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Alkaline Hydrolysis of Glycosidic Linkages

IV. The Action of Alkali on Some Glucopyranosides

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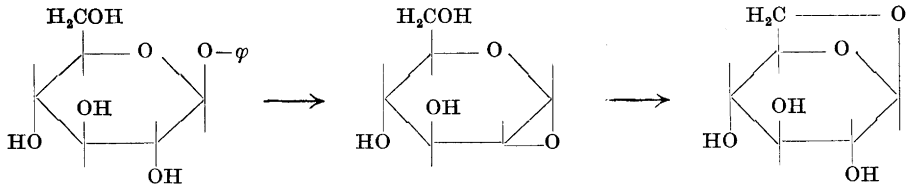
The alkaline hydrolysis of a number of glucopyranosides has been investigated. The results show that the hydrolysis may proceed by a number of different routes of comparable importance; one of those probably involves the intermediate formation of 1,2-anhydroglucose. Attempted transglycosidation of one β-glucoside and two β-xylosides by treatment with sodium methoxide in methanol at 170° yielded only traces of the corresponding methyl β-glycoside.

It is thought probable that the route by which 1,6-anhydro-D-glucose (III) is formed on the alkaline hydrolysis of phenyl β-D-glucoside (I) involves the intermediate formation of 1,2-anhydro-D-glucose (II). (For details of this and other reactions of glycosides with alkali, see Ref.[1])



I II III

Such a hypothesis offers an explanation of why the β-glucoside is much more sensitive to alkali than is the α-glucoside. The hydroxyl group at $C_{(2)}$ is in the *trans*-position to the phenoxyl group at $C_{(1)}$ and this makes it sterically possible for the first step in the reaction (I → II) to take place. McCloskey and Coleman [2] noted that phenyl 2,3-di-*O*-methyl-β-D-glucoside was quite stable to alkali. This may be explained in terms of the above mechanism. With different phenyl-β-glucosides, substituted in the *meta*- or *para*-position it was observed that the more acidic the phenol corresponding to the aglucone,

that is, the greater the electron attracting power of the phenoxyl group, the higher was the sensitivity to alkali [3].

It has been shown that alkyl glycosides are attacked by alkali only at higher temperatures [4]. Of the various methyl glycopyranosides studied, the "*trans*"-glycosides were always more reactive than were the "*cis*"-anomers, but this difference in reactivity was much less pronounced than in the case of the phenyl glycosides. The reactivity was also found to increase with the conformational instability of the most stable chair form of the glucoside (Part III) [5].

In the present paper the investigation of a number of glucopyranosides is reported. The method was the same as that previously used, that is treatment of the glucoside with 10 % aqueous sodium hydroxide at 170° and estimation of the percentage of unchanged starting material. The data for the various glucosides are summarised in Table 1.

Table 1. Rate and extent of hydrolysis of D-glucopyranosides with 10 % sodium hydroxide.

	Glucoside	Neutral residue, %			$10^3 \times k$ *
		6 h	24 h	48 h	
a	Methyl β-	98.2	88.3	73.9	2.6
b	Methyl 2-*O*-methyl β-	98.6	92.7	87.3	1.2
c	Methyl α-	96.4	93.8	89.6	1.0
d	Methyl 2-*O*-methyl α-	98.3	95.8	91.2	0.8
e	Ethyl β-	95.9	84.9	72.2	2.9
f	*Iso*propyl β-	93.8	80.1	61.6	3.9
g	*Tert.*-butyl β-	79.4	44.5	30.9	12.0
h	2-Methoxyethyl β-	95.6	90.6	81.3	1.7
i	2-Hydroxyethyl β-	89.7	73.6	58.0	4.5
j	2-Hydroxyethyl α-	97.0	90.1	81.0	1.8
k	2-Methoxyethyl α-	97.7	94.4	88.6	1.0

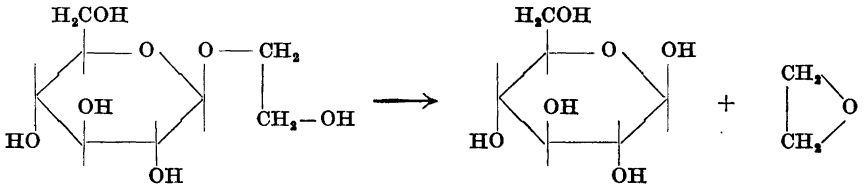
* Rate constants are expressed in Briggs logarithms and in hours.

If the hydroxyl at $C_{(2)}$ in methyl β-D-glucopyranoside (a in Table 1) is replaced by a methoxyl group (giving compound b), then the rate of alkaline hydrolysis is reduced by more than a half. In the α-series (compounds c and d) a similar substitution produced a much smaller effect. This observation, and the differences mentioned above between the reactivity of "*trans*"- and "*cis*"-glycosides, strongly support the view that, during the alkaline hydrolysis of *trans*-glycosides, an important route is that by way of the 1,2-anhydride. But as "*cis*"-glycosides and compound b show considerable reactivity, there must be other routes of importance.

The reaction velocities increase in the order methyl<ethyl<*iso*-propyl<*tert.*-butyl β-D-glucopyranoside (a,e,f,g resp.) and 2-methoxyethyl β-D-glucopyranoside (h) is even less reactive than is methyl-β-D-glucopyranoside. It is generally assumed that the electron attracting power decreases from methyl to *tert.*-butyl and therefore, by analogy with the phenyl glycosides, the reversed

order of reactivity would be expected. There are several competing mechanisms involved during alkaline hydrolysis and it is difficult to distinguish between the polar and the steric influence of alkyl groups. For these reasons, and without further studies, it is not at present possible to fully interpret the results.

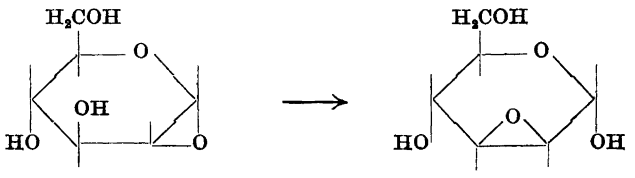
When cellobiitol was heated with alkali one of the main reaction products was 1,4-anhydro-D-glucitol [6]. This observation indicated the existence of another reaction route. The 1,4-anhydro-D-glucitol is probably formed by a nucleophilic attack on $C_{(4)}$ in the glucitol residue, either by the primary hydroxyl group at $C_{(1)}$ or by a hydroxyl group adjacent to that on $C_{(4)}$. In this last case there would be the intermediate formation of an ethylene oxide ring. Those possibilities have been studied by examining the alkaline hydrolysis of the α- and β-glucopyranosides both of ethylene glycol (monoglucosides, i and j) and of its monomethyl ether (compounds h and k). As expected, the glycol glucosides reacted much faster than did the glycol monomethyl ether glucosides. This indicated that in the hydrolysis of the former a major route involved the intermediate formation of an ethylene oxide ring (IV—V)



IV V

It is highly possible that this mechanism also operates under the conditions obtaining during sulphate and soda pulping and then leads to the hydrolysis of glycosidic linkages.

By treatment of suitable phenyl glycosides with alkali in the presence of an alcohol, transglycosidation reactions have been effected [1,7]. These reactions obviously proceed by way of the 1,2-anhydro sugars, and the possibility of transglycosidation reactions during the alkaline treatment of alkyl glycosides was inferred from previous investigations [6]. The formation of 1,6-anhydro sugars is of course an intramolecular transglycosidation. *Tert.*-butyl β-D-glucopyranoside was treated with sodium methoxide in methanol at 170° until about half of the starting material had been changed into acidic products. Only traces of methyl β-D-glucopyranoside and 1,6-anhydro-D-glucose could be chromatographically detected in the deionised reaction mixture. In similar



II VI

experiments with ethyl and *tert.*-butyl β-D-xyloside only traces of methyl β-D-xyloside were detected. These results are rather unexpected and the reason for the low yields of transglycosidation products is uncertain. One possible explanation is that the intermediate 1,2-anhydride (*e.g.* II) may preferably rearrange to a 2,3-anhydride (VII), which in turn is transformed into acidic products.

The rate constant for the hydrolysis of methyl β-D-glucopyranoside was in good agreement with that determined previously (Part III[5]) but the constant for methyl α-glucoside was found to be much higher than that recorded earlier. The amount of unchanged starting material in the hydrolysates of the various glucosides was previously determined gravimetrically. Those determinations suffered from the drawback that significant errors might be introduced due to imperfect drying or to the presence of small amounts of impurities praticularly when, as in case of methyl α-glucoside, only a small percentage of the material was hydrolysed. In the present work the quantitative determinations of the rate and degree of hydrolysis were made polarimetrically. This method would be expected to yield more reliable results especially for the α-glucosides with their high specific rotation. Some of the glycosides studied in this investigation had not been hitherto prepared. They, and the others, were prepared by conventional methods, outlined in the experimental part.

EXPERIMENTAL

All melting points are corrected. All distillations were carried out under reduced pressure. Unless otherwise stated, optical rotations were determined in aqueous solutions, $c \simeq 2$.

For chromatography, Whatman No. 1 paper and the following irrigants were used.

A. Ethyl acetate-acetic acid-water 3:1:1
B. Butanol-pyridine-water 6:2:3
C. Methyl ethyl ketone, saturated with water.

Those synthesis are described below which are of new glycosides or of glycosides prepared by methods other than those given in the literature.

2-Hydroxyethyl α-D-glucopyranoside. A mixture of glucose (57 g), glycol (500 g) and Amberlite IR 120 (H^+) (120 g) was heated on the steam bath with stirring for 72 h. The ion exchange resin was then filtered off and the solution was concentrated to a syrup, which was dissolved in 2 N aqueous sodium hydroxide (250 ml) and kept at 100° overnight. After deionisation and concentration a syrup was obtained which did not crystallise. Chromatographic investigation revealed that, amongst several compounds present, one was chromatographically indistinguishable from the expected β-glucoside. Part of the syrup was fractionated by carbon column chromatography, using aqueous ethanol as irrigant and the gradient elution technique. The main fraction did not crystallise but was chromatographically pure and both its R_F-value and its high specific rotation (98°) accorded with the high calculated approximate values for hydroxyethyl-α-glucoside. The β-anomer was obtained in lower yield from another fraction and had a rather higher mobility on electrophoresis in borate buffer.

A few months after the investigation of this substance was completed, it crystallised. Recrystallisation from ethyl acetate-ethanol yielded the pure substance, m. p. 99°—101°, $[\alpha]_D^{23}$ +139° (*c* 0.05, in water). (Found C 42.5; H 7.1. Calc. for $C_8H_{16}O_7$: C 42.9; H 7.2).

2-Methoxyethyl α-D-glucopyranoside was prepared in the same way as the above substance. It was purified by carbon column chromatography and gave a homogeneous syrup having $[\alpha]_D$ +94°.

Methyl 2-O-methyl-α-D-glucopyranoside. 2-*O*-methyl-D-glucose (6 g) prepared by the method of Lock and Richards [8], and *p*-toluene sulphonic acid (2.2 g) were dissolved in anhydrous methanol (20 ml) and the solution boiled overnight under reflux. The methanol was distilled off, the syrup dissolved in water, and acid removed by passing the solution through a column of IR 4B. The concentrated eluate was treated overnight with 2 N aqueous sodium hydroxide and after deionisation was again concentrated. The product was crystallised (1.9 g) from ethyl acetate. It had m. p. 146°–150° and $[\alpha]_D^{20}$ +155°.

Methyl 2-O-methyl-β-D-glucopyranoside. 2-*O*-Methyl-D-glucose (4 g), dissolved in a mixture of acetic anhydride (8 ml) and pyridine (25 ml), was heated on a steam bath for 30 min. The reaction mixture was taken to dryness and traces of pyridine were removed by co-distillation with acetic acid. The syrup was dissolved in a mixture of acetic acid (20 ml) and acetyl bromide (1.75 ml). This solution was cooled in ice-water and a solution of water (0.38 ml) in acetic acid (2 ml) was added over 30 min. The reaction mixture was kept at room temperature for 2 h. Then chloroform (25 ml) was added and the mixture, after being washed successively with ice-water, sodium hydrogen carbonate solution and water, was firstly dried over calcium chloride and calcium carbonate and then concentrated to a thick syrup (7.6 g). The syrup was dissolved in a mixture of anhydrous benzene (10 ml) and anhydrous methanol (20 ml). After the addition of anhydrous calcium sulphate (3 g) small portions of silver carbonate (9.5 g) were added and the flask was shaken for 90 min and then allowed to stand overnight. After filtration, the solution was concentrated, then treated with sodium hydroxide and the reaction mixture deionised as described above and concentrated to a syrup. The product, after crystallisation from ethyl acetate, had m. p. 95°–97°, $[\alpha]_D^{20}$ −38°. Yield 1.4 g.

Tert.-*butyl β-D-xyloside.* Tri-*O*-acetyl-α-D-xylopyranosylbromide (11.2 g) was dissolved in a mixture of benzene (15 ml) and *tert.*-butanol (15 ml). Silver carbonate (27 g) was added and the mixture was shaken overnight. After filtration and concentration the resultant syrup was dissolved in ethyl ether and the solution extracted with water. Crystalline 2,3,4-tri-*O*-acetyl-D-xylose, m. p. 136°–139°, $[\alpha]_D^{20}$ +45° (equilibr.) was isolated from the aqueous phase. The ether phase on concentration yielded a syrup which, on crystallisation from 50 % ethanol gave *tert.*-butyl 2,3,4-tri-*O*-acetyl-β-D-xylopyranoside (2.6 g). After recrystallisation the substance had m. p. 132°–134° and $[\alpha]_D^{25}$ −45° (*c*, 1.5 in chloroform). (Found C 54.4; H 7.2. Calc. for $C_{15}H_{24}O_8$: C 54.2; H 7.3.) The product on deacetylation yielded the free xyloside, which was crystallised from methyl ethyl ketone. M. p. 122°–123°, $[\alpha]_D^{25}$ −29°. (Found C 52.5; H 8.6. Calc. for $C_9H_{18}O_5$: C 52.4; H 8.8.)

Ethyl β-D-xylopyranoside was prepared by deacetylation of the corresponding acetate [9] and was crystallised from methyl ethyl ketone. M. p. 95°–96°, $[\alpha]_D^{25}$ −38°. (Found: C 47.0; H 7.6. Calc. for $C_7H_{14}O_5$: C 47.2; H 7.9.)

Alkaline hydrolysis. The samples (0.5 g) of glucoside were separately dissolved in 2.65 N sodium hydroxide (5 ml) and the solutions, in stainless steel bombs and under nitrogen, were heated at 170° in a thermostat oil bath for different times. When cold the solutions were deionised by filtration through a mixed bed of Amberlite IR 120 (H^+) and Dowex 2 (OH^-). The bed was thoroughly washed with water and the filtrate and washings were combined and concentrated. A chromatographic investigation, in the irrigants listed earlier, showed that the reaction mixtures contained unchanged starting material and, amongst the faint traces of other components, one which was chromatographically indistinguishable from 1,6-anhydro-D-glucose. The glycol glucosides yielded substantial amounts of ethylene glycol in addition. The recovery of unchanged starting material was determined polarimetrically.

A recovery of 98–100 % was achieved in control experiments in which the glucoside was treated as above but omitting the heating stage.

Transglycosidation reactions. Samples of the glycosides were separately dissolved in 2.65 N methanolic sodium methoxide and the solutions heated at 170° as previously. The reaction mixtures were then treated in the same way as those obtained by alkaline hydrolysis. The *tert.*-butyl β-glucoside, *tert.*-butyl β-xyloside and ethyl β-xyloside were heated for 48, 27 and 48 h, respectively, and the recoveries of unchanged starting materials were 43, 60 and 54 %, respectively. All products crystallised and, after recrystallisation, small

amounts of the corresponding methyl β-glycosides were chromatographically detected in the mother liquors. The glucoside gave in addition a compound chromatographically indistinguishable from 1,6-anhydro-D-glucose.

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REFERENCES

1. Ballou, C. E. *Advances in Carbohydrate Chem.* **9** (1954) 59.
2. Mc Closkey, C. M. and Coleman, G. H. *J. Org. Chem.* **10** (1945) 184.
3. Dyfverman, A. and Lindberg, B. *Acta Chem. Scand.* **4** (1950) 878.
4. Lindberg, B. *Svensk Papperstidn.* **59** (1956) 531.
5. Dryselius, E., Lindberg, B. and Theander, O. *Acta Chem. Scand.* **12** (1958) 340.
6. Dryselius, E., Lindberg, B. and Theander, O. *Acta Chem. Scand.* **11** (1957) 663.
7. Häggroth, S. and Lindberg, B. *Svensk Papperstidn.* **59** (1956) 870.
8. Lock, M. V. and Richards, G. N. *J. Chem. Soc.* **1955** 3024.
9. Asp, L. and Lindberg, B. *Acta Chem. Scand.* **4** (1950) 1447.

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