896. *Mechanisms of Reactions in the Sugar Series. Part II.* Nucleophilic Substitution in 2,3,4,6-Tetra-O-methylglycopyranosyl Chlorides.*

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The methanolysis of 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl chloride and 2,3,4,6-tetra-*O*-methyl-α-D-mannopyranosyl chloride has been shown to proceed by way of carbonium ion intermediates. The former compound gives an almost completely inverted product; the latter gives the two possible stereoisomers in roughly equal amounts. The glucopyranosyl compound reacts with thiophenoxide ions in propan-1-ol by a second-order process: the mannopyranosyl compound does not react by the S_N2 path. The mechanism of these reactions is discussed in detail.

In a study of the hydrolysis of glycosides (*a*) under acidic conditions [1] and (*b*) with enzyme catalysts [2] we required information about the relative ease and the stereochemical consequences of S_N1 and S_N2 processes involving $C_{(1)}$ of glycopyranoside rings. Nucleophilic displacements, particularly those involving methanolysis, have been much studied with fully acetylated or benzoylated pyranosyl halides.[3] However, much of the available information is unsuitable for our purpose since (i) the stereochemical and kinetic data do not, in general, relate to the same conditions, (ii) neighbouring-group effects involving 2-acetoxyl or -benzoyl groups largely determine the stereochemistry of the reactions studied, and (iii) the rôle of the S_N2 processes has not been completely elucidated.

The present work is concerned, therefore, with systems in which the complications due to migration and displacement of neighbouring groups are absent, so that the stereochemical and kinetic data relate to the same conditions; we have also been concerned to determine the conditions favouring the two possible mechanisms of substitution.

We chose 2,3,4,6-tetra-*O*-methylglycopyranosyl chlorides. They have not been previously well characterised, although they have served occasionally, without isolation, as intermediates in synthesis. The only relevant work is that by Irvine and Moodie [4] who prepared 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl chloride from 2,3,4,6-tetra-*O*-methyl-D-glucose and phosphorus pentachloride. The substance obtained was not, however, chemically pure and may also have contained some of the β-isomer.

Experimental

A. Materials.—Anhydrous methanol was made as described by Vogel.[5] Anhydrous propan-1-ol was prepared similarly; it was carefully fractionated and the fraction of b. p. 97·2°/760 mm. was collected.

* Part I, *J.*, 1955, 4419.

[1] Bunton, Lewis, Llewellyn, and Vernon, *J.*, 1955, 4419.
[2] Bunton, Lewis, Llewellyn, Tristram, and Vernon, *Nature*, 1954, **124**, 560.
[3] Cf. Haynes and Newth, *Adv. Carbohydrate Chem.*, 1955, **10**, 207; Lemieux, *ibid.*, 1954, **9**, 1.
[4] Irvine and Moodie, *J.*, 1908, **93**, 95.
[5] Vogel, "Practical Organic Chemistry," Longmans Green and Co., London, 1948, p. 175.

Anhydrous lithium chloride was prepared from a commercial sample. A solution in anhydrous methanol was evaporated to small bulk, and the resulting solid twice recrystallised from fresh anhydrous methanol. The final solid, dried at 160° for 4 hr., had 99·9% of the theoretical chloride content. Anhydrous lithium perchlorate and acetate were prepared similarly.

2,3,4,6-*Tetra*-O-*methyl*-D-*glucopyranosyl acetate*. 2,3,4,6-Tetra-*O*-methyl-D-glucose [6] (40 g.) and anhydrous sodium acetate (15 g.) in pure acetic anhydride (200 ml.) were refluxed for 2 hr. Ether (200 ml.) and toluene (200 ml.) were added and the mixture was shaken, then evaporated to small bulk under reduced pressure at 50°. Addition of toluene (200 ml.) and evaporation under reduced pressure were carried out twice more. Analysis at this stage showed that the product contained *ca.* 92% of the acetate. The remaining 8% appeared to be 2,3,4,6-tetra-*O*-methyl-D-glucose. Neither distillation nor chromatography appreciably separated the acetates from the unsubstituted sugar. Only by repeating the acetylation could the content of 2,3,4,6-tetra-*O*-methyl-D-glucose be reduced. The final product was distilled (at 104°/0·25 mm.) and was obtained as a colourless viscous liquid, n_D^{25} 1·4440 (Found: C, 51·6; H, 7·8; OAc, 20·5. Calc. for $C_{12}H_{22}O_7$: C, 51·8; H, 8·0; OAc, 21·1%). It did not crystallise and probably still contained 2—3% of 2,3,4,6-tetra-*O*-methyl-D-glucose. The infrared spectrum indicated that it was a mixture of the α- and the β-form. No separation of the isomers was achieved.

2,3,4,6-*Tetra*-O-*methyl*-α-D-*glucopyranosyl chloride*. 2,3,4,6-Tetra-*O*-methyl-D-glucopyranosyl acetate (12 g.) was dissolved in pure, dry chloroform (120 c.c.) at 0°. A solution of titanium tetrachloride (30 c.c.) in pure, dry chloroform (100 c.c.) was added dropwise. Throughout the addition the mixture was vigorously stirred and the temperature was not allowed to rise about 5°. When addition was complete the mixture was stirred for a further 2 hr. The chloroform solution was then poured into ice-water, separated, and washed quickly with cold water, cold sodium hydrogen carbonate solution, and cold water again, then dried as rapidly as possible (Na_2SO_4), and finally filtered. The chloroform was removed at reduced pressure at $\not>0°$. 2,3,4,6-Tetra-*O*-methyl-α-D-glucopyranosyl chloride remained as a colourless syrup. It could be distilled at 0·5 mm. but no improvement in purity was thus achieved and considerable decomposition occurred. The physical constants were: b. p. 109/0·5 mm., n_D^{25} 1·4595, $[\alpha]_D^{25}$ +205·3° (*c ca.* 1·0 in $CHCl_3$) (Found: C, 47·4; H, 7·5; Cl, 13·5. $C_{10}H_{19}ClO_5$ requires C, 47·1; H, 7·5; Cl, 13·9%). Chlorine and infrared analyses indicated that the compound was 97% pure. The impurity seemed to be 2,3,4,6-tetra-*O*-methyl-D-glucose. This arose partly because the starting material could not be completely freed from this substance and partly because some hydrolysis of the chloro-compound occurred during washing. Unless the washing procedure was carried out quickly and with very cold solutions the final product contained considerably more 2,3,4,6-tetra-*O*-methyl-D-glucose. The infrared spectrum showed a strong absorption at 11·63 μ. This is characteristic of the α-D-glucose configuration.[7] A peak at 11·45 μ, characteristic of the β-D-glucose configuration was not seen. The compound was stable for long periods in the absence of moisture.

2,3,4,6-*Tetra*-O-*methyl*-α-D-*mannopyranosyl chloride*. This compound was prepared from 2,3,4,6-tetra-*O*-methyl-D-mannose, by the same technique as described above, as a very pale yellow syrup, n_D^{21} 1·4605, $[\alpha]_D^{25}$ +99·2° (*c ca.* 1·0 in $CHCl_3$) (Found: Cl, 13·1%). It appeared, on the basis of the chlorine analysis, to be *ca.* 95% pure. The impurity was undoubtedly 2,3,4,6-tetra-*O*-methyl-D-mannose. It was less stable than the glucopyranosyl compound: after a few days *in vacuo* at 0° it began to darken and to evolve hydrogen chloride.

Methyl 2,3,4,6-*tetra*-O-*methyl*-α-D-*glucopyranoside*. This had b. p. 80—82°/0·1 mm., n_D^{25} 1·4420, $[\alpha]_D^{25}$ +158° (*c* 1·45 in H_2O).

Methyl 2,3,4,6-*tetra*-O-*methyl*-β-D-*glucopyranoside*. This was prepared from methyl β-D-glucopyranoside by methylation with dimethyl sulphate. The product contained a small amount of the α-isomer, and was purified as follows: a light petroleum solution (1 g. in 25 c.c.; b. p. 40—60°) was passed down a column of alumina (50 × 2 cm.), and then eluted with 2 : 1 ether–light petroleum. Fractions with high negative rotation gave, on evaporation, the crystalline product, m. p. 37°, $[\alpha]_D^{25}$ −17·5° (*c* 1·4 in MeOH).

Methyl 2,3,4,6-*tetra*-O-*methyl*-α-D-*mannopyranoside*. Prepared by methylation of methyl α-D-mannopyranoside, this had n_D^{25} 1·4470, $[\alpha]_D^{25}$ +71·0 (*c* 1·26 in MeOH).

S-*Phenyl* 2,3,4,6-*tetra*-O-*methyl*-β-D-*thioglucopyranoside*. A solution of thiophenol (24 c.c.)

[6] West and Holden, *Org. Synth.*, **20**, 98.

[7] Barker, Bourne, Stacey, and Whiffen, *J.*, 1954, 171.

in aqueous sodium hydroxide (10 g. in 50 c.c.) was added to a solution of pure acetobromoglucose (75 g.) in ether (500 c.c.). The mixture was stirred for 2 hr. at room temperature. Overnight the thioglucoside separated; recrystallised from ethanol–water, it had m. p. 117°, $[\alpha]_D^{25}$ −40·1° (*c* 1·0 in toluene) (Found: C, 54·6; H, 5·5. $C_{20}H_{24}O_9S$ requires C, 54·5; H, 5·5%). This tetra-*O*-acetyl compound (18 g.) was dissolved in acetone (100 c.c.) and placed in a flask equipped with an efficient stirrer and maintained at 50°. Dimethyl sulphate (250 c.c.) and 50% sodium hydroxide solution (200 c.c.) were added dropwise and at such rates that the mixture was always alkaline. After dilution with water the mixture was extracted with chloroform. Removal of the solvent gave the crystalline product which, recrystallised from ethanol–water, had m. p. 72°, $[\alpha]_D^{25}$ −43·1° (*c* 1·01 in PrOH) (Found: C, 57·5; H, 7·2. $C_{16}H_{24}O_5S$ requires C, 58·4; H, 7·3%).

B. Kinetic Measurements.—Runs were followed both by acid–base titration and polarimetrically. About 1 g. of halide was weighed into a standard flask which was then placed in a thermostat at the appropriate temperature. The solution was made up by solvent previously brought to the same temperature. Some of the solution (*ca.* 12 c.c.) was placed in a polarimeter tube (2 dm.) kept at constant temperature. The optical rotation was measured at appropriate intervals. Samples (5 c.c.) were also withdrawn, diluted with acetone, and cooled to −60°, and titrated with standard base (or acid if appropriate) in ethanol, with lacmoid as indicator. The annexed details of a run with 2,3,4,6-tetra-*O*-methyl-α-D-mannopyranosyl chloride (0·0255M) in methanol (25°) are typical:

Time (min.)	Titre (c.c. of 0·0044N-NaOEt)	10^2k_1 (min.$^{-1}$)	α	10^2k_1 (min.$^{-1}$)	Time (min.)	Titre (c.c. of 0·0044N-NaOEt)	10^2k_1 (min.$^{-1}$)	α	10^2k_1 (min.$^{-1}$)
2·75	—	—	1·200°	3·94	18·30	—	—	0·545°	3·94
3·85	3·82	3·91	—	—	24·35	17·65	4·00	—	—
5·85	5·86	3·92	—	—	25·67	—	—	0·337	4·04
7·40	—	—	0·962	3·91	30·95	19·77	4·03	—	—
8·35	7·93	3·94	—	—	33·90	—	—	0·200	3·86
9·60	—	—	0·859	3·97	36·70	21·27	3·97	—	—
10·74	9·88	4·04	—	—	39·80	—	—	0·120	3·80
12·59	—	—	0·735	4·00	42·60	22·57	3·86	—	—
16·65	13·93	4·06	—	—	∞	27·65		−0·230	

C. Products of Reaction in Methanol.—Infrared spectroscopy provides a rapid and accurate method for the analysis of mixtures of methyl 2,3,4,6-tetra-*O*-methyl-D-glucopyranosides since the α-isomer shows a strong characteristic absorption at 11·73 μ well removed from any absorption due to the β-isomer. Mixtures of known composition of the two isomers were placed in a cell (thickness 0·06 mm.) and the absorptions at 11·73 and 12·04 μ (where neither isomer absorbs strongly) measured on a Grubb–Parsons double-beam infrared spectrometer.

log (T_2/T_1) is proportional to C_α where T_2 and T_1 are the percent transmissions at 12·04 and 11·73 μ, respectively, and C_α is the proportion of the α-isomer in the mixture. The results were:

log (T_2/T_1)	0·945	0·908	0·675	0·593	0·464	0·336	0·216	0·178
C_α	1·00	0·93	0·61	0·50	0·36	0·18	0·073	0·0 *

* This point, which corresponds to the pure β-isomer, was determined with the liquid t-butyl 2,3,4,6-tetra-*O*-methyl-β-D-glucopyranoside since the pure methyl compound is a solid.

A simple plot shows the expected straight line relationship.

The procedure for any particular reaction mixture was as follows: methanol (*ca.* 50 c.c.) was removed at −5° under reduced pressure. Water (5 c.c.) was added and the aqueous solution was repeatedly extracted with small quantities of chloroform. The extracts were dried (Na_2SO_4) and the chloroform was then removed at −5° under reduced pressure. The resulting syrup was placed in the spectrometer cell and the proportion of the α-isomer determined from the calibration data given above. Results were reproducible within 1%.

The composition of the products of methanolysis were also determined from optical-rotation data. The following experiment is typical: A 0·027M-solution of 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl chloride in methanol was kept at 25° until reaction was complete. The rotation of the solution was then −6·48° (D line). From the specific rotations of the isomeric products (+158° and −17° for the α- and the β-isomer, respectively, in methanol) the proportion of

the α-isomer was found to be 0·06. Analysis of the same mixture by the infrared method gave the same value.

Mixtures of the isomeric methyl 2,3,4,6-tetra-*O*-methyl-D-mannopyranosides cannot be conveniently analysed by an infrared method. Consequently the composition of the products of methanolysis of 2,3,4,6-tetra-*O*-methyl-α-D-mannopyranosyl chloride was determined from optical-rotation data. The following experiment is typical: a 0·029M-solution of the chloro-compound in methanol was left at 25° until reaction was complete. The rotation of the solution was then −0·245° (D line). From the specific rotations of the isomeric products (+70° and −79° for the α- and the β-isomer,[8] respectively, in methanol) the proportion of the α-isomer is found to be 0·41.

Results.—Table 1 shows the results obtained with 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl chloride in methanol. The kinetic experiments were done with the concentration of chloro-compound in the range 0·03—0·05M and good first-order rate coefficients were obtained throughout any experiment. The proportion of α-product was determined under the conditions used for the kinetic measurements and usually on the same solutions. The superscripts O and I refer to determinations made by the optical rotation and the infrared method respectively.

TABLE 1. *Tetra-O-methyl-α-D-glucopyranosyl chloride in methanol.*

Temp.	Electrolyte X	[X]	10^2k_1 (min.$^{-1}$)	Proportion of α-form	Temp.	Electrolyte X	[X]	10^2k_1 (min.$^{-1}$)	Proportion of α-form
0°	—	—	0·202	0·07^O	25°	NaOMe	0·492	7·36	—
17·5	—	—	1·53	0·06^O, 0·06^I	,,	$LiClO_4$	0·357	5·00	0·06^I
18·3	—	—	1·70	—	,,	LiOAc	0·605	5·55	0·06^I
25·0	—	—	3·58	0·07^O, 0·06^I	,,	NaSEt	0·160	5·02	—
40·0	—	—	—	0·06^I	,,	NaSEt	0·554	10·10	—
25·0	NaOMe	0·040	4·00	0·07^O, 0·06^I	,,	NaSPh	0·268	8·22	—
,,	NaOMe	0·094	4·30	0·06^I	,,	NaSPh	0·69	16·7	—
,,	NaOMe	0·310	6·04	0·06^I					

TABLE 2. *Tetra-O-methyl-α-D-mannopyranosyl chloride in methanol.*

Temp.	Electrolyte X	[X]	10^2k_1 (min.$^{-1}$)	Proportion of α-form	Temp.	Electrolyte X	[X]	10^2k_1 (min.$^{-1}$)	Proportion of α-form
0°	—	—	1·77	—	25·0°	NaOMe	0·658	3·34	0·42
25·0	—	—	4·00	0·42	,,	NaOMe	1·040	2·60	0·43
34·5	—	—	11·50	0·41	,,	$LiClO_4$	0·438	6·96	0·42
25·0	NaOMe	0·231	4·00	0·41	,,	NaSPh	0·948	2·75	—

TABLE 3. *Kinetic results in propanol at 25°.*

	Electrolyte X	[X]	10^2k_1 (min.$^{-1}$)		Electrolyte X	[X]	10^2k_1 (min.$^{-1}$)
G-Cl	—	—	0·200	M-Cl	—	—	0·030
	LiSPh	0·0279	2·37 *		LiOPr	0·260	0·030
	,,	0·0390	3·11 *		LiSPh	0·260	0·046
	,,	0·0789	6·54 *				
	,,	0·126	10·20 *	* Initial first-order rate coefficients, with			
	,,	0·187	16·00 *	G-Cl = 0·03M.			

TABLE 4. *Methanolysis in the presence of lithium chloride at 25°.*

RCl	LiCl	10^2k_1 (min.$^{-1}$)	Proportion of α-form	RCl	LiCl	10^2k_1 (min.$^{-1}$)	Proportion of α-form
G-Cl	0·225	5·40	0·25^O	M-Cl	0·513	4·45	0·42
	0·466	6·57	0·31^O, 0·30^I		0·615	4·40	0·42
	0·942	7·15	0·35^O		1·000	4·40	0·43
	0·948	7·18	0·35^O				

The Arrhenius parameters for the methanolysis can be calculated from the data below to be E = 18·6 kcal. mole^{-1} and B = 13·3. The reactions in the presence of thioethoxide and thiophenoxide ions gave mixed products and these were not completely analysed.

Table 2 gives a similar set of results for 2,3,4,6-tetra-*O*-methyl-α-D-mannopyranosyl chloride in methanol. The Arrhenius parameters are E = 20·1 kcal. mole^{-1}, B = 12·3.

[8] Bott, Haworth, and Hirst, *J.*, 1930, 2653.

Results obtained in propanol at 25° are shown in Table 3, where G-Cl and M-Cl refer to 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl chloride and 2,3,4,6-tetra-*O*-methyl-α-D-mannopyranosyl chloride respectively.

The reaction between the glucosyl chloride and thiophenoxide ions is obviously of the second order since the solvolysis is comparatively slow and a plot of initial first-order rate coefficients against thiophenoxide concentration gives a good straight line. Consistently good second-order rate coefficients were obtained from each of the reactions, the following being an example. For a solution containing G-Cl (0·0292M) and lithium thiophenoxide (0·0279M) the values of the second-order rate coefficients (l. mole min.$^{-1}$, 25°) were:

Reaction (%)	19	23	25·1	28·5	34·6	39·0	44·2	55·5
k_2	1·31	1·31	1·27	1·27	1·20	1·12	1·10	1·15

From a reaction mixture initially containing G-Cl (0·03M) and lithium thiophenoxide (0·19M) there was obtained, after removal of solvent and recrystallisation from aqueous ethanol, *S*-phenyl 2,3,4,6-tetra-*O*-methyl-β-D-thioglucopyranoside, m. p. 72°, $[\alpha]_D^{25}$ −43·1° (*c* 1·0 in PrOH) (Found: C, 58·1; H, 7·5. $C_{15}H_{24}O_5S$ requires C, 58·4; H, 7·3%). The m. p. was unchanged on admixture with a specimen prepared as previously described. The yield was nearly quantitative. The rotation of the reaction mixture at complete reaction agreed, within the experimental error, with the value calculated on the assumption that *S*-phenyl tetra-*O*-methyl-β-D-thioglucopyranoside was the sole product.

Table 4 shows the results obtained in methanol (RCl *ca.* 0·05M) in the presence of varying amounts of added lithium chloride.

Discussion

The preparation of chemically pure 2,3,4,6-tetra-*O*-methylglycopyranosyl chlorides was difficult chiefly because all attempts at crystallisation failed and distillation, under the conditions tried by us, invariably resulted in some decomposition. Nevertheless the compounds derived from D-glucose and D-mannose were obtained sufficiently pure (97 and 95%, respectively) for kinetic studies and for investigations of the stereochemistry of their replacement reactions. The α-configuration was assigned to both compounds for the following reasons. (*a*) The specific rotations calculated by Hudson's isorotation rules,[9] +190° and +100°, agreed reasonably with the observed values, +200° and +99°, for the D-glucose and D-mannose compounds respectively. (*b*) For the D-glucose compound the infrared spectrum was completely diagnostic and showed no peak characteristic of the β-configuration.[7] For the D-mannose compound the spectrum was very similar to that observed with methyl 2,3,4,6-tetra-*O*-methyl-α-D-mannopyranoside. (*c*) The kinetic behaviour of the compounds under a variety of conditions indicated that, in each case, only one isomer was present.*

The methanolysis of both 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl chloride and 2,3,4,6-tetra-*O*-methyl-α-D-mannopyranosyl chloride has been found to follow uncomplicated first-order kinetics. In each experiment, the values of the first-order rate coefficients were constant and the rate coefficients calculated from optical data were the same as those calculated from simple analytical data. Addition of methoxide ions produced no large changes in rate with either compound. Both reactions, therefore, proceed through carbonium ion intermediates. Consistently, positive salt effects were observed on addition of lithium perchlorate or acetate.

The methanolysis of these compounds represents one extreme of mechanistic behaviour, *i.e.*, nucleophilic displacement *via* carbonium ions. To observe the alternative, synchronous

* Contrasting behaviour was shown by 2,3,4,6-tetra-*O*-methyl-α-D-galactopyranosyl chloride which was prepared by the method described above. The specific rotation was about half the expected value and the infrared spectrum indicated the presence of both α- and β-forms. The kinetic behaviour was consistent with this. For example, in propanol anomerisation occurred and produced a rapid initial change in optical rotation. A much slower change, due to propanolysis, followed. This system is being further investigated.

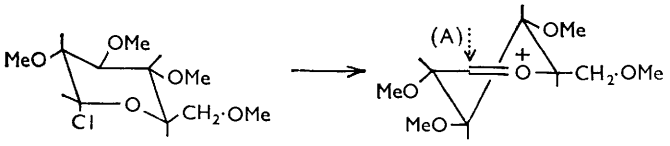
[9] " The Carbohydrates," ed. W. Pigman, Academic Press Inc., New York, 1957, p. 70.

mechanism (*i.e.*, S_N2 displacement) different conditions were chosen. A less ionising solvent (*i.e.*, propanol) was used and a powerful nucleophile (*e.g.*, EtS^- or PhS^-) was added. The results gave a clear-cut distinction between the two compounds. The reaction of 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl chloride with thiophenoxide ions was found to obey the second-order equation $v = k_2[\alpha\text{-G-Cl}][SPh^-]$, and the product, *S*-phenyl 2,3,4,6-tetra-*O*-methyl-β-D-thioglucopyranoside, was isolated in nearly quantitative yield. As required by the geometry of the S_N2 process, the reaction proceeds with complete inversion at position 1. With 2,3,4,6-tetra-*O*-methyl-α-D-mannopyranosyl chloride, on the other hand, addition of thiophenoxide ions produced no large increase in rate and the product, which was not analysed in detail, appeared to be largely a mixture of the propyl mannosides.

This difference in the behaviour of the two compounds is presumably steric in origin. The D-mannose compound has, in the C1 configuration, a *trans*-axial relation between the 2-methoxy-group and the chlorine atom. Models show that the formation of a transition state of the S_N2 type is impeded by steric compression between the incoming and the 2-methoxy-group. In the D-glucose compound, in which the 2-methoxy-group is equatorial and *cis* to the chlorine atom, this effect is absent and bimolecular substitution can take place given a sufficiently powerful nucleophile.

No example of uncomplicated bimolecular substitution at $C_{(1)}$ of a pyranosyl ring has previously been reported. Chapman and Laird,[10] in their study of the reactions of 2,3,4,6-tetra-*O*-acetylpyranosyl bromides with amines in acetone, found that substitution was accompanied by elimination and deacetylation. They were able to conclude, however, consistently with the present findings, that 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide is relatively resistant to bimolecular substitution and that this arises primarily from steric factors.

The most interesting aspect of the present work is concerned with the conformations of the intermediate carbonium ions. In methanol solvent the D-glucose and the D-mannose compound form carbonium ions at about the same rate, showing, consistently with findings of Winstein and his colleagues,[11] that assistance to ionisation from the 2-methoxy-group in the D-mannose compound is slight. Nevertheless, the carbonium ions cannot have the same structures since (*a*) the ratios in which the isomeric products are formed are widely different and (*b*) the kinetic effects of added nucleophiles are different. 2,3,4,6-Tetra-*O*-methyl-α-D-glucopyranosyl chloride gives, on methanolysis of dilute solutions, a mixture of isomers containing 94% of the product of inverted configuration, *i.e.*, methyl 2,3,4,6-tetra-*O*-methyl-β-D-glucopyranoside. Since addition of chloride ions decreases this figure, the true value (*i.e.*, that in the absence of effects due to recombination with kinetically



free chloride ions) must be even higher. The reaction proceeds, therefore, with nearly complete inversion at position 1. Addition of nucleophiles increases the reaction rate. Methoxide ions produce a small increase (in contrast to a decrease with the D-mannose compound); thiophenoxide ions produce a larger increase. Clearly, by changing conditions a continuous change from one extreme of mechanism (*i.e.*, the S_N1 type) to the other (*i.e.*, the S_N2 type) can be observed.[12,13]

There has been controversy about the mechanism which gives rise to the high yields

[10] Chapman and Laird, *Chem. and Ind.*, 1954, 20.
[11] Winstein, Grunwald, and Ingram, *J. Amer. Chem. Soc.*, 1948, **70**, 821.
[12] Gleave, Hughes, and Ingold, *J.*, 1935, 236.
[13] Winstein, Grunwald, and Jones, *J. Amer. Chem. Soc.*, 1951, **73**, 2700.

of products with inverted configurations in the nucleophilic displacement reactions of the 1,2-*cis*-acetohalogeno-sugars (*e.g.*, in the Koenigs–Knorr reaction). Isbell and Frush,[14] for example, suggested that the formation of methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside from tetra-*O*-acetyl-α-D-glucopyranosyl bromide in 94% yield occurs by an S_N2 process. This view has been challenged by Newth and Phillips.[15] It is clear from the present work that substitution at position 1 in α-D-glucose compounds *can* give nearly complete inversion by a mechanism which must, on kinetic grounds, be classified as S_N1. A similar conclusion has been reached by Lemieux and Huber [16] from their work on the 3,4,6-tri-*O*-acetyl-α- and -β-D-glucopyranosyl chlorides. These authors suggest that the intermediate carbonium ions have the half-chair conformation. For 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl chloride, the formulation would be as shown, attack in the direction (A) giving the inverted product. However, in the present case it appears from models that the half-chair conformation does not account for the very high proportion of inverted product. Nor can this explanation account for the tendency of the D-glucose compound to react by the S_N2 path.* A more rational explanation can be given in terms of the shielding effect of the departing anion.[18] It need only be assumed that reaction with the nucleophile occurs at a point corresponding to no very large extension of the carbon–chlorine bond. In the transition state, therefore, the α-configuration of the ion persists and is maintained by the close proximity of the departing anion. If, further, as seems reasonable although not formally required by the results of the present work, structures of some stability containing a chloride ion and a carbonium ion in the α-configuration are present in solution, then the reaction would be formulated as attack by a solvent molecule on an ion-pair.[19,20] In this way the high stereospecificity of the methanolysis and the tendency of the α-D-glucose system to pass over into reaction by the S_N2 path are explained.

The behaviour of 2,3,4,6-tetra-*O*-methyl-α-D-mannopyranosyl chloride is different. Methanolysis gives the isomeric products in roughly equal amounts and the addition of methoxide ion produces a slight decrease in rate.† Bimolecular attack by powerful nucleophiles is not observed even in propanol. The $C_{(1)}$ atom cannot, for steric reasons, be approached by the nucleophile along a direction reciprocal to the axial chlorine. When the chloride ion is removed to a large distance, *i.e.*, when the carbonium ion is kinetically free, the nucleophile can react along an equatorial direction, thus giving the product of inverted configuration, or along the direction of original axial chlorine, thus giving the product of retained configuration. The essential difference between the ions derived from the D-glucose and D-mannose compounds is then, on this view, that whereas the former can react as an ion-pair the latter must be effectively free before combination with the nucleophile.

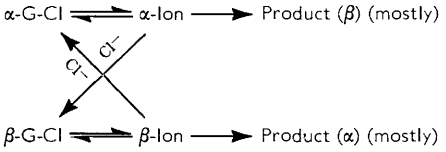
The effect of added chloride ions on the methanolysis of the two compounds is of interest in this respect. With 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl chloride addition of

* The existence of the half-chair conformation is also unlikely on energetic grounds since it involves a structure in which the whole positive charge is located on the oxygen atom. Obviously some overlap between the vacant orbital on the $C_{(1)}$ atom and the filled orbitals of the ring-oxygen atom must occur. However, it should be remembered that stabilisation of the carbonium ion produced by the ring-oxygen atom is very much smaller (judged by relative ease of solvolysis) than in simple open-chain compounds such as $MeO{\cdot}CH_2Cl$.[17]

† Similar cases of rate-retardation by lyate ions in carbonium ion reactions have been discussed by Ingold.[21]

[14] Isbell and Frush, *J. Res. Nat. Bur. Stand.*, 1949, **43**, 161.
[15] Newth and Phillips, *J.*, 1953, 2896, 2900, 2904.
[16] Lemieux and Huber, *Canad. J. Res.*, 1955, **33**, 128.
[17] Ballinger, de la Mare, Prest, and Kohnstam, *J.*, 1955, 3641.
[18] Hughes, *Quart. Rev.*, 1951, **5**, 244.
[19] Winstein, Clippinger, Fainberg, and Robinson, *Chem. and Ind.*, 1954, 644.
[20] Winstein and Robinson, *J. Amer. Chem. Soc.*, 1958, **80**, 169.
[21] Ingold, " Structure and Mechanism in Organic Chemistry," Bell and Sons Ltd., London, 1953, p. 366.

lithium chloride (0·2—1·0M) slightly increases the rate, as does addition of lithium perchlorate, but the proportion of α-isomer rises sharply. This can be accounted for by assuming that the carbonium ion (α-ion) reacts either with methanol to give methyl 2,3,4,6-tetra-*O*-methyl-β-D-glucopyranoside or with chloride ions to give 2,3,4,6-tetra-*O*-methyl-β-D-glucopyranosyl chloride. This compound (β-G-Cl) ionises to give an ion (β-ion) in which the β-configuration is preserved: reaction with solvent then gives largely methyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside and with chloride ion regenerates the starting material.



This scheme accounts for the observed kinetics only if the rate of methanolysis of [β-G-Cl] is much greater than that of its isomer. Unfortunately, attempts to prepare a pure specimen of this compound have so far failed. However, support for our interpretation comes from the work of Lemieux and Huber [16] on the isomeric tri-*O*-acetyl-D-glucopyranosyl chlorides. They found that the β-isomer undergoes acetolysis *ca.* 100 times faster than the α-isomer and that both reactions proceed with predominant inversion.

The products from the methanolysis of 2,3,4,6-tetra-*O*-methyl-α-*D*-mannopyranosyl chloride are not affected by addition of lithium chloride. In this case either ion recombination is unimportant or the ions derived from the two isomeric chloro-compounds have the same configuration. Investigation of this aspect of the problem is continuing.

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