participation is involved. These compounds can only be made to react by an S_N2 mechanism under forcing conditions, *i.e.*, by reaction in a poorly ionising solvent in the presence of a strong nucleophile. The only kinetic investigation of the reactions of *O*-acetylglycosyl halides under such conditions was reported by Chapman and Laird,[6] who studied reactions with amines in acetone. Rhind-Tutt and Vernon [7] studied the reactions of the closely related tetra-*O*-methyl-α-D-glucopyranosyl and α-D-mannopyranosyl chlorides with lithium phenyl sulphide in propan-1-ol. They found that, whereas the 1,2-*cis*-glucosyl compound underwent a bimolecular reaction with phenylthio anion, the 1,2-*trans*-mannosyl compound underwent a unimolecular solvolysis.

In this Paper we report an examination of the kinetics of the solvolyses in aqueous acetone, and of the reactions with lithium phenyl sulphide in n-pentanol–toluene of a series of *O*-acetylglycosyl halides.

Experimental

The physical properties of the acetylglycosyl halides are given in Table 1.

Tetra-O-acetyl-α-D-glucopyranosyl and -α-D-galactopyranosyl Bromide.—These compounds were prepared by the method of Barczai-Martos and Korosy.[8] Pure materials were obtained after four recrystallisations from anhydrous ether.

[1] Part IV, Bamford, Capon, and Overend, *J.*, 1962, 5138.
[2] (*a*) Fletcher, Hudson, and Ness, *J. Amer. Chem. Soc.*, 1950, **72**, 2200, 4173; 1951, **73**, 959; (*b*) Ness, Fletcher, and Hudson, *ibid.*, p. 296.
[3] Newth and Phillips, *J.*, (*a*) 1953, 2896; (*b*) 1953, 2900; (*c*) 1953, 2904.
[4] Mattok and Phillips, *J.*, (*a*) 1956, 1836; (*b*) 1957, 268; (*c*) 1958, 130.
[5] Lemieux and Huber, *Canad. J. Chem.*, 1955, **33**, 128.
[6] Chapman and Laird, *Chem. and Ind.*, 1954, 20.
[7] Rhind-Tutt and Vernon, *J.*, 1960, 4637.
[8] Barczai-Martos and Korosy, *Nature*, 1950, **165**, 369.

Tri-O-*acetyl*-α-D-*xylopyranosyl and* -β-L-*arabinopyranosyl Bromide.*—Attempts to prepare these bromides by known methods [8,9] gave crystalline materials which even after several recrystallisations had low bromine contents (~5%). However, the following method (A) gave materials of satisfactory purity. Gaseous hydrogen bromide (*ca.* 25 g.) was passed over moist red phosphorus and phosphoric oxide and into anhydrous ether (100 ml.) at −30° during 30 min. To this solution either finely powdered tetra-*O*-acetyl-α-D-xylopyranose (10 g.) [10] or -α-L-arabinopyranose (10 g.) [11] was added, and the mixture was stored at 15° for 30 min. The

TABLE 1.

Acetylglycosyl halides.

Configuration	Halogen (%) Found	Calc.	M. p.	$[\alpha]_D$ (*c*)	Lit. values M. p.	$[\alpha]_D$	Ref.
			Tetra-O-*acetylhexopyranosyl bromide*				
α-D-*gluco* (I)	19·4	19·4	87—88°	+186° (2·0 *)	88—89°	+198 †	*a*
α-D-*galacto* (IV)	19·4	,,	83—84	+205° (2·7 *)	84—85	+217 †	*a*
α-D-*manno* (V)	19·5	,,	53—54	+128° (1·8 †)	53—54	+123 †	*b*
			Tetra-O-*acetylhexopyranosyl chloride*				
α-D-*gluco* (VII)	9·7	9·7	75—76	+159° (0·81 *)	75—76	+166 †	*a*
β-D-*gluco* (VIII)	9·7	,,	98—99	−6·0° (3·5 *)	98—99	−18·6 ‡	*a*
			Tri-O-*acetyl*-6-*deoxyhexopyranosyl bromide*				
α-D-*gluco* (II)	—	—	150—151	+250° (3·2 †)	150—152	+247 †	*a*
α-L-*manno* (VI)	22·6	22·6	64—65	−170° (1·2 †)	71—72	−170 †	*c*
6-*Iodo*-α-D-*gluco* (III) §	16·5 ¶	16·7	166 (decomp.)	+164° (3·0 †)	168—177 (decomp.)	+179 †	*a*
			Tri-O-*acetylpentopyranosyl bromide*				
α-D-*xylo* (IX)	23·5	23·6	100—101	+212° (1·4 †)	101—102	+212 †	*d*
β-L-*arabino* (X)	23·5	,,	138—139	+287° (2·5 †)	139	−283 † (D-form)	*a*
β-D-*ribo* (XI, XII)	22·8	,,	95—96	−210° (1·1 †)	96	−209 †	*a*

* In acetone. † In chloroform. ‡ In carbon tetrachloride. § Found: C, 29·8; H, 3·6. $C_{12}H_{16}BrIO_7$ requires C, 30·1; H, 3·4%. ¶ Determined by treating the halide with silver nitrate in aqueous acetone. The iodine in tetra-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranose did not react under these conditions.

[a] Haynes and Newth, *Adv. Carbohydrate Chem.*, 1955, **10**, 207. [b] Levene and Tipson, *J. Biol. Chem.*, 1931, **90**, 89. [c] Fischer, Bergmann, and Rabe, *Ber.*, 1920, **53**, 2362. We were unable to obtain the m. p. reported, even after repeated recrystallisation from di-isopropyl ether and n-pentanol. [d] Brauns, *J. Amer. Chem. Soc.*, 1925, **47**, 1280.

solvent was evaporated under reduced pressure, and sodium-dried toluene (2 × 50 ml.) was added and evaporated at 35°. A solution of the residue in sodium-dried benzene (75 ml.) was decolourised with activated charcoal and evaporated to a white solid which was recrystallised from anhydrous ether–light petroleum (b. p. 40—60°).

Tri-O-*acetyl*-β-D-*ribopyranosyl Bromide.*—This was prepared similarly from tetra-*O*-acetyl-β-D-ribopyranose.[12]

Tetra-O-*acetyl*-α-D-*mannopyranosyl Bromide.*—Nicholas and Smith [13] reported that acetylation of commercial D-mannose, with perchloric acid as catalyst, yields an oil. We find that a crystalline acetate is obtainable if β-D-mannose is used. For example, it was noted that D-mannose supplied by L. Light & Co. readily affords a crystalline β-penta-acetate when treated with perchloric acid and acetic anhydride, whereas D-mannose from the Eastman Kodak Company does not. {The former ($[\alpha]_D^{20}$ −15·2° ⟶ +14·2°, *c* 2·0 in H_2O) is mainly the β-anomer ($[\alpha]_D^{20}$ −17·0° in H_2O); [14] the latter ($[\alpha]_D^{20}$ +26° ⟶ +14·2°, *c* 1·8 in H_2O) is predominantly the α-form ($[\alpha]_D^{20}$ +29·3° in H_2O).[14]} Finely powdered β-D-mannose (10 g.)

[9] Hudson and Johnson, *J. Amer. Chem. Soc.*, 1915, **37**, 2748.
[10] Stone, *Amer. Chem. J.*, 1893, **15**, 653.
[11] Deriaz, Overend, Stacey, Teece, and Wiggins, *J.*, 1949, 1879.
[12] Levene and Tipson, *J. Biol. Chem.*, 1931, **92**, 109.
[13] Nicholas and Smith, *Nature*, 1948, **161**, 349.
[14] Isbell and Pigman, *J. Res. Nat. Bur. Stand.*, 1937, **18**, 141.

(L. Light) was added portionwise to a stirred solution of 60% perchloric acid (0·3 ml.) in acetic anhydride (40 ml.) at 0°. After 30 min., ice–water (500 ml.) was added with stirring. The oily product soon solidified, and after 12 hr. at 0° was filtered off (10·4 g.). The mother-liquors were extracted with chloroform, and the oil obtained on evaporation of the extract was crystallised from methylated spirit to give more material (1 g.). The combined product was recrystallised twice from methylated spirit, to yield pure penta-*O*-acetyl-β-D-mannopyranose (9·5 g., 44%), m. p. 117—118°, $[\alpha]_D^{20}$ −24·4° (*c* 1·1 in $CHCl_3$) (lit.,[15] m. p. 117—118°, $[\alpha]_D^{20}$ −25·2° in $CHCl_3$). When this experiment was repeated with α-D-mannose (Eastman), the oily product crystallised in low yield only after 6 weeks. It was mainly 1,2,3,4,6-penta-*O*-acetyl-α-D-mannose.

The penta-*O*-acetyl-β-D-mannopyranose (8 g.) was brominated by method (A). A seed crystal was obtained from the resulting syrup by extracting it for 5 min. with boiling light petroleum (b. p. 40—60°). The solution was decanted, and after 1 day at 0° an oil separated containing several crystals. The oil from subsequent experiments crystallised from di-isopropyl ether on seeding (see ref. 16 for full details). We thank Dr. W. E. Laird for advice on this crystallisation.

Tri-O-*acetyl*-L-*rhamnopyranosyl Bromide*.—This was prepared from oily tetra-*O*-acetyl-L-rhamnose [17] by method (A), and recrystallised from di-isopropyl ether.

Tri-O-*acetyl*-6-*deoxy*-6-*iodo*-α-D-*glucopyranosyl Bromide*.—Methyl tri-*O*-acetyl-6-*O*-tosyl-α-D-glucopyranoside [18] (53 g.) was heated under reflux overnight with sodium iodide (55 g.) in ethyl methyl ketone (45 ml.). The cooled solution was filtered, and evaporated to dryness under reduced pressure. Chloroform and water were added to the residue, and the chloroform layer was washed with 5% sodium thiosulphate solution (200 ml.) and water, dried (Na_2SO_4), and evaporated to dryness, to give methyl tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside (28 g.), m. p. 148·5—149·0° (from methanol), $[\alpha]_D$ +114° (*c* 2·42 in $CHCl_3$) (lit.,[18] m. p. 149—150°, $[\alpha]_D$ +113·8°). This glucoside (5 g.) was dissolved in acetic anhydride (70 ml.), acetic acid (30 ml.), and concentrated sulphuric acid (2 ml.), and the solution, after 24 hr. at room temperature, was poured into water (500 ml.). *Tetra*-O-*acetyl*-6-*deoxy*-6-*iodo*-α-D-*glucopyranose* separated, and was filtered off and washed with aqueous sodium hydrogen carbonate, and water (3·5 g., 65%), m. p. 182° (from ethanol), $[\alpha]_D^{21}$ +99·1° (*c* 3·116 in $CHCl_3$) (Found: C, 36·4; H, 4·6; I, 27·0. $C_{14}H_{19}IO_9$ requires C, 36·7; H, 4·2; I, 27·7%) (M_D +45,400; M_D for the α-anomer calculated from Hudson's Rules +41,300; for the β-anomer −6100). The iodo-compound (3·5 g.) was added to a freshly prepared mixture of hydrogen bromide (145 g.) and anhydrous ether (100 ml.). The mixture became homogeneous after 30 min. at room temperature, during which time it was frequently shaken. Soon afterwards, crystallisation began and, after a further 30 min. more ether (50 ml.) was added to achieve homogeneity. After a further 1 hr. the solution was evaporated *in vacuo* and the residue dissolved in chloroform. The solution was washed with ice–water and ice-cold aqueous sodium hydrogen carbonate, dried (Na_2SO_4) and decolourised simultaneously, and evaporated below 45° under diminished pressure. *Tri*-O-*acetyl*-6-*deoxy*-6-*iodo*-α-D-*glucopyranosyl bromide* (1·5 g.) was recrystallised from toluene (see Table 1).

Tri-O-*acetyl*-6-*deoxy*-α-D-*glucopyranosyl Bromide*.—Methyl tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside (22 g.) in tetrahydrofuran (sodium-dried; 70 ml.) was hydrogenated with Raney nickel and triethylamine (13 ml.) at room temperature and in a slight over-pressure of hydrogen. When hydrogen uptake was complete the solution was filtered and washed four times with water, which was back-washed with ether. The combined organic solutions were dried (Na_2SO_4), and evaporated under reduced pressure, to give methyl tri-*O*-acetyl-6-deoxy-α-D-glucopyranoside (11·2 g.), m. p. 73° [from light petroleum (b. p. 40—60°)] (lit.,[18] 77—78°). It was converted into tri-*O*-acetyl-6-deoxy-α-D-glucopyranosyl bromide by Compton's method,[18] and the product was recrystallised from di-isopropyl ether.

Tetra-O-*acetyl*-β-D-*glucopyranosyl Chloride*.—This was prepared by reaction of penta-*O*-acetyl-β-D-glucopyranose with aluminium chloride in chloroform,[19] and was recrystallised four times from ether.

[15] Dale and Hudson, *J. Amer. Chem. Soc.*, 1915, **37**, 1280.
[16] Collins, M.Sc. Thesis, London, 1959.
[17] Fischer, Bergmann, and Rabe, *Ber.*, 1920, **53**, 2362.
[18] Compton, *J. Amer. Chem. Soc.*, 1938, **60**, 395.
[19] Korytnyk and Mills, *J.*, 1959, **636**.

Tetra-O-acetyl-α-D-glucopyranosyl Chloride.—This was obtained from the reaction of penta-*O*-acetyl-β-D-glucopyranose with titanium tetrachloride in chloroform,[20] and was recrystallised from ether.

Solvents.—Acetone was purified as described by Vogel.[21] 60% (v/v) Aqueous acetone was made by mixing this acetone (60 vol.) with distilled water (40 vol.), 75% (w/w) aqueous acetone was obtained by mixing 750·0 g. with distilled water (250·0 g.), and 90% (w/w) aqueous acetone by mixing 900·0 g. with distilled water (100·0 g.).

n-Pentanol was dried (K_2CO_3), filtered, and fractionally distilled (nitrogen leak). The fraction collected had b. p. 61°/23 mm.

Toluene (sodium-dried) was distilled, and the fraction boiling at 110·5—111·0° was collected and stored over sodium wire.

Lithium Phenyl Sulphide Solution.—Clean lithium (1 g.) was rinsed, and dissolved in boiling ethanol (75 ml.). The excess of ethanol was distilled off *in vacuo* and pentanol was run in simultaneously. Distillation was continued until the distillate contained an appreciable amount of pentanol, and the solution was cooled to room temperature *in vacuo*. This stock solution was standardised; it could be kept for about 2 weeks. It was converted into lithium phenyl sulphide as required by adding a slight excess of thiophenol, filtering, and diluting to the appropriate concentration.

Procedure for Solvolyses in Aqueous Acetone.—At intervals, aliquots (5 ml.) of the reaction solutions were removed and added to either absolute ethanol or anhydrous acetone (50 ml.) at −70°. The hydrohalic acid was titrated with ethanolic sodium ethoxide (~0·03M) with lacmoid indicator. The titrations were carried out at −20° in ethanol or at −50° in acetone. (Below −20° in ethanol the indicator did not function.) For the less reactive compounds both methods were satisfactory but for those more reactive (*e.g.*, rhamnose and ribose derivatives) it was necessary to use the latter. That the reaction was stopped by the procedure adopted was checked for each compound. In some runs the reaction was followed by titrating the free halide ions, after extraction of the glycosyl halide with chloroform or benzene.

TABLE 2.

Deacetylation of acetylglycosyl halides during solvolysis in 75% (w/w) aqueous acetone at 21 ± 1°.

Compound	Time	Approx. no. of half-lives	% Loss of one acetyl group
Tetra-*O*-acetyl-α-D-glucopyranosyl bromide	7 days	10	50
	2 days	3	30
	27 hr.	1·5	0
Tetra-*O*-acetyl-α-D-galactopyranosyl bromide ...	10 hr	1	3
Tri-*O*-acetyl-α-D-xylopyranosyl bromide	5 days	500	16
	15 hr.	60	1
Tri-*O*-acetyl-α-D-rhamnopyranosyl bromide	7 hr.	60	1

The initial concentration of the acetylglycosyl halide was checked in every run from the titre at " infinite " time (ten times the half-life). For all reactions giving reliable rate constants it corresponded to 99·2—100·3% of the weight of material.

Procedure for Reactions with Lithium Phenyl Sulphide.—These were carried out under nitrogen in an apparatus similar to that described by Wiberg and Mill.[22] Aliquots were removed periodically, quenched in an excess of standard ethanolic hydrogen chloride at −20°, and titrated, first with sodium ethoxide and then with aqueous iodine. Infinity titrations were performed after 20—30 half-lives for the disappearance of the acetylglycosyl halide.

Deacetylation in Solvolyses.—Deacetylation has been observed in the solvolyses of *O*-acetylglycopyranosyl halides.[2b,23] We investigated this as follows: two aliquots (5 ml.) of the reaction solution were each added to anhydrous acetone (free from carbon dioxide) (150 ml.) at about 0°. The samples were titrated under nitrogen with alcoholic potassium hydroxide, one with phenolphthalein as indicator and the other with lacmoid. (Hydrohalic acid only is

[20] F. J. Bates and Associates, " Polarimetry, Saccharimetry and the Sugars," National Bureau of Standards, Washington, 1942, p. 499.
[21] Vogel, " Practical Organic Chemistry," Longmans, London, 1956, p. 171.
[22] Wiberg and Mill, *J. Amer. Chem. Soc.*, 1958, **80**, 3022.
[23] Koenigs and Knorr, *Ber.*, 1901, **34**, 957.

titrated with lacmoid as indicator; both hydrohalic acid and acetic acid are titrated when phenolphthalein is used.) The above conditions had to be used, since phenolphthalein fails to indicate at low temperatures. The slower reactions were stopped under these conditions and the fast reactions were investigated only at the end of the solvolysis. The extent of deacetylation observed in the solvolysis of four acetylglycosyl halides is shown in Table 2.

Solvolyses in Aqueous Acetone.—Isolation of the products was complicated by their undergoing anomerisation and acetyl migration at rates not much slower than the rates of the solvolyses. Some information about the first-formed products was obtained, however, from the change in the optical rotations of the reacting solutions.

Tetra-O-*acetyl*-α-D-*glucopyranosyl bromide.* A solution of the bromide (5 g.) in 60% (v/v) aqueous acetone (100 ml.) was treated after 15 hr. at 30° with the calculated amount of sodium hydrogen carbonate solution. The neutral solution was evaporated to small bulk and extracted with chloroform (7 × 50 ml.). Evaporation of the chloroform gave an oil (3·3 g., 78%), $[\alpha]_D^{20}$ +71·2° (*c* 2·2 in EtOH), $[\alpha]_D^{20}$ +76·6° [*c* 1·7 in 60% (v/v) H_2O–Me_2CO]. Crystalline 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose was obtained in very low yield from a similar experiment in which the solution was not evaporated before extraction. It had m. p. 138—139°, $[\alpha]_D^{20}$ +5·8° ⟶ +83° (*c* 0·5 in EtOH) (lit.,[24] m. p. 136—138°, $[\alpha]_D$ −4·2° ⟶ +75° in EtOH).

The approximate optical rotation of the first-formed product was obtained by making large-scale plots of optical rotation against time and of percentage reaction (determined titrimetrically) against time for the same reaction conditions. From these plots optical rotations at given times and percentage reactions were determined (Table 3). The contributions of the unreacted acetylglucosyl bromide to the total rotations at the various times were calculated, and the difference between these values and the measured rotations gave the contribution to the rotation of the reaction product. The specific rotation of the product was calculated on the assumption that it was a tetra-*O*-acetyl-D-glucose. The values obtained indicate that early in the reaction, when anomerisation and acetyl migration are least, the product had $[\alpha]_D$ −30° ±50%. This result indicates the absence of appreciable quantities of 2,3,4,6-tetra-*O*-acetyl-α-D-glucose, for which $[\alpha]_D$ +138·9° in $CHCl_3$ is reported.[25] Probably the major product is the β-anomer, $[\alpha]_D^{20}$ −4·2° (in EtOH),[24] the reaction proceeding with a

TABLE 3.

Optical rotation of the solvolysis product from tetra-*O*-acetyl-α-D-glucopyranosyl bromide in 60% (v/v) aqueous acetone at 30·7°.

Time (min.)	0	14·4	21·6	29·5	38·0	46·5	56·2
% Reaction	0	10	15	20	25	30	35
Total rotation	+3·68°	+3·26°	+3·07°	+2·88°	+2·69°	+2·53°	+2·36°
Rotation of the bromide	—	+3·31°	+3·13°	+2·94°	+2·76°	+2·5°	+2·39°
Rotation of the product	—	−0·05°	−0·06°	−0·06°	−0·07°	−0·05°	−0·03°
$[\alpha]_D$ of the product (±50%)	—	−30°	−24°	−18°	−16°	−10°	−5°

high degree of inversion. Similar conclusions have been reached about the steric course of the methanolysis of tetra-*O*-benzoyl-α-D-glucopyranosyl bromide [2] and tetra-*O*-methyl-α-D-glucopyranosyl chloride.[7]

Tetra-O-*acetyl*-α-D-*galactopyranosyl bromide.* The rotation (+25° ±5%) of the first-formed product, calculated as above, strongly suggests that the product is 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranose, for which a value of +24° has been reported [26] (cf. $[\alpha]_D$ +144° in $CHCl_3$ for the α-anomer [27]).

Tri-O-*acetyl*-α-D-*xylopyranosyl bromide.* Antia [28] reported the isolation of three tri-*O*-acetylxyloses from this solvolysis when the water content of the solvent was 4—5% by volume. In our case a solution of the bromide (4·9 g.) in 75% (w/w) aqueous acetone (500 ml.) was neutralised with lead carbonate after 3 hr. at 20°. The filtered solution was shaken with chloroform (12 × 75 ml.). Evaporation of the chloroform gave a solid (3·8 g., 96%), $[\alpha]_D^{20}$ +53° (*c* 1·2 in $CHCl_3$), which was recrystallised from anhydrous ether–light petroleum (b. p. 40—

[24] Hendricks, Wulf, and Liddel, *J. Amer. Chem. Soc.*, 1936, **58**, 1997.
[25] Schlubach and Wolf, *Ber.*, 1929, **62**, 1507.
[26] Compton and Wolfrom, *J. Amer. Chem. Soc.*, 1934, **56**, 1157.
[27] Schlubach and Gilbert, *Ber.*, 1930, **63**, 2292.
[28] Antia, *J. Amer. Chem. Soc.*, 1958, **80**, 6138.

60°). An attempt was made to compare the physical properties of the two crops of crystals obtained with those given by Antia.[28] The first crop (2·6 g.) had m. p. 122—127°, $[\alpha]_D^{21}$ +45° ⟶ +52° (equilib. after 9 days) (*c* 1·1 in $CHCl_3$), $[\alpha]_D^{21}$ +43° [*c* 1·8 in 75% (w/w) H_2O–Me_2CO]. The infrared spectrum of this material, when compared with the data given by Antia, indicated that it was predominantly 2,3,4-tri-*O*-acetyl-α-D-xylose (Antia's isomer B), with some 2,3,4-tri-*O*-acetyl-β-D-xylose (Antia's product C) and 1,3,4-tri-*O*-acetyl-α-D-xylose (isomer A of Antia). The infrared spectrum of the second crop (0·6 g.), m. p. 115—120°, $[\alpha]_D^{20}$ +75° ⟶ +51·8° (equilib. after 10 days) (*c* 1·2 in $CHCl_3$), $[\alpha]_D^{21}$ +80° [*c* 0·6 in 75% (w/w) H_2O–Me_2CO], indicated that it was fairly pure 2,3,4-tri-*O*-acetyl-α-D-xylose, possibly containing only traces of the other two isomers.

Tri-O-*acetyl*-α-L-*rhamnopyranosyl bromide*. A solution of the bromide (6·8 g.) in 75% (w/w aqueous acetone (450 ml.) was treated after 2 hr. at 20° in the same way as the reaction product from xylosyl bromide. A solid product (5·7 g., 98%) was obtained, $[\alpha]_D^{20}$ +29·6° ⟶ −8·1° (equilib. after 9 days) (*c* 1·5 in EtOH–$CHCl_3$, 5 : 1), $[\alpha]_D^{20}$ +25·2° ⟶ −17·0° (equilib. after 8 days) [*c* 1·2 in 75% (w/w) H_2O–Me_2CO]. The second crop (2·74 g.) had $[\alpha]_D^{20}$ −13·7° (constant for 9 days) (*c* 1·1 in EtOH), $[\alpha]_D^{20}$ −14·8° [*c* 2·4 in 75% (w/w) H_2O–Me_2CO]. Fischer *et al.*[29] give $[\alpha]_D^{20}$ +28·1° ⟶ −18·6° (in EtOH) for 2,3,4-tri-*O*-acetyl-β-L-rhamnose. The rotation of the first-formed product was calculated to be $[\alpha]_D$ +25 ± 4°, indicating the absence of appreciable quantities of 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranose which would be expected to have a negative rotation. It is consistent with the initial product's being 2,3,4-tri-*O*-acetyl-β-L-rhamnopyranose, $[\alpha]_D^{20}$ +28·1° (in EtOH),[29] or 1,3,4-tri-*O*-acetyl-β-L-rhamnose, since it has been shown [30] that the analogous compounds in the mannose series have almost identical rotations.

Tetra-O-*acetylmannopyranosyl bromide*. Bonner [30a] isolated the following products from the reaction of syrupy tetra-*O*-acetylmannopyranosyl bromide with silver carbonate in moist ether: 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranose, $[\alpha]_D^{25}$ +22·7° (in 60% aqueous acetone), 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranose, $[\alpha]_D^{25}$ −20·0° ⟶ +19·6° (after 1 hr.) (in 60% aqueous acetone), and an isomer in which an acetyl group had migrated, $[\alpha]_D^{25}$ −28·0° ⟶ +19·3° (after 139 min.) (in 60% aqueous acetone). It was calculated from the rotational change occurring in the solvolysis in 75% (w/w) aqueous acetone that the rotation of the first-formed product was −40° (±50%). This indicated the absence of appreciable quantities of 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranose.

Tetra-O-*acetyl*-β-D-*glucopyranosyl chloride*. The rotational change during this reaction in 75% aqueous acetone indicated that the rotation of the first-formed product was +130° (±10%), a value which suggests that it is largely 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose ($[\alpha]_D$ +138·9° in $CHCl_3$ [25]).

Reactions with Lithium Phenyl Sulphide.—All reactions were allowed to proceed for 20 half-lives of the disappearance of glycosyl halide except that of the 6-deoxy-6-iodoglucosyl bromide which was stopped after 5 half-lives because displacement of the 6-iodo-group became significant if the reaction was left longer. The mixture was added to an equal volume of benzene and the benzene layer was washed several times with water. A slight excess of a solution of iodine in benzene was added to oxidise thiophenol to diphenyl disulphide. The benzene solution was washed again with sodium hydrogen carbonate solution and water, dried (Na_2SO_4), and evaporated under reduced pressure below 45°. The residue was washed with approx. 2 ml. of light petroleum (b. p. 40—60°) to remove diphenyl disulphide, and recrystallised from aqueous ethanol. The products isolated were: phenyl tetra-*O*-acetyl-1-deoxy-1-thio-β-D-glucopyranoside, m. p. 117—117·5° $[\alpha]_D$ −17·5° (*c* 2·6 in $CHCl_3$) (lit.,[30b] m. p. 117°, $[\alpha]_D$ −17·5°); *phenyl tri*-O-*acetyl*-1-*deoxy*-1-*thio*-α-L-*arabinopyranoside*, b. p. 200°/10^{-5} mm., $[\alpha]_D$ +5·7° (*c* 1·52 in $CHCl_3$) (Found: C, 55·4; H, 5·6; S, 7·9. $C_{17}H_{20}O_7S$ requires C, 55·4; H, 5·5; S, 8·7%); *phenyl tetra*-O-*acetyl*-1-*deoxy*-1-*thio*-β-D-*galactopyranoside*, m. p. 70·5°, $[\alpha]_D$ +4·6° (*c* 1·8 in $CHCl_3$) (Found: C, 54·8; H, 5·4; S, 7·4. $C_{20}H_{24}O_9S$ requires C, 54·5; H, 5·5; S, 7·3%); *phenyl tri*-O-*acetyl*-1,6-*dideoxy*-6-*iodo*-1-*thio*-β-D-*glucopyranoside*, m. p. 131—131·5°, $[\alpha]_D$ −6·4° (*c* 2·5 in $CHCl_3$) (Found: C, 42·8; H, 4·2; I, 25·0; S, 6·0. $C_{18}H_{21}IO_7S$ requires C, 42·5; H, 4·2; I, 25·0; S, 6·3%); *phenyl tri*-O-*acetyl*-1,6-*dideoxy*-1-*thio*-β-D-*glucopyranoside*, m. p. 111·5°, $[\alpha]_D$ −11·9° (*c* 2·4 in $CHCl_3$) (Found: C, 56·4; H, 5·8; S, 8·2.

[29] Fischer, Bergmann, and Rabe, *Ber.*, 1920, **53**, 2362.
[30] (*a*) Bonner, *J. Amer. Chem. Soc.*, 1958, **80**, 3372; (*b*) Purves, *ibid.*, 1929, **51**, 3619.

$C_{18}H_{22}O_7S$ requires C, 56·5; H, 5·8; S, 8·4%); phenyl tri-*O*-acetyl-1-deoxy-1-thio-β-D-xylopyranoside, m. p. 77·5°, $[\alpha]_D$ −65·6° (*c* 1·5 in $CHCl_3$) (lit.,[30b] m. p. 78°, $[\alpha]_D$ −58·9°). Attempts to isolate a phenyl tetra-*O*-acetyl-1-deoxy-1-thiomannoside failed.

Results

Solvolyses in Aqueous Acetone.—Rate coefficients were calculated from the integrated first-order rate equation. For the faster reactions the time of withdrawal of the first aliquot was taken as zero time. Those halides in which the acetoxyl at C-2 was *trans* to halogen gave steady rate coefficients, but those in which it was *cis* gave coefficients which increased with increasing time. These rising coefficients were plotted against time, and the initial value, at the time of mixing of the solution, was obtained by extrapolation. Each kinetic run was performed at least twice. The difference in the velocity coefficient was never greater than 3·2%. The mean values of the rate coefficients of all the solvolyses are collected in Table 4. Representative results for a selection of reactions are given in detail in Table 5. Times of observation are in minutes or seconds but the velocity coefficients are alway given in $sec.^{-1}$. Some of the reactions were studied at three temperatures, and the Arrhenius parameters are also listed in Table 4.

Table 4.

Rate coefficients and kinetic parameters for solvolyses in aqueous acetone.

Compound	Temp. (±0·04°)	10^5k ($sec.^{-1}$)	*E* (kcal. $mole^{-1}$)	log *A*
60% (v/v) *Aqueous acetone*				
(I)	20·2°	4·02	19·2	9·9
(I)	30·6	12·3		
(I)	39·8	31·4		
(I)	30·2	11·5 *		
(I) (0·0485M, +0·0407M-NaBr)	21·2	5·38		
(IV)	20·9	12·4	16·9	8·6
(IV)	28·9	26·7		
(IV)	42·0	85·1		
75% (w/w) *Aqueous acetone*				
(I)	22·4	0·72	20·3	9·9
(I)	32·3	2·18		
(I)	42·7	6·70		
(II)	22·0	6·68		
(III)	42·0	1·58		
(IV)	22·4	1·95	20·1	10·2
(IV)	32·3	5·95		
(IV)	42·7	17·6		
(V)	11·8	11·0	20·4	11·7
(V)	22·1	39·6		
(V)	32·0	119		
(VI)	−0·3	8·88	20·2	12·1
(VI)	11·4	41·8		
(VI)	22·2	151		
(VI) (0·0596M, +0·0532M-NaBr)	22·1	149		
(VI) (0·0471M, +0·738M-NaBr)	11·5	40·3		
(VII)	31·9	0·0254		
(VIII)	12·4	27·8	19·2	11·1
(VIII)	22·0	87·8		
(VIII)	31·9	240		
(IX)	12·5	21·4	16·6	9·1
(IX)	22·4	57·7		
(IX)	33·2	142		
(X)	11·1	6·09	18·6	10·1
(X)	22·5	21·4		
(X)	32·6	61·5		
(X)	42·0	154		
(XI, XII)	−18·3	34·4		
90% (w/w) *Aqueous acetone*				
(I)	22·4	0·052		
(IX)	12·5	1·0		

* Reaction followed by titrating bromide.

TABLE 5.

Typical kinetic results.

Solvolysis of tetra-*O*-acetyl-α-D-glucopyranosyl bromide (0·0496M) in 75% (w/w) aqueous acetone at 32·3°.

Time (min.)	60·7	133·5	186·0	262·0	329·5	397·0	446·5	528·5
Solvolysis (%)	8·1	18·0	25·5	35·4	43·6	51·9	59·1	65·9
10^5k (sec.$^{-1}$).....	2·32	2·49	2·64	2·76	2·90	3·07	3·20	3·39

At zero time $k = 2·17 \times 10^{-5}$ sec.$^{-1}$ by extrapolation.

Solvolysis of tetra-*O*-acetyl-α-D-mannopyranosyl bromide (0·0349M) in 75% (w/w) aqueous acetone at 22·1°.

Time (sec.)	515	1015	1255	1828	2208	2608	3080	3755
Solvolysis (%)	17·8	32·4	39·4	51·6	58·8	64·4	70·6	76·9
10^4k (sec.$^{-1}$).....	3·82	3·86	4·00	3·98	4·02	3·96	3·97	3·90

Mean $k = 3·96 \pm 0·06 \times 10^{-4}$ sec.$^{-1}$.

Reaction of tetra-*O*-acetyl-α-D-glucopyranosyl bromide ($3·28 \times 10^{-2}$M) with lithium phenyl sulphide ($3·92 \times 10^{-2}$M) at 22·0°.

Time (min.)	0	3·75	28·3	75·6	112·5	144·0	172·0	202·5	∞
[Base] $\times 10^2$M	3·92	3·80	3·19	2·45	2·10	1·88	1·72	1·59	0·65
[Thiophenol] $\times 10^2$M	—	4·50	3·88	3·13	2·80	2·55	2·40	2·33	1·35
Loss of base after 3·75 min.....	—	—	0·61	1·35	1·70	1·92	2·08	2·21	3·15
Loss of thiophenol after 3·75 min. ...	—	—	0·62	1·37	1·70	1·95	2·10	2·17	3·15
k_2 (base titre)	—	2·48	2·51	2·59	2·58	2·58	2·60	2·60	—
k_2 (iodine titre)	—	—	2·52	2·61	2·58	2·62	2·64	2·54	—

TABLE 6.

Substitution reactions in n-pentanol–toluene mixtures at 22·0°.

			Reaction with lithium phenyl sulphide.			Solvolysis	
10^2A *	10^2B †	R ‡	10^3k_2 (l. mole^{-1} sec.$^{-1}$) Base titre	10^3k_2 (l. mole^{-1} sec.$^{-1}$) Iodine titre	10^3k_2 (l. mole^{-1} sec.$^{-1}$) Polarimetric	10^2[$LiClO_4$]	10^6k_1 (sec.$^{-1}$)
Tetra-O-*acetyl*-α-D-*glucopyranosyl bromide* (5% *toluene by volume*)							
3·22	1·99	1·06	4·2	4·3	—	3·74	0·58
6·61	1·99	1·03	3·7	3·6	—	7·48	0·75
3·92	3·28	1·00	4·3	4·3	—	—	—
8·22	1·97	—	—	—	4·3	—	—
Tri-O-*acetyl*-6-*deoxy*-α-D-*glucopyranosyl bromide* (5% *toluene by volume*)							
7·59	1·55	0·98	16·6	16·6	—	7·13	5·2
3·72	1·55	—	—	—	17·5	—	—
Tri-O-*acetyl*-6-*deoxy*-6-*iodo*-α-D-*glucopyranosyl bromide* (20% *toluene by volume*)							
3·80	0·327	1·06	3·0	3·2	3·6	14·2	—
Tetra-O-*acetyl*-α-D-*galactopyranosyl bromide* (5% *toluene by volume*)							
3·51	1·95	0·99	8·0	8·0	—	3·74	5·1
6·85	1·97	0·99	7·6	7·6	—	—	—
3·47	3·24	1·04	7·7	7·9	—	—	—
3·55	1·95	—	—	—	8·4	—	—
Tri-O-*acetyl*-α-D-*xylopyranosyl bromide* (5% *toluene by volume*)							
3·77	1·99	0·92	51	52	—	3·84	45
3·70	1·00	0·95	44	45	—	—	—
2·26	1·98	0·95	50	48	—	—	—
3·48	2·00	—	—	—	47	—	—
Tri-O-*acetyl*-β-L-*arabinopyranosyl bromide* (5% *toluene by volume*)							
3·41	1·91	0·97	14·8	—	—	3·64	22
6·71	1·82	0·94	13·8	—	—	7·12	30
3·33	3·12	0·94	13·5	—	—	—	—
3·38	1·93	—	—	—	14·5	—	—

* Concentration of lithium phenyl sulphide. † Concentration of acetylglycosyl bromide. ‡ Ratio of thiophenol consumed to base consumed during run.

Displacement Reactions with Lithium Phenyl Sulphide.—For those reactions for which solvolysis was judged to be negligible, rate coefficients were calculated from the base titres, using the integrated second-order equation. Rate coefficients were then calculated from the iodine titres at each point by multiplying by the ratio of the change in iodine titre (mequiv./l.) to the corresponding change in base titre.[31] For those reactions for which solvolysis proceeded at an appreciable rate the method of Brown and Hudson [32] was used to calculate rate coefficients from the base titres. In these reactions the rate of disappearance of acetylglycosyl halide is more rapid than the rate of disappearance of thiophenol. Hence the change in concentration of acetylglycosyl halide, and therefore the rate coefficients, cannot be determined from the iodine titre alone.

In polarimetric runs the extents of reaction at various times were calculated from the optical rotations, and the rate coefficients were calculated using the integrated second-order expression. The mean values of the rate coefficients of the displacement reactions are given in Table 6 and detailed results are given in Table 5.

The rates of the solvolyses in pentanol, in the presence of lithium perchlorate at concentrations similar to those of the lithium thiophenoxide used, were measured as described for solvolyses in aqueous acetone.

Discussion

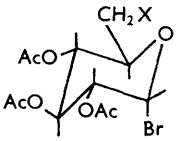
Conformations of the Acetylglycosyl Halides.—The acetylglycosyl halides exist preferentially in one form, the α-anomer being usually the more stable.[33] With an acetyl-α-D-glycosyl halide in the generally preferred C1 conformation, the halogen will be axially disposed. In the cyclohexyl series the preferred position for chlorine and bromine is equatorial, but this preference is less strong than for other substituents (*e.g.*, Me, OH).[34] The increased preference of the halogens in the acetylglycosyl halides for axial positions is probably due to a decreased stability of the equatorial form owing to a repulsive interaction with the lone-pair electrons on the ring-oxygen atom. The acetyl-hexosyl halides studied may be assigned the conformations (I)—(VIII). These conformations are all reasonable since none of them possesses any strong elements of instability. Similarly, of the pentose derivatives studied, the α-D-xylosyl and β-L-arabinosyl bromides probably exist in the conformations (IX) and (X). However, neither the C1 (XI) nor the 1C conformation (XII) of the β-D-ribosyl bromide would be expected to be particularly stable, since in the former there is an equatorial bromine on C-1, and in the latter there are two axial acetoxyl substituents on the same side of the ring, attached to C-2 and C-4. Possibly this compound exists in a non-chair conformation. Arabinose and ribose do not form α-bromides, probably because, in the conformation in which the bromine is in the normally favoured axial position, there is a 1,3-interaction with the axial acetoxyl substituent on C-3.

Solvolyses in Aqueous Acetone.—The first-order rate coefficients for the solvolyses in 75% (w/w) aqueous acetone of the halides with a 1,2-*cis*-configuration increased as the reaction proceeded (see Table 7). This effect became greater as the water content of the solvent was decreased (see Table 7). The initial rate constants, obtained by extrapolation, increased rapidly with increasing water content of the solvent. The rate of solvolysis of tetra-*O*-acetyl-α-D-glucopyranosyl bromide in 60% (v/v) aqueous acetone was increased by about 20% on addition of 0·05M-sodium bromide. This behaviour is characteristic of S_N1-type solvolyses in which halide ions do not compete very successfully for carbonium ions with the solvent.[35] We conclude therefore, as have previous workers,[3] that the mechanism of these solvolyses is S_N1.

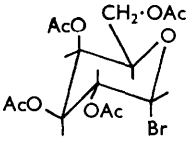
The solvolyses of the four 1,2-*trans*-compounds studied all yielded steady rate

[31] Eliel and Haber, *J. Amer. Chem. Soc.*, 1959, **81**, 1249.
[32] Brown and Hudson, *J.*, 1953, 3352.
[33] *Cf.* Haynes and Newth, *Adv. Carbohydrate Chem.*, 1955, **10**, 207.
[34] (*a*) Eliel and Gianni, *Tetrahedron Letters*, 1962, 97; (*b*) Reeves and Strømme, *Canad. J. Chem.*, 1960, **38**, 1241.
[35] Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, New York, 1953, (*a*) p. 360, (*b*) p. 346.

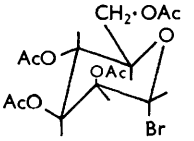
coefficients from the integrated first-order expression. Addition of sodium bromide (to 0·08M) had no effect on the rate of solvolysis of tetra-*O*-acetyl-α-L-rhamnopyranosyl bromide. Variation of the water content [4b] has less effect on the rate of solvolysis of



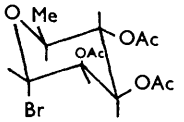
(I : X = OAc)
(II : X = H)
(III : X = I)



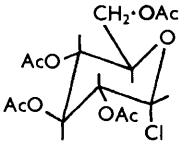
(IV)



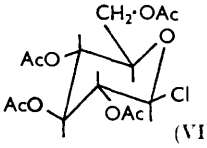
(V)



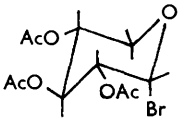
(VI)



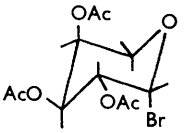
(VII)



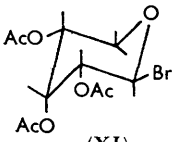
(VIII)



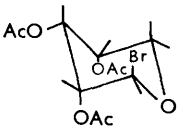
(IX)



(X)

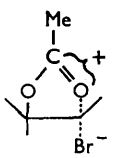


(XI)

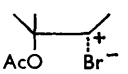


(XII)

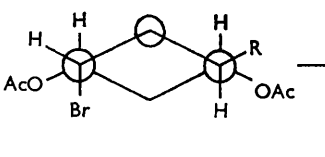
β-D-glucosyl chloride (*m* in Mattok and Phillips's equation [4b] = 0·5) (1,2-*trans*-disposition) than on the α-anomer (*m* = 0·7) (1,2-*cis*-disposition). All these observations show that the effect of changes in solvent polarity and solvating power on solvolysis rates is much less for the four 1,2-*trans*-halides than for the 1,2-*cis*-halides, which is consistent with solvolysis of the former with neighbouring-group participation by the acetoxyl group at C-2. In the transition state (XIII) the charge will be more dispersed than in (XIV), for a reaction not involving participation, and hence the rate should vary much less with solvent polarity and solvating power.[35b] The ratios (see Table 8) of the rates of solvolysis in 75% (w/w) aqueous acetone of the 1,2-*trans*- and corresponding 1,2-*cis*-halides vary from 20 ($\Delta\Delta G^{\ddagger}$ ~2 kcal.) for the α-L-rhamnosyl (VI)–6-deoxy-α-D-glucosyl (II) pair to 10,000 ($\Delta\Delta G^{\ddagger}$ ~5 kcal.) for the β-D-glucosyl (VIII)–α-D-glucosyl (VII) pair. This



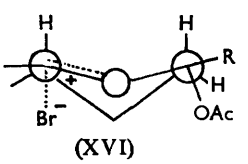
(XIII)



(XIV)



(XV)



(XVI)

compares with a rate ratio of about 1000 ($\Delta\Delta G^{\ddagger}$ ~4 kcal.) for the acetolysis of the *trans*- and *cis*-cyclohexyl toluene-*p*-sulphonates.[36] Less anchimeric assistance might be expected for the reactions we have studied. Since a more nucleophilic solvent was used, and since the glycosyl carbonium ion is already stabilised by conjugation with the ring oxygen atom, any additional stabilisation by the 2-acetoxyl group might be expected to be smaller. The very high rate difference between the α- and β-D-glucosyl chlorides does not appear therefore to be wholly ascribable [4] to anchimeric assistance by the *trans*-acetoxyl group in the solvolysis of compound (VIII). Undoubtedly a large part of this difference in reactivity must be ascribed to the lower free energy of the α-anomer. Tetra-*O*-acetyl-α-D-glucosyl chloride and related α-chlorides have been isolated in high yield (90%) from

[36] Winstein, Grunwald, Buckles, and Hanson, *J. Amer. Chem. Soc.*, 1948, **70**, 816.

TABLE 7.

The first-order rate coefficients at 0 and 70% reaction for 1,2-*cis*-*O*-acetylglycopyranosyl bromides in aqueous acetone.

Composition of acetone	90% (w/w)			75% (w/w)			60% (v/v)		
10^6k (sec.$^{-1}$) Compound	k_0	k_{70}	k_{70}/k_0	k_0	k_{70}	k_{70}/k_0	k_0	k_{70}	k_{70}/k_0
Tetra-*O*-acetyl-α-D-glucopyranosyl bromide	0·52	2·9 at 22·4°	5·6	7·2	11 at 22·3°	1·5	40·2	44·4 at 20·2°	1·1
Tetra-*O*-acetyl-α-D-galactopyranosyl bromide				19·5	30 at 22·5°	1·5	120	140 at 20·9°	1·1
Tri-*O*-acetyl-β-L-arabinopyranosyl bromide				214	278 at 22·5°	1·3			
Tri-*O*-acetyl-α-D-xylopyranosyl bromide	10	50 at 12·5°	5·0	577	825 at 22·4°	1·4			

the anomerisation of the corresponding β-chlorides.[19,37] Hence, at least 1·5—2 kcal. of the 5 kcal. difference in the free energy of activation is attributable to the difference in free energies of the initial states.

There is about an eighty-fold variation in solvolysis rates of the 1,2-*cis*-acetylglycosyl halides studied. Secondary steric effects would be expected to operate in these reactions in a manner first suggested by Chapman and Laird.[6] Since mesomeric stabilisation of the carbonium ion will be maximised when C-5, O, C-1, and C-2 all lie in one plane, steric features in the halide which favour the transformation of the chair conformation of the halide into a partly planar conformation of the ion will cause an increase in reaction rate. This idea was developed by Edward[38] in a discussion of the rates of hydrolysis of glycosides, and by others workers[4,16,39] in connexion with the reactivity of acetylglycosyl halides in S_N1 reactions. Exception[7] has been taken to the formulation of glycosyl carbonium ions in half-chair conformations on energetic grounds and on the grounds that " stabilisation of the carbonium ions produced by the ring-oxygen atom is very much smaller (judged by relative ease of solvolysis) than in simple open-chain compounds such as $MeO{\cdot}CH_2Cl$." However, this decreased reactivity is consistent with a half-chair transition state with raised free energy owing to steric interactions, or with a non-half-chair transition state with increased free energy owing to reduced mesomeric stabilisation. The results obtained in this investigation indicate that, in the transition state at least, some conformational change towards a half-chair form must have occurred.

Substitution of a methyl group at C-5 in tri-*O*-acetyl-α-D-xylopyranosyl bromide to give tri-*O*-acetyl-6-deoxy-α-D-glucosyl bromide causes an eight-fold decrease in rate. This is in the reverse direction to that expected for an electronic effect, but is easily explicable as due to a secondary steric effect on the ease of formation of a half-chair transition state. Transformation to a half-chair form results in a decrease in the dihedral angle between substituents on C-4 and C-5 [see (XV) ⟶ (XVI)] and an increase in non-bonded interactions, which will be larger the larger the 5-substituent. Hence, the free energy of a half-chair transition state for the 6-deoxyglycosyl bromide would be greater relative to the intial state than that of the xylosyl bromide. The further decrease in rates for the glucosyl and 6-deoxy-6-iodoglucosyl bromides may result from increased steric effects of this kind, or may be due to the $-I$ effects of the substituents at C-6.

The galactosyl (IV) and glucosyl bromides (I) and the arabinosyl (X) and xylosyl bromides (IX) are two pairs of compounds epimeric at C-4. Replacement of an equatorial acetoxyl group by one which is axial affects the rates in opposite ways, albeit by small amounts. In the initial states the free energies of the galactosyl and arabinosyl derivatives should be greater than those of the glucosyl and xylosyl bromides by about 0·7 kcal., this being the conformational free-energy difference between an axial and equatorial acetoxyl

[37] Lemieux, *Adv. Carbohydrate Chem.*, 1954, **9**, 1.
[38] Edward, *Chem. and Ind.*, 1955, 1102.
[39] Capon and Overend, *Adv. Carbohydrate Chem.*, 1960, **15**, 11.

TABLE 8.

A comparison of the solvolyses in 75% (w/w) aqueous acetone of 1,2-*cis*- and -*trans*-acetylglycosyl halides.

cis-Compound	Temp.	10^5k	*trans*-Compound	Temp.	10^5k	$\Delta\Delta G^{\ddagger}$ (cal. deg.$^{-1}$)
(I)	22·0°	0·66 *	(V)	22·0°	39·4 *	2·4
(X)	−18·3	0·16 *	(XI, XII)	−18·3	34·4	2·7
(II)	22·0	6·68	(VI)	22·0	149 *	1·7
(VII)	31·9	0·0254	(VIII)	31·9	240	5·5

* Extrapolated from rate constants at other temperatures.

group.[34a] Differences in the change in non-bonded interactions on going to a half-chair transition state for two such epimers results from (i) the increase in separation of axial substituents at C-2 and C-4, and (ii) the decrease in separation of substituents at C-4 and C-5. Differences resulting from (i) should favour the formation of a half-chair form from compounds with an axial acetoxyl group at C-4, and those resulting from (ii) should favour the formation of a half-chair form from compounds with an equatorial acetoxyl substituent at C-4. Hence it appears that (i) is more important in the reactions of the acetylated hexosyl bromides but that (ii) is predominant in the reactions of the acetylated pentosyl bromides. This would result if there were more twisting about the 4,5-bond in the transition state for the latter than for the former, which is not unreasonable.

Reactions with Lithium Phenyl Sulphide in n-Pentanol–Toluene.—All the reactions studied except that of the mannosyl bromide gave second-order rate coefficients independent of concentration within experimental error of ±5%. This kinetic form does not result from a salt-promoted ionisation of the type described by Winstein and his co-workers [40] since the rates of solvolyses in the presence of lithium perchlorate were much slower than the rates of reaction with lithium phenyl sulphide. The second-order kinetics therefore indicate an S_N2 mechanism.

The relative reaction rates of the 1,2-*cis*-bromides parallel very closely the rates of solvolysis in aqueous acetone, suggesting that the same steric factors are operative in both reactions. This is consistent with a transition state in which contributions of structure (XVII) are important.

The rate of disappearance of base from the reaction of tetra-*O*-acetyl-α-D-mannopyranosyl bromide in the presence of lithium phenyl sulphide was only slightly greater

TABLE 9.

The reaction of tetra-*O*-acetyl-α-D-mannopyranosyl bromide with lithium phenyl sulphide at 22·0°.[a]

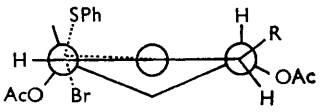
Time (min.)	Solvolysis (%) [b]	Time (min.)	Disappearance of base [c, d]	Disappearance of base after t = 3·8 min.[c, d]	Disappearance of thiophenol after t = 3·8 min.[c, d]
88	16·5	3·8	3·1		
140	24·5	121	32·4	28·3	12·0
171	30·5	188	43·8	40·7	17·0
206	35·1	239	51·0	48·9	17·5
279	43·2	292	56·4	53·3	18·5
426	58·6	360	60·3	60·3	19·6

[a] Solvent n-pentanol–toluene (19 : 1 v/v). [b] Initial concentrations: [Bromide] 1·64 × 10^{-2}M; [$LiClO_4$] 3·61 × 10^{-2}M. [c] Expressed as percentage of initial concentration of bromide. [d] Initial concentrations: [Bromide] 1·94 × 10^{-2}M; [LiSPh] 3·84 × 10^{-2}M.

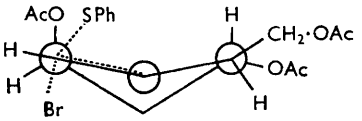
than the rate of formation of acid in the presence of an equal concentration of lithium perchlorate (see Table 9). Also, the disappearance of thiophenol, as measured by iodine titration, was slow compared with the disappearance of base. It is clear, therefore, that under our reaction conditions the acetylmannosyl bromide undergoes little or no reaction by a bimolecular mechanism. Rhind-Tutt and Vernon [7] also observed no bimolecular

[40] Winstein, Smith, and Darwish, *Tetrahedron Letters*, 1959, No. 16, 24.

reaction with tetra-*O*-methyl-α-D-mannopyranosyl chloride under similar conditions. The small decrease in the iodine titres suggests that some phenyl thiomannoside is formed, but attempts to isolate this compound failed. The lack of reactivity of the mannosyl bromide



(XVII)



(XVIII)

is undoubtedly due to a primary steric effect, the free energy of the transition state being raised by the non-bonded interaction between the axial-acetoxyl group at C-2 and the incoming thiophenate ion (see XVIII).

We thank Imperial Chemical Industries Limited and the D.S.I.R. for support.

CHEMISTRY DEPARTMENT, BIRKBECK COLLEGE,
MALET STREET, LONDON W.C.1.

[*Received, April 4th,* 1963.]