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Short Communications

The Oxidation of Glycosides

XVI.* The Acid Hydrolysis of Methyl β-D-gluco-hexodialdo-1,5-pyranoside and its 4-O-methyl Ether

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Acidic degradation of the 2-keto and 3-keto derivatives of methyl β-D-glucopyranoside (methyl β-D-*arabino*-hexopyranosidulose and methyl β-D-*ribo*-hexopyranosid-3-ulose) yielded a complex mixture.[1] The amounts of keto glycosides decreased with a rate, which was only slightly higher than the rate of hydrolysis of methyl β-D-glucopyranoside, but it is questionable whether the hydrolysis of the glycosidic linkage is the primary reaction.

In the present investigation the acidic hydrolysis of the 6-aldehydo derivatives of methyl β-D-glucopyranoside and its 4-O-methyl ether (methyl β-D-*gluco*-hexodialdo-1,5-pyranoside (I A) and methyl 4-O-methyl β-D-*gluco*-hexodialdo-1,5-pyranoside (I B), respectively) has been studied. The hydrolysis was carried out in 0.5 M sulphuric acid at different temperatures, and the reaction was followed polarimetrically and also by paper chromatography and electrophoresis. For comparison, the corresponding unoxidised methyl glucosides were also hydrolysed under the same conditions. The results are summarised in Table 1.

Table 1. Rate constants for the hydrolysis of methyl β-D-glucopyranoside and methyl β-D-*gluco*-hexodialdo-1,5-pyranoside and their 4-O-methyl ethers in 0.5 M sulphuric acid.

Compound	Rate constants × 10^6 sec^{-1}				Apparent activation energy (kcal mole^{-1})
	60°	70°	80°	90°	
Methyl β-D-glucopyranoside	—	6.38	25.3	95.9	33.6
Methyl 4-O-methyl-β-D-glucopyranoside	—	5.20	21.6	84.8	34.2
Methyl β-D-*gluco*-hexodialdo-1,5-pyranoside	—	136	411	1250	27
Methyl 4-O-methyl-β-D-*gluco*-hexodialdo-1,5-pyranoside	125	372	1080	—	25

It was found that the reaction products present when the "infinity" optical rotation was reached, were almost exclusively the expected dialdoses (III A and B), which were isolated from the slightly yellow solution in good yields and further characterised. D-*gluco*-Hexodialdose which was indistinguishable from an authentic sample on paper chromatography and electrophoresis, was reduced by borohydride to D-glucitol, characterised as the crystalline hexaacetate. Electrophoresis of 4-O-methyl-D-*gluco*-hexodialdose (III B) in sulphonated phenylboronic acid and subsequent detection with anisidine hydrogen chloride gave a spot with the same characteristic, intense violet colour as that given by D-*gluco*-hexodialdose. The product obtained by borohydride reduction was indistinguishable from 4-O-methyl-D-gluci-

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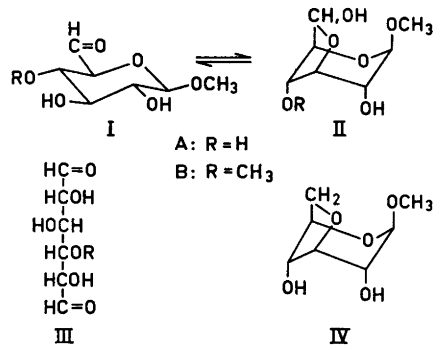
tol on paper chromatography and electrophoresis. In a separate experiment it was shown that D-*gluco*-hexodialdose, in 0.5 M sulphuric acid at 90°, was almost as stable as D-glucose. The final reading could not be compared with any theoretical rotation as the starting materials were syrups. The values for the rate constants were reasonably constant for the first half of the reaction.

It can be seen (Table 1) that the two aldehydo compounds were hydrolysed considerably faster than the corresponding unoxidised methyl glucosides (I A about 20 and I B about 70 times faster at 70°). A difference in the apparent activation energy between the two groups is also evident. A probable explanation for this unexpected effect is that the aldehydo compounds in aqueous solution exist to a large extent as cyclic hemiacetals formed by the interaction of the aldehydo group with the hydroxyl group at C-3. In order for this to be possible, the molecule must be in the *1C* conformation (II) in which all bulky substituents are in axial positions. As with 3,6-anhydro-glycosides, the dicyclic form (II) would be expected to be hydrolysed faster (conversion to carbonium ion in a half-chair conformation as suggested by Edward[2]) than the monocyclic form (I) having all bulky substituents equatorial. For compound II B, with the bulky methoxyl group at C-4, the rate of hydrolysis is higher than that of compound II A.



The rate constants and apparent activation energy of methyl β-D-glucopyranoside are similar to those previously [3] reported. The somewhat lower rate of hydrolysis of the 4-*O*-methyl glucoside is in accord with the postulate that the transformation to the half-chair conformation will be somewhat hindered by a substituent at C-4.[2]

Table 2. Paper electrophoresis in borate buffer (*a*) and in sulphonated phenylboronic acid (*b*).

Compound	M_G-values *a*	*b*
Methyl β-D-*gluco*-hexodialdo-1,5-pyranoside	0.62	0.59
Methyl 4-*O*-methyl-β-D-*gluco*-hexodialdo 1,5-pyranoside	0	0
D-*gluco*-Hexodialdose	1.15	6.1
4-*O*-Methyl-D-*gluco*-hexodialdose	0.78	0.52
Methyl β-D-glucopyranoside	0.18	0
Methyl 3,6-anhydro-β-D-glucopyranoside	0.76	0.69
1,2-*O*-Isopropylidene-α-D-glucofuranose	0.66	3.4
D-Glucitol	0.89	5.0
4-*O*-Methyl-D-glucitol	0.71	5.0

Paper electrophoresis in borate [4] (*a*) and sulphonated phenylboronic acid [5] (*b*) strongly supported the presence of the dicyclic structure (II A), and was also valuable for following the course of hydrolysis, and gave some indications about the structure of the dialdoses (Table 2). It can be seen that the mobility of methyl β-D-*gluco*-hexodialdo-1,5-pyranoside is only slightly lower than that of methyl 3,6-anhydro-β-D-glucopyranoside. As it is restricted to the *1C* conformation (IV), complex formation can only take place across the *cis*-1,3-diol system of the axially disposed hydroxyl groups at C-2 and C-4. The results strongly indicate a high proportion of the dicyclic form II A to be present. The M_G-values of the 3,6-anhydro-glucoside show the contribution to the mobility of a *cis*-1,3-grouping of a six-membered ring; previously suggested by Garegg and Lindberg [5] as possibly contributing to the movement of *epi*-inositol in buffer *b*.

The monocyclic form I A would be expected to have the same mobility as methyl β-D-glucopyranoside, which moves slowly in buffer *a* (complex formation across the 4,6-hydroxyls) and does not move in buffer *b*. The 4-*O*-methyl derivative of methyl β-D-*gluco*-hexodialdo-1,5-pyranoside cannot form complexes in any of the conformations.

The conformations of the dialdoses, however, are not restricted to a few forms. The rather low M_G-value of 4-*O*-methyl-D-*gluco*-hexo-dialdose (III B) in buffer *b* compared with the high values of D-glucitol and its 4-*O*-methyl ether, indicates a low proportion of the open form of III B and by analogy also of III A. The high M_G-values of D-*gluco*-hexodialdose (III A) in both buffers (compared with the monofuranosidic 1,2-*O*-isopropylidene-α-D-glucofuranose) indicates a high proportion of difuranosidic forms.

Marchessault and Rånby [6] proposed that the presence of carboxyl or other electronegative groups at C-5 in polysaccharides should give linkages which are more sensitive towards acid hydrolysis than ordinary linkages, and that this effect was inductive. Thus the glucosidic linkage to an uronic acid residue in a cellulose chain should be weakened. A recent investigation from this Department,[7] however, showed that such a linkage (in pseudocellobiouronic acid) was hydrolysed at the same rate as a "normal" linkage (in cellobiose). Recent results by Timell [3] also show that there is little evidence for the proposed effect.

The present results indicate the possibility that by the oxidation of some primary alcoholic groups in a polysaccharide (*i.e.* cellulose) to aldehyde groups, linkages are obtained, which are considerably more labile towards acid hydrolysis than ordinary linkages, and that the effect is conformational. This supported by the report that "weak linkages" disappeared on borohydride reduction.[6]

Experimental. The buffers used for electrophoresis (Whatman 3 MM papers) were 0.1 M borate, pH 10, and 0.1 M sulphonated phenylboronic acid, pH 6.5 (used at 40°). The mobilities in Table 2 are $M_{Glucose}$-values. The solvents for paper chromatography (Whatman No. 1 paper) were butan-1-ol-ethanol-water, 10:3:5, and ethyl acetate–acetic acid–water, 3:1:1. The spray reagents used were: silver nitrate-sodium hydroxide, periodate-benzidine and anisidine hydrogen chloride. With the latter spray, heating at 120° for 2 min and subsequent spraying with 5 % hydrogen chloride, methyl 3,6-anhydro-β-D-glucopyranoside appeared as a yellow spot after *ca.* one hour at room temperature. The kinetic experiments in 0.500 M sulphuric acid were carried out in a 10 cm jacketted polarimeter tube, through which water was circulated from a thermostat-bath. The temperature was measured directly in the tube and the optical rotation, at 436 mμ, was recorded by a Perkin Elmer 141 photoelectric polarimeter, 1 % solutions of methyl β-D-glucopyranoside and its 4-*O*-methyl ether and 0.25 % solutions of the aldehydo glycosides (these being less readily available) were used. The latter two compounds, methyl β-D-*gluco*-hexodialdo-1,5-pyranoside,[8] and methyl 4-*O*-methyl-β-D-*gluco*-hexodialdo-1,5-pyranoside,[9] were chromatographically and electrophoretically pure syrups. The solution was prepared at the reaction temperature and immediately transferred to the polarimeter tube. The rotation noted when thermal equilibrium was attained was used as the initial reading for the rate equation. The rate constants were calculated in the ordinary manner, assuming first order kinetics. A typical kinetic run is given in Table 3.

Table 3. Hydrolysis of methyl β-D-gluco-hexodialdo-1,5-pyranoside in 0.5 M sulphuric acid at 90°.

Time (min), α°, rate constant × 10^6 sec^{-1}; 0, −0.170,−; 3, −0.125, 1220; 5, −0.096, 1310; 7, −0.076, 1270; 10, −0.047, 1290; 13, −0.024, 1310; 15, −0.016, 1250; 17, −0.005, 1260; 20, +0.006, 1230; 25, +0.021, 1210; 30, +0.031, 1180; ∞(>60), +0.058,−. Mean value 1250.

Methyl β-D-*gluco*-hexodialdo-1,5-pyranoside (50 mg) was hydrolysed in 0.5 M sulphuric acid at 90° for 60 min after which time the optical rotation was almost constant and the product consisted almost exclusively of a component, which was indistinguishable from an equilibrium solution of D-*gluco*-hexodialdose.[10] After neutralisation with barium carbonate the dialdose was isolated (42 mg) by chromatography (butan-1-ol–ethanol–water, 10:3:5) on thick filter paper, and then reduced with an excess of borohydride in aqueous solution at pH 9.5. After deionisation, a product (34 mg), indistinguishable from D-glucitol was obtained, which gave a crystalline hexaacetate, m.p. and mixed m.p. 99–100° (corr.).

In a similar way 4-*O*-methyl-D-*gluco*-hexodialdose (39 mg) was isolated from methyl 4-*O*-methyl-β-D-*gluco*-hexodialdo-1,5-pyrano-

side (50 mg) in 0.5 M sulphuric acid at 90° for 40 min. It was characterised as described in the text. Further the pentaacetate obtained after borohydride reduction and acetylation was shown to be indistinguishable from an authentic sample of 4-*O*-methyl-D-glucitol pentaacetate by paper chromatography using dimethyl sulphoxide as stationary phase and light petroleum as irrigant.[11]

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Oxidation of Azide Ions by Hydrogen Peroxide

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During an analytical investigation the question arose whether hydrogen peroxide does react with azide ions at a pH about 9, or is only catalytically decomposed. Riegger [1] has shown that an aqueous solution of free hydrazoic acid is not oxidized by 3 % hydrogen peroxide solution. The work of Turrentine [2] is that usually quoted in connection with azide ions and hydrogen peroxide in basic solution. He could not detect any oxidation of azide ions, but his estimations of these were colorimetric (ferric azide) and he does not give any analytical results.

The question has been dealt with in the following way. Equal volumes of 0.1 M sodium azide and 0.1 M hydrogen peroxide solutions were mixed and the gas evolved collected over water. The solutions were made from deaerated water. The gas was analysed according to the method of Christiansen and Wulff.[3] Two different experiments carried out at room temperature (20–22°C) gave the results: 94.3 % oxygen and 5.7 % nitrogen, and 94.1 % oxygen and 5.9 % nitrogen.

Evidently most of the hydrogen peroxide is just catalytically decomposed, while a minor quantity oxidizes azide ions with formation of nitrogen gas.

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