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Alkaline Hydrolysis of Glycosidic Linkages

III. An Investigation of some Methyl α- and β-Glycopyranosides

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The alkaline hydrolysis of the α- and β-glycopyranosides of glucose, galactose, mannose, xylose and arabinose has been investigated. The glycosides with the aglyconic group and the hydroxyl at $C_{(2)}$ in the *trans* position reacted much faster than the corresponding *cis* anomers, indicating that the former reacts *via* the 1,2-anhydrosugars. Within each group of glycosides, the reactivity increases with the conformational instability of the most stable chair form of the glycoside.

An investigation of the alkaline hydrolysis of cellobiitol and lactitol was described in Part II of this series and it was demonstrated that cleavage of the glycosidic linkage in these substances followed at least two different mechanisms. One of these was assumed to proceed *via* the 1,2-anhydrosugar to the 1,6-anhydrosugar, which was isolated from the reaction products in both cases. The other mechanism, resulting in the formation of 1,4-anhydrosorbitol, was assumed to involve a nucleophilic attack upon the $C_{(4)}$ carbon atom of the sorbitol unit, thus leading to a fission on the other side of the glycosidic oxygen atom.

The present paper describes an investigation of the methyl α- and β-glycopyranosides of D-glucose, D-galactose, D-mannose, D-xylose and L-arabinose. The glycosides were treated with 10 % aqueous sodium hydroxide at 170° for varying times, the solutions were then deionised and the yields of neutral material were determined. The neutral products consisted essentially of unchanged starting material with traces only of other components such as 1,6-anhydroglucopyranose, 1,6-anhydrogalactopyranose and unknown substances. The rate constants for the alkaline hydrolysis were calculated for a first order reaction, assuming that the concentration of alkali, which was present in considerable excess, was constant during the reaction. The values determined in this way are not very accurate, especially for the short reaction times when only a small amount of the material had reacted. Nevertheless they should give an idea of the relative reactivities of the glycosides investigated. The yields and rate constants are summarised in Table 1. It is evident from Table 1 that in all pairs of glycosides, the anomer with methoxyl and

Table 1. Alkaline hydrolysis of methyl glycopyranosides in 10 % sodium hydroxide at 170°.

Sugar	Configuration(1)	Relationship between OCH_3 and $C_{(2)}$-hydroxyl	Neutral residue, %			$k^* \times 10^{-3}$
			6 h	24 h	48 h	
D-Glucose	α	*cis*	99.1	98.5	97.5	0.25
»	β	*trans*	91.1	86.1	77.9	2.5
D-Galactose	α	*cis*	97.1	95.5	88.8	0.97
»	β	*trans*	94.3	72.9	46.5	5.7
D-Mannose	α	*trans*	95.6	85.0	73.8	2.8
»	β	*cis*	98.2	93.9	88.8	1.1
D-Xylose	α	*cis*	98.0	92.4	88.2	1.2
»	β	*trans*	94.6	70.6	54.9	5.8
L-Arabinose	α	*trans*	89.5	56.2	33.6	10
»	β	*cis*	95.6	94.1	90.6	1.0

* Rate constants expressed in Briggs logarithms and in hours.

$C_{(2)}$ hydroxyl group *trans*, react considerably faster than the *cis* anomer. The same is true for the alkaline degradation of the phenyl glycosides (summarised in Ref.[2]) and is explained by the ready formation of the corresponding 1,2-anhydrosugar. The latter is highly reactive and, in the hexose series, when the configuration is favourable, gives the 1,6-anhydrosugar in good yield. As previously demonstrated [1], these 1,6-anhydrosugars are more sensitive to alkaline hydrolysis than the alkyl glycosides and consequently only small amounts accumulate. The presence of 1,6-anhydroglucose and 1,6-anhydrogalactose after alkaline treatment of the methyl β-glucoside and β-galactoside was demonstrated by paper chromatography and further supports the assumption that the reaction *via* the 1,2-anhydride is of major importance for the alkaline hydrolysis of the "*trans*"glycosides.

The relative rates of acid (Ref.[3], p. 209) and alkaline hydrolysis for the "*cis*" and "*trans*" glycosides are given in Tables 2 and 3. For the acid hydrolysis, the relative rates of hydrolysis are explicable by the principles of conformational analysis, as shown by Edward [4] and Huber [5]. A similar analysis of the alkaline hydrolysis, which obviously proceeds by at least two different mechanisms, is not intended. However, some generalisations seem to be

Table 2. Relative rates for acid and alkaline hydrolysis of the *cis* methyl glycopyranosides.

Methyl glycopyranoside	Acid hydrolysis, k_{rel} *	Alkaline hydrolysis, k_{rel} *
α-D-glucoside	1.0	1.0
α-D-galactoside	5.2	3.9
β-D-mannoside	5.7	4.4
α-D-xyloside	4.5	4.8
β-L-arabinoside	9.0	4.0

* $k_{rel} = 1$ for methyl α-D-glucopyranoside.

Table 3. Relative rates for acid and alkaline hydrolysis of the *trans* methyl glycopyranosides.

Methyl glycopyranoside	Acid hydrolysis, k_{rel} *	Alkaline hydrolysis, k_{rel} *
β-D-glucoside	1.9	10
β-D-galactoside	9.3	23
α-D-mannoside	2.4	11
β-D-xyloside	9.0	23
α-L-arabinoside	13.1	40

* $k_{rel} = 1$ for methyl α-D-glucopyranoside.

valid. Firstly, as stated above, the reaction is considerably facilitated by a *trans* arrangement of the aglyconic group and the hydroxyl at $C_{(2)}$, and it is most probable that the hydrolysis of these glycosides involves the intermediate formation of an 1,2-anhydride. Secondly, there is a qualitative agreement between the rates of acid and alkaline hydrolysis within each group. The value for the alkaline hydrolysis of the β-L-arabinoside is somewhat low, but, with that exception, the agreement is remarkably good. This shows that the acid and alkaline hydrolysis are influenced in a similar way by steric factors in the glycosides, and that they both increase with the conformational instability of the most stable chair form of the glycoside (*cf.* Ref.[3], p. 209).

EXPERIMENTAL

The glycosides were prepared by conventional methods and purified until m. p. and specific rotation were in agreement with the accepted values and no impurities could be detected by paper chromatography.

The glycoside (1.000 g) was dissolved in 10 % sodium hydroxide (7 ml, 2.62 N). The solution, in a stainless steel autoclave, was heated at 170° in an oil thermostat for different times. When cold the solution was deionised by filtering through a column, containing a mixed bed of the ion exchange resins Amberlite IR 120 and Dowex 2, in their hydrogen and hydroxyl states, respectively. The column was carefully washed, the solution was concentrated to dryness under reduced pressure in a rotary evaporator and the residue was dried to constant weight over phosphorus pentoxide in a vacuum. The product was usually crystalline. It was investigated by paper chromatography in three different solvent systems. In most cases, only unchanged starting material was detected, but the products from the β-glucoside and β-galactoside also contained small amounts of material, which was chromatographically indistinguishable from the corresponding 1,6-anhydrosugars and traces of unknown components.

Methyl β-mannopyranoside was investigated in the form of its crystalline tetraacetate, in this case using a larger excess of 10 % sodium hydroxide to compensate for the acetic acid liberated.

When a glycoside was dissolved in the alkali and recovered without heating by the procedure above, the recovery was between 99 and 100 %.

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