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Action of Strong Acids on Acetylated Glycosides

XIII *. Studies on the Mechanism of the Anomerisation Reaction **

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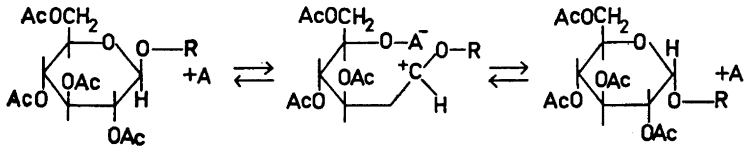
The anomerisation of some acetylated glycosides in sulphuric acid-acetic anhydride-acetic acid has been studied. Replacement of the 2-*O*-acetyl group of *iso*propyl-tetra-*O*-acetyl-β-D-glucopyranoside with a methyl group results in a higher rate of reaction. Thus participation of the 2-*O*-acetyl group does not seem to facilitate the reaction. For a 2-deoxy-glucopyranoside and a galactofuranoside the acetolysis was so fast that no anomerisation could be observed.

The anomerisation of acetylated glycosides, a reaction of considerable preparative interest, is known to be catalysed by strong acids in the generalised sense, *e.g.* titanium tetrachloride and boron trifluoride. The mechanisms of this and similar reactions have recently been discussed by Lemieux [1]. The anomerisation is known to be intramolecular [2,3] and two alternative mechanisms have been suggested. Lindberg [2] assumed that the acid (A) coordinates with



I II III

the ring oxygen in (I) and that the open chain intermediate (II) could reclose to give either of the anomeric glycosides (I or III) while Lemieux on the other hand has assumed that the acid coordinates with the oxygen of the aglycone group (IV). In this case the bond between $C_{(1)}$ and OR is further weakened by participation of the *O*-acetyl group at $C_{(2)}$ (V). When it is finally broken

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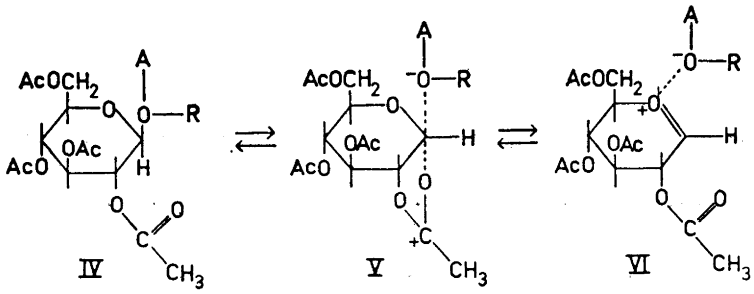


the two ions are not dissociated but exist as an ion pair, formulated as VI. This ion pair can then collapse, giving either the *α*-or the *β*-anomer.

The postulated participation of the neighbouring *O*-acetyl group could be studied by investigating the anomerisation of glycosides in which there is no such group. The anomerisation of *iso*propyl-tetra-*O*-acetyl-*β*-D-glucopyranoside in acetic anhydride-acetic acid (10:3), catalysed by sulphuric acid, is known to proceed 50—60 times faster than the anomerisation of penta-*O*-acetyl-*β*-D-glycopyranose. The corresponding glycoside of 2-*O*-methyl-D-glucose was prepared and its anomerisation studied under the same conditions. The velocity constant for the reaction was about twice that of the glucoside indicating that participation of the 2-*O*-acetyl group does not facilitate the reaction. The acetylated 2-*O*-methyl-*α*-D-glucopyranoside was isolated from the reaction mixture.

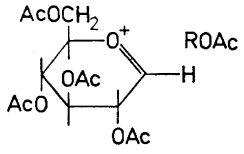
There is a remote possibility that the methoxyl group at $C_{(2)}$ might also participate. In a 2-deoxy-glycoside however, participation from a $C_{(2)}$ substituent is eliminated, and *iso*propyl-tri-*O*-acetyl-2-deoxy-*β*-D-glucopyranoside was therefore prepared and investigated in the acetic anhydride-acetic acid-sulphuric acid system. However, the acetolysis of this substance was too fast to allow a study of its anomerisation. A substance, m.p. 111—112°, $[\alpha]_D$ + 104° (chloroform) was isolated from the reaction mixture. It analysed for a tetra-acetate of 2-deoxy-D-glucose, and gave 2-deoxy-D-glucose on deacetylation. The same acetate was also obtained by treating tetra-*O*-acetyl-2-deoxy-*β*-D-glucopyranose with sulphuric acid in acetic anhydride-acetic acid. Overend *et al.*[4] have reported the preparation of two acetates of 2-deoxy-D-glucose. One, m.p. 91°, $[\alpha]_D$ + 12° (ethanol), claimed to be the *α*-acetate, was prepared by acetylation of 2-deoxy-D-glucose with acetic anhydride in pyridine. The other, m.p. 75—78°, $[\alpha]_D$ + 30° (ethanol), claimed to be the *β*-acetate, was prepared by acetylation with acetic anhydride and sodium acetate. On repeating these acetylations using the conditions described by Overend *et al.* the same substance m.p. 91—93°, $[\alpha]_D$ −2° (chloroform) was obtained with both acetylating agents. This substance is apparently tetra-*O*-acetyl-2-deoxy-*β*-D-glucopyranose while the compound with the high optical rotation, + 104°, is the corresponding *α*-acetate, and the product, m.p. 75—78°, reported by Overend *et al.*[4], is a mixture. On these assumptions,there is good agreement between the optical rotations of the anomeric acetates of D-glucose and 2-deoxy-D-glucose (Table 1) and between the methods of preparation.

Table 1. Optical rotations of acetylated pyranosidic D-glucose and 2-deoxy-D-glucose.

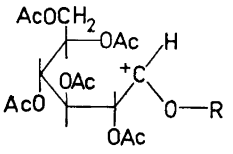
Parent sugar	Anomeric form	$[\alpha]_D$ in chloroform
D-Glucose	α	+ 101°
D-Glucose	β	+ 4°
2-Deoxy-D-glucose	α	+ 104° a) + 12° b)
2-Deoxy-D-glucose	β	− 2° a) + 30° b)

a) Present investigation.
b) Ref.[4], optical rotation in ethanol.

If $CH_3\overset{+}{C}O$ is the catalyst in the acetic anhydride-acetic acid-sulphuric acid system, which seems plausible (*cf. e.g.* Refs.[5,6]) then the mechanism proposed by Lemieux becomes less probable. When the acetyl ion is added to the glycosidic oxygen and the linkage between this oxygen and $C_{(1)}$ is broken, the product would be not an ion pair but an ion (VII) and an alkyl acetate, the recombination of which seems most improbable. If the acetyl ion adds to the



VII



VIII

ring oxygen, the opening of the ring to VIII and the re-formation of either of the forms is possible. As previously suggested [2,7] this theory also acounts for the formation of the open chain acetates that are known to be formed during these reactions. According to this mechanism a furanoside would give the same intermediate as a pyranoside, and it should therefore be possible to convert an acetylated furanoside into the pyranoside by treating it with sulphuric acid in acetic anhydride-acetic acid. When this experiment was done with ethyl-tetra-*O*-acetyl-β-D-galactofuranoside, acetolysis was very rapid and the furanosidic β-acetate of galactose was the only product isolated from the reaction mixture. In contradistinction to the behaviour of the galactopyranosides the β-form thus seems to be the most stable furanosidic acetate. Bearing in mind the ease with which 2-deoxyglycosides and furanosides are hydrolysed in acids, the fast acetolysis of these products is not surprising.

Acid-catalysed hydrolysis, the formation of glycosides and the interconversion of pyranosides and furanosides, recently discussed by Shafizadeh [8], involve protonation of the sugar and the rate determining step should involve the formation of a carbonium ion. These reactions are thus similar to the anomerisations of acetylated glycosides with acids in the generalised sense,

and in neither case has it been possible to decide between the cyclic or the acyclic route. The interconversion of pyranosides and furanosides however is best interpreted by a mechanism involving an acyclic intermediate though it may well be that for all these reactions both pathways are possible and that one or the other predominates, depending on the substances in question and the conditions of the reaction.

EXPERIMENTAL

All melting points are corrected. Concentrations were done under reduced pressure at a bath temperature of 50° or less.

Isopropyl-tri-O-*acetyl-2*-O-*methyl-β*-D-*glucopyranoside.* Tri-*O*-acetyl-2-*O*-methyl-α-D-glucopyranosyl bromide [9] (6.5 g) was dissolved in benzene (20 ml) and *iso*propyl alcohol (15 ml), silver carbonate (8 g) and Drierite (4 g) were added. The mixture was shaken for 3 h at room temperature and allowed to stand overnight. After filtration and concentration a syrup was obtained, which was dissolved in ether and extracted with water. The ether solution was concentrated and the residue was crystallised from aqueous ethanol. The crystals (2.2 g) melted at 64–69°. Further crystallisation raised the m. p. to 67–69°, $[\alpha]_D^{26}$ +1° (*c*, 2.0, chloroform). (Found C 53.2; H 7.2. Calc. for $C_{16}H_{26}O_9$: C 53.0; H 7.2.)

Isopropyl-tri-O-*benzoyl-2-deoxy-β*-D-*glucopyranoside.* Tri-*O*-benzoyl-2-deoxy-α-D-glucopyranosyl bromide [10] (10.4 g) was dissolved in toluene (100 ml) and *iso*propyl alcohol (75 ml), silver carbonate (9 g) and Drierite (10 g) were added. The mixture was shaken for 3 h and left overnight. After filtration the solution was concentrated and crystallised from ether-light petroleum yielding the pure substance (6.0 g), m. p. 107–108°. Further crystallisation raised the m. p. to 108–109°, $[\alpha]_D^{23}$ −57° (*c*, 2.4, chloroform). (Found: C 70.0; H 5.7. Calc. for $C_{30}H_{30}O_8$: C 69.5; H 5.8.)

Isopropyl-2-deoxy-β-D-*glucopyranoside.* The benzoylated glycoside (5.0 g) was debenzoylated with alkali in the usual way and the product (1.4 g) was crystallised twice from butanone. M. p. 120–122°, $[\alpha]_D^{20}$ −51° (*c*, 2.4, water). (Found: C 52.7; H 8.6. Calc. for $C_9H_{18}O_5$: C 52.4; H 8.8.)

Isopropyl-tri-O-*acetyl-2-deoxy-β*-D-*glucopyranoside.* The debenzoylated product (1.3 g) was treated with acetic anhydride and pyridine and then worked up in the usual way. The product (1.9 g), was crystallised from ether-light petroleum. M. p. 67–68°, $[\alpha]_D^{23}$ −37° (*c*, 2.7, chloroform). (Found: C 54.8; H 7.2. Calc. for $C_{15}H_{24}O_8$: C 54.2; H 7.2.)

Ethyl-tetra-O-*acetyl-β*-D-*galactofuranoside* was prepared by acetylation of ethyl-β-D-galactofuranoside [11] with acetic anhydride and pyridine. Its m. p. 55–57° and optical rotation, −52° in chloroform, agreed with the values previously reported [12].

Kinetic experiments. The measurements were made as previously described [2]. Velocity constants were calculated for first order reactions (time in minutes) and expressed in Brigg's logarithms. The values obtained are summarised in Table 2.

Table 2.

Acetylated sugar	M. H_2SO_4	$\alpha_{initial}$	$\alpha_{max.}$	10^3 k	$K_{rel.}$
*Iso*propyl-β-D-glucopyranoside	0.037	−1.24	5.79	52.2	52
β-D-Glucopyranose	0.037	−0.37	4.93	1.00	—
*Iso*propyl-2-*O*-methyl-β-D-glucopyranoside	0.037	−0.14	5.48	103	110
β-D-Glucopyranose	0.037	−0.37	4.93	0.94	—
*Iso*propyl-2-deoxy-glucopyranoside	0.018	−1.50	7.05	—	—
Ethyl-β-D-galactofuranoside	0.018	−1.27	0.58	—	—

Isopropyl-tri-O-*acetyl-2*-O-*methyl-α*-D-*glucopyranoside*. The reaction mixture from the anomerisation of *iso*propyl-tri-*O*-acetyl-2-*O*-methyl-*β*-D-glucopyranoside (0.50 g) yielded a product (0.20 g), m. p. 152—154°, $[\alpha]_D^{25}$ +151° (*c*, 1.0, chloroform) which was obviously *iso*propyl-tri-*O*-acetyl-2-*O*-methyl-α-D-glucopyranoside. (Found: C 53.4; H 7.1. Calc. for $C_{16}H_{26}O_9$: C 53.0, H 7.2.)

Tetra-O-*acetyl-2-deoxy-α*-D-*glucopyranose*. The reaction mixture from attempted anomerisation of *iso*propyl-tri-*O*-acetyl-2-deoxy-*β*-D-glucopyranoside (0.20 g) yielded a product (0.034 g), m. p. 111—112°, $[\alpha]_D^{24}$ +104° (*c*, 1.6, chloroform). (Found: C 50.6; H. 5.8 Calc. for $C_{14}H_{20}O_9$: C 50.6; H 6.1.)

Penta-O-*acetyl-β*-D-*galactofuranose*. The reaction mixture from attempted anomerisation of ethyl-tetra-*O*-acetyl-*β*-D-galactofuranoside (0.25 g) yielded penta-*O*-acetyl-*β*-D-galactofuranose (0.03 g), with m. p. 97—98°, $[\alpha]_D^{24}$ —40° (*c*, 2.3, chloroform) in good agreement with the values reported for that substance [13].

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