The Mechanism of the Anomerisation of the Methyl D-Glucopyranosides

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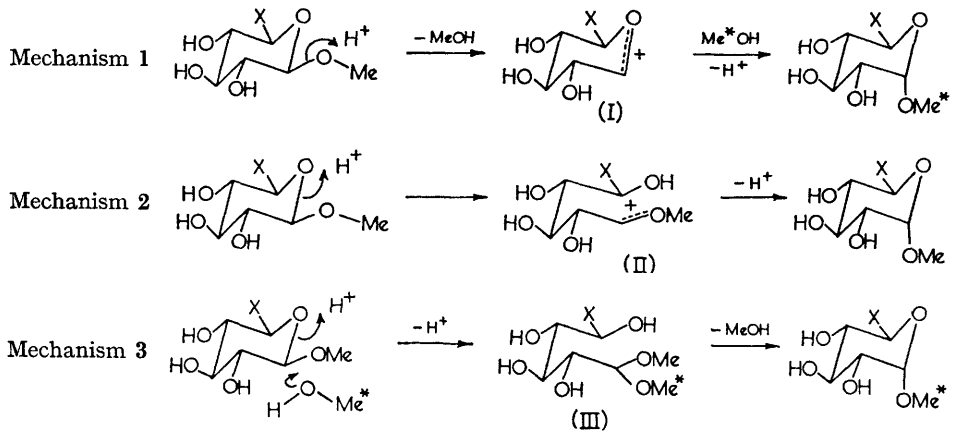
THE anomerisation of the methyl glucopyranosides which takes place readily in acidic methanol, is the final step in the Fischer glucoside synthesis.[1] The equilibrium mixture contains approximately 73% of the α- and 27% of the β-anomer.[2] There have been several kinetic investigations of this reaction[2,3] and of the anomerisation of other glycosides[4] but the mechanism has not been elucidated. Reasonable mechanisms involve a cyclic ion (I) (mechanism 1) and an acyclic ion (II) (mechanism 2) and these should be easily distinguishable by carrying out the reaction in labelled methanol. In addition there is the possibility that the glucose acetal (III) is an intermediate. If this were formed and

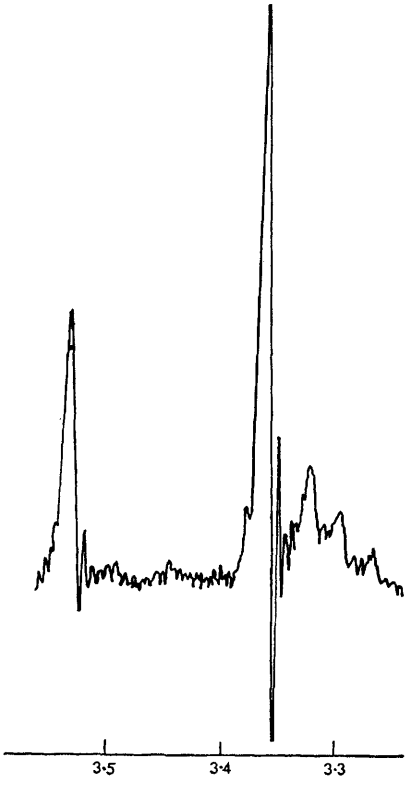


(X = CH_2·OH)

underwent ring closure stereospecifically with inversion (mechanism 3), the anomerisation in labelled methanol as solvent would proceed with complete incorporation of the label into the anomerised glucoside.

To distinguish between these possibilities, the anomerisation of methyl β-D-glucoside (0·5 M) in CD_3OD containing methanesulphonic acid (0·39 M) at 70° was followed by n.m.r. spectroscopy. The extent of anomerisation was determined by the areas under the signals of the anomeric protons at $\delta = 4{\cdot}70$ p.p.m. (α) and 4·21 p.p.m. (β). Since the signals of the methoxyl groups of the two glucosides at $\delta = 3{\cdot}41$ p.p.m. (α) and 3·53 p.p.m. (β) are well resolved from one another and from that of CH_3OH ($\delta = 3{\cdot}36$ p.p.m.) it is easy to see if α-glucoside formed on anomerisation of β-glucoside contains protonated methoxyl group. As an example of the results obtained the spectrum of the reaction mixture after 74 min. at 70° (45 ± 5% conversion into α-anomer) is given in the Figure. Any methyl α-D-glucoside with a proton-containing methoxyl group should show a signal at $\delta = 3{\cdot}41$ p.p.m. Its absence indicates that less than 10% of the methyl-α-D-glucoside had been formed with retention of the methoxyl group of the original β-glucoside. After 50 scans of this region of the spectrum using a computer of average transients no signal corresponding to methyl (CH_3) α-D-glucoside was discernable, thus reducing the above limit to 2%.

Similar results were obtained starting with methyl α-D-glucoside, although here the presence of signals of the ring protons which overlap with that of the methoxyl group of methyl β-D-glucoside do not allow the limits of the proportion of proton containing methoxyl group to be determined so accurately.



FIGURE

These results exclude mechanism 2 and a mechanism involving the acetal as an intermediate in which it is formed by nonstereospecific processes, but they are consistent with both mechanisms 1 and 3. The latter could be excluded however since it was found that when the acetal (III) was subjected to the reaction conditions the n.m.r. spectrum initially showed signals at $\delta = 4{\cdot}93$ p.p.m. and $\delta = 4{\cdot}78$ p.p.m. corresponding to the anomeric protons of methyl α- and β-D-glucofuranoside and that these only disappeared after several hours with concurrent appearance of the signals of the anomeric protons of the pyranosides. If the acetal (III) were an intermediate, on ring closure, it would therefore yield furanosides which are not converted rapidly into pyranosides under the reaction conditions. Since the former are not observed the acetal (III) cannot be an intermediate and mechanism 1 is therefore the most likely one.

This conclusion is of relevance to the question of the mechanism of the hydrolysis of these glucopyranosides, for which the cyclic and acyclic carbonium ions (I) and (II) have also been considered as intermediates,[5] since if their methanolyses proceed *via* the cyclic ion (I) it seems likely that their hydrolyses will do the same.

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