ACTA CHEMICA SCANDINAVICA 20 (1966) 2363–2369

Acid Hydrolysis of the Mono-isopropyl Ethers of Methyl α- and β-D-Glucopyranoside

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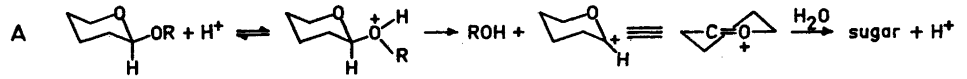
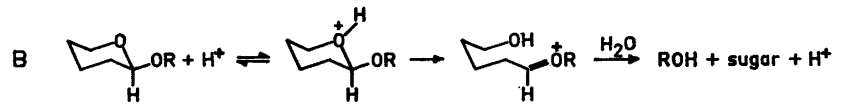
The eight mono-isopropyl ethers of methyl α- and β-D-glucopyranoside have been prepared and their acid hydrolysis investigated. All but the 6-ethers were hydrolysed at a higher rate than the unsubstituted glucosides, indicating that the inductive effect of the substituent is more important than the steric.

Differences in substituent effects in the α- and β-series indicate that the glucosides of the two series may be hydrolysed by different mechanisms.

The accepted mechanism for the hydrolysis of glycopyranosides (Edward,[1] Banks *et al.*[2], Overend *et al.*[3]) involves a rapid equilibrium-controlled protonation of either the glycosidic oxygen atom (A) or the ring oxygen atom (B), to give the corresponding conjugate acid, followed by heterolysis of the latter.





The overall rate of hydrolysis depends both upon the equilibrium of the protonation reaction and upon the rate of heterolysis of the protonated product. When the reaction follows route A, the cyclic ion formed on heterolysis will assume a half-chair conformation. Edward [1] concluded that the rate of hydrolysis should then depend upon the configuration at C-1 and upon steric interactions between the substituents at C-2, C-3, C-4, and C-5, which could either support or suppress the reaction. By such arguments he could rationalise the relative rates of hydrolysis of the methyl glycopyranosides.

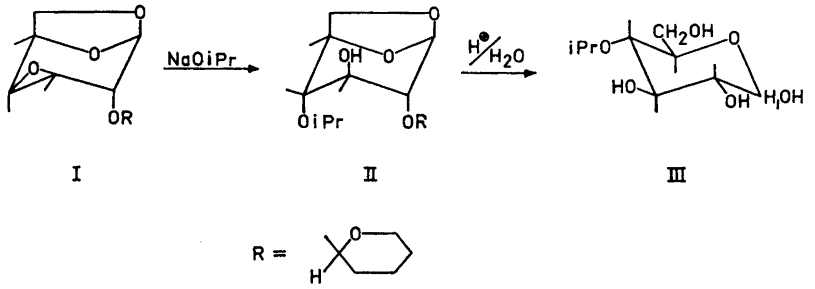
Inductive effects are also important and electron withdrawing groups are known to stabilise the glycosidic linkage; thus glycuronides are more stable than the corresponding glycosides to acid hydrolysis (Timell,[4] Capon [5]).

In polysaccharides, the rate of hydrolysis of a glycosidic linkage depends upon the substitution pattern. In homoglucans, therminal linkages are generally hydrolysed faster than central linkages and there are also differences between different types of central linkages.

In the present study, which is part of a program, aiming at the elucidation of how steric and inductive effects influence the hydrolysis of polysaccharides, the different hydroxyls in methyl α- and β-D-glucopyranoside have been etherified by the bulky isopropyl group and the acid hydrolysis of the eight monoethers have been investigated.

The 2- and 3-isopropyl ethers of methyl α- and β-D-glucopyranoside were prepared by partial isopropylation of methyl 4,6-*O*-benzylidene-α- and β-D-glucopyranoside, respectively, fractionation of the product by silicic acid chromatography and hydrolytic removal of the benzylidene groups. The glucosides were characterised by hydrolysis to the corresponding mono-*O*-isopropyl-D-glucoses, which had the expected mobilities relative to glucose ($M_G = 0$ and 1.35, respectively) on paper electrophoresis in germanate buffer.[6] The 6-*O*-isopropyl derivatives were prepared by Fisher synthesis with 6-*O*-isopropyl-D-glucose,[4] followed by fractionation of the product on a basic (OH^-) ion exchange resin.[7]

Attempted isopropylation of different methyl glucosides or glucose derivatives, in which all hydroxyl groups, but that in the 4-position, were protected, gave unsatisfactory yields, probably due to the low reactivity of this position and the tendency of the isopropyl iodide to undergo elimination. 4-*O*-Isopropyl-D-glucose was therefore prepared from 1,6:3,4-di-anhydro-β-D-galactopyranose.[8] Protection of the C-2 hydroxyl as the tetrahydropyranyl ether (I) allowed diaxial opening of the epoxide (II) with sodium isopropoxide in isopropanol and subsequent acid hydrolysis to yield the desired substance (III). This was



then subjected to a Fisher synthesis and the anomers separated by ion exchange chromatography.

Aqueous solutions, 0.05 M in glycoside and 0.5 M in sulphuric acid, were kept at different temperatures (70°, 80°, 93°) and hydrolyses were followed polarimetrically. All reactions were of the first order, the same end values were obtained within each anomeric pair and the plots of log *k versus* $1/T$, to obtain

Table 1.

Methyl α-D-glucopyranoside *O*-isopropylated in position	$k \times 10^6$ sec^{-1}			k rel * 80°	E kcal/mole	$\Delta S^{\ddagger}$ 80° **
	70.0°	80.0°	93.0°			
None	2.82	13.8	76.1	1.00	33.8	13.2
2	3.38	16.1	94.4	1.16	34.9	16.8
3	3.57	18.4	100.0	1.33	34.5	15.8
4	2.94	14.1	85.5	1.02	35.5	17.8
6	2.30	10.7	64.4	0.78	35.0	17.4

Table 2.

Methyl β-D-glucopyranoside *O*-isopropylated in position	$k \times 10^6$ sec^{-1}			k rel * 80°	E kcal/mole	$\Delta S^{\ddagger}$ 80° **
	70.0°	80.0°	93.0°			
None	6.01	25.4	141.0	1.00	33.9	14.0
2	10.6	50.6	276.5	1.99	33.7	15.7
3	10.4	46.6	248.0	1.84	33.0	13.5
4	6.12	28.2	162.1	1.11	34.5	16.7
6	4.26	21.4	129.1	0.84	35.4	18.6
2,3	13.2	63.0	364.0	2.48	34.6	17.5

* k rel refers to the parent unsubstituted glucoside.
** cal/degr. mole.

the energies and entropies of activation, (three points only) gave straight lines. The results of the kinetic studies are summarised in Tables 1 and 2.

The activation energies for the unsubstituted glucosides are in reasonably good agreement with values obtained by other investigators (Timell [4,9]). From the variations in these values, and also from the fact that the differences in energy and entropy of activation for the substances studied in the present investigation are rather small, it is obvious that an analysis of the observed effects in terms of these parameters would hardly be justified. Timell [4] has also studied the hydrolysis of methyl 6-*O*-isopropyl-β-D-glucopyranoside, and his values (E 34,8, $\Delta S^{\ddagger}$ 17.1 at 60°) are in good agreement with the present values.

The deviations found are probably, to a considerable extent, due to errors in the temperature control and determination. In the present study, all measurements at a given temperature were run in sequence, without adjustment of temperature between different runs. Thus, for example, the slightly higher reactivity observed for the methyl 4-*O*-isopropyl-α-D-glucoside over that of the unsubstituted glucoside is probably significant.

All the isopropyl ethers, except the 6-derivatives, are hydrolysed more readily than the parent glucosides. This somewhat unexpected result means that, in the 2-, 3-, and 4-positions, steric effects of the bulky substituents are

more than compensated by inductive effects. The isopropyl group is electron releasing as compared to hydrogen and should therefore increase the rate of hydrolysis. The lower rates of hydrolysis of central than of terminal linkages in homoglucans (*e.g.* cellulose and cellodextrins) may thus be essentially due to inductive effects.

The lower rate of hydrolysis of the 6-*O*-substituted glucosides could depend upon an increased steric or a decreased inductive effect of the substituent in this position and is probably a result of both. As a substituent in the 4-position interferes with the bulky C-5-substituent (CH_2OR) in the transition state (route A), an increased steric effect of a substituent in this position compared to the 2- and 3-positions should be expected. The inductive effect is also expected to be stronger in the 2- and 3- than in the 4-position. The combined effects should account for the minimal change in reactivity through etherification in the 4-position. The complicated balance between steric and inductive effects is illustrated by the results of Timell,[4] who studied the hydrolysis of some 6-*O*-substituted methyl β-D-glucopyranosides and found that the rates decrease in the series OH > OiPr > OEt > OMe.

If α- and β-glucosides were hydrolysed by the same mechanism, one might expect the relative effects of substituents to be the same in the two series. This is, however, not observed, the relative rates being 3>2>4>6 in the α- and 2>3>4>6 in the β-series. Lemieux and Morgan [10] recently studied the conformation of *N*-(tetra-*O*-acetyl-α-D-glucopyranosyl)-4-methylpyridinium bromide by NMR and found that it existed in the 1-C conformation, with the pyridinium group in an equatorial position and all the other bulky groups in axial positions. They ascribed this to the effect of a dipole-dipole interaction, analogous to the anomeric effect.[1,11] They also suggested that, due to a similar reverse anomeric effect, α-glucosides may be preferentially protonated at the ring oxygen atom and β-glucosides at the glucosidic oxygen atom. The present results also lend some support to the assumption that α- and β-glucosides are hydrolysed by different mechanisms. The effects of the substituents are, however, far too small to allow a rational interpretation of the results in terms of different reaction mechanisms and steric and inductive effects.

EXPERIMENTAL

All melting points are corrected. Evaporations were done under reduced pressure at a bath temperature below 40°.

Paper electrophoresis was performed on Whatman No. 3MM filter paper, using 0.05 M germanate buffer at pH 10.7.[6]

Thin layer chromatography was performed on Silica gel G (E. Merck, AG) and column chromatography on silicic acid (100 mesh, Mallinckrodt).

Isopropylation of methyl 4,6-*O*-benzylidene-α-D-glucoside

The title compound (15 g) [12] was dissolved in dimethyl formamide (250 ml), isopropyl iodide (80 ml) was added and the solution kept at room temperature and stirred vigorously. Silver oxide (35 g) was added over a period of 8 h and stirring continued for further 24 h. The silver salts were then removed by filtration and washed with dimethyl formamide (20 ml). Chloroform (300 ml) was added to the combined filtrates, which were then washed

with 6 % aqueous potassium cyanide (400 ml). The aqueous phase was extracted with chloroform (2 × 100 ml) and the combined chloroform solution was washed with water (2 × 100 ml), dried over calcium chloride and concentrated. The remaining syrup was fractionated on a silicic acid column (6.5 × 70 cm) using ethyl acetate—light petroleum, 1:1, as irrigant. The fractionation was followed by thin layer chromatography (same solvent system) and fractions containing pure components were combined, concentrated and crystallised from ethyl acetate—light petroleum. The components, having on thin layer chromatography the R_F-values 0.92, 0.76, and 0.60, respectively, were eluted in the following order:

Methyl 4,6-O-benzylidene-2,3-di-O-isopropyl-α-D-glucoside (0.55 g), m.p. 165.5—166°, $[\alpha]_{578}^{21}$ + 102° (*c*, 1.0, chloroform). (Found: C 65.6; H 8.52; O 26.1. $C_{20}H_{30}O_6$ requires: C 65.6; H 8.20; O 26.2).

Methyl 4,6-O-benzylidene-2-O-isopropyl-α-D-glucoside (4.0 g), m.p. 149—150°, $[\alpha]_{578}^{21}$ + 87° (*c*, 1.0, chloroform). (Found: C 62.9; H 7.34; O 29.8. $C_{17}H_{24}O_6$ requires: C 62.9; H 7.41; O 29.6).

Methyl 4,6-O-benzylidene-3-O-isopropyl-α-D-glucoside (4.2 g), m.p. 181.5—182°, $[\alpha]_{578}^{21}$ + 99° (*c*, 1.0, chloroform). (Found: C 63.0; H 7.46; O 29.8. $C_{17}H_{24}O_6$ requires: C 62.9; H 7.41; O 29.6).

Isopropylation of methyl 4,6-*O*-benzylidene-β-D-glucoside

Isopropylation of the title compound (18 g) [12] as well as fractionation and crystallisation of the products was performed in the same manner as reported above for the α-isomers. The compounds, having on thin layer chromatography the R_F-values 0.95, 0.88, and 0.76, respectively, were eluted in the following order:

Methyl 4,6-O-benzylidene-2,3-di-O-isopropyl-β-D-glucoside (1.2 g), m.p. 104—105°, $[\alpha]_{578}^{21}$ —67° (*c*, 1.0, chloroform). (Found: C 66.1; H 8.49; O 25.4. $C_{20}H_{30}O_6$ requires C 65.6; H 8.20; O 26.2).

Methyl 4,6-O-benzylidene-2-O-isopropyl-β-D-glucoside (5.0 g), m.p. 123—124°, $[\alpha]_{578}^{21}$ —54° (*c*, 1.0, chloroform). (Found: C 62.9; H 7.42; O 29.6. $C_{17}H_{24}O_6$ requires: C 62.9; H 7.41; O 29.6).

Methyl 4,6-O-benzylidene-3-O-isopropyl-β-D-glucoside (4.9 g), m.p. 125—126°, $[\alpha]_{578}^{21}$ —53° (*c*, 1.0, chloroform). (Found: C 62.8; H 7.55; O 29.5. $C_{17}H_{24}O_6$ requires: C 62.9; H 7.41; O 29.6).

Hydrolytic removal of benzylidene groups

The benzylidene derivative (1 part) was dissolved in acetone:water, 3:1, (10 parts). M aqueous hydrochloric acid (0.13 parts) was added and the solution refluxed for 4 h. The cooled solution was neutralised with Dowex 3 (free base), concentrated and the product was crystallised from suitable solvents. The following products were prepared by this procedure in almost quantitative yields.

Methyl 2-O-isopropyl-α-D-glucopyranoside, m.p. 141.5—142.5° (from ethyl acetate—light petroleum), $[\alpha]_{578}^{21}$ + 140° (*c*, 1.0, water). (Found: C 50.8; H 8.37; O 40.8. $C_{10}H_{20}O_6$ requires: C 51.0; H 8.46; O 40.5). The electrophoretic mobility of the free sugar, relative to glucose (M_G) was 0.0.

Methyl 3-O-isopropyl-α-D-glucopyranoside, amorphous $[\alpha]_{578}^{21}$ + 126° (*c*, 2.0, water). M_G of the free sugar 1.35.

Methyl 2,3-di-O-isopropyl-β-D-glucopyranoside, amorphous, $[\alpha]_{578}^{21}$ —30° (*c*, 2.0, water).

Methyl 2-O-isopropyl-β-D-glucopyranoside, m.p. 131—132° (from ethyl acetate—light petroleum $[\alpha]_{578}^{21}$ —29°. (Found: C 50.8; H 8.59; O 40.6. $C_{10}H_{20}O_6$ requires: C 51.0; H 8.46; O 40.5). M_G of the free sugar 0.0.

Methyl 3-O-isopropyl-β-D-glucopyranoside, m.p. 97—105°. Despite several recrystallisations from different solvents, the substance showed a wide m.p. range, $[\alpha]_{578}^{21}$ —22° (*c*, 1.0, water). (Found: C 50.9; H 8.30; O 40.8. $C_{10}H_{20}O_6$ requires: C 51.0; H 8.46; O 40.5). M_G of the free sugar 1.35.

Isopropylation of 1,2:5,6-di-O-isopropylidene-D-glucose. In order to obtain 3-*O*-isopropyl-D-glucose by an unambiguous route, the title compound was isopropylated as above. The product on acid hydrolysis yielded a mixture (about 1:1) of glucose and 3-*O*-isopropyl-D-glucose, as revealed by thin-layer chromatography and paper electrophoresis.

Methyl 4-*O*-isopropyl-α- and β-D-glucoside

Attempted isopropylation of methyl 2,3,6-tri-*O*-acetyl-β-D-glucopyranoside,[12] methyl 2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside,[13] and 2,3:5,6-di-*O*-isopropylidene-D-glucose dibenzylmercaptal [14] gave unsatisfactory yields of the desired products. Another route, involving alkaline opening of an epoxide, was therefore investigated.

1,6:3,4-Dianhydro-β-D-galactose. 1,6-Anhydro-β-D-glucopyranose was tosylated to give the ditosylate [15] and treated with sodium methoxide in methanol to give the 1,6:3,4-dianhydro-2-*O*-tosyl-β-D-galactose [16] (*cf.* also Ref. 17). This substance (6 g) was dissolved in 80 % aqueous methanol (500 ml) and treated with 4 % sodium amalgam (30 g) at room temperature for 2 h. The solution was then neutralised with carbon dioxide and concentrated. The solid residue was broken up and extracted with boiling chloroform (3 × 50 ml). Concentration of the chloroform solution yielded a syrup, which crystallised from ethyl acetate—light petroleum. The product (3.2 g) had m.p. 69—71° and $[\alpha]_{578}^{21}$ −81° (*c*, 1.0, water). Černý *et al.*[8] who prepared this substance by a different route, report m.p. 67—69° and $[\alpha]_D^{20}$ −80°.

4-O-Isopropyl-D-glucose. 1,6:3,4-Dianhydro-β-D-galactopyranose (4.0 g) and 37 % hydrochloric acid (12 drops) in dry dihydropyran (35 ml) was shaken overnight at room temperature, after which a clear solution was obtained. The solution was then diluted with acetone (60 ml), neutralised with silver oxide and concentrated to a yellow syrup (4.2 g). Crystallisation of this product, which would consist of a mixture of two isomers, was not attempted. This material was dissolved in 0.5 M sodium isopropoxide in isopropanol (120 ml) and refluxed for 18 h. Water (50 ml) was added and the solution filtered through a column of Dowex 50 (H^+) and concentrated. The residue was dissolved in 2 M aqueous hydrochloric acid (50 ml), kept at 100° for 3 h, neutralised with Dowex 3 (free base) and concentrated to a light-brown syrup (2.9 g). Paper electrophoresis revealed one main component (M_G 0.2) together with a small amount of glucose. 4-*O*-Methyl-D-glucose has $M_G = 0.3$.[6]

Fisher synthesis of methyl 4-O-isopropyl-D-glucosides. Crude 4-*O*-isopropyl-D-glucose (2.9 g) was dissolved in anhydrous methanol (70 ml) and Dowex 50 (H^+) (10 g), previously washed with anhydrous methanol, was added. The mixture was stirred under reflux overnight, filtered and concentrated. The resulting syrup was added to the top of a Dowex 1 (OH^-) column (6.5 × 85 cm),[7] which was irrigated with water. The separation was followed polarimetrically and the first products eluted, the α- and β-isopropyl-D-glucosides, were well separated from each other and from other components.

Methyl 4-O-isopropyl-α-D-glucopyranoside (1.3 g) amorphous, $[\alpha]_{578}^{21}$ + 145° (*c*, 2.0, water).

Methyl 4-O-isopropyl-β-D-glucopyranoside (0.98 g) crystallised after long standing and was recrystallised from ethyl acetate—light petroleum, m.p. 69—72°, $[\alpha]_{578}^{21}$ −19° (*c*, 1.0, water). (Found: C 50.3; H 8.52; O 40.3. $C_{10}H_{20}O_6$ requires: C 51.0; H 8.46; O 40.5).

Both glucosides were acetylated with acetic anhydride and sodium acetate. The anomeric acetates were readily separated by thin layer chromatography in ethyl ether—toluene (2:1) and thereby the purity of the parent compounds could be confirmed.

The *methyl 2,3,6-tri-O-acetyl-4-O-isopropyl-β-D-glucoside* crystallised from ethyl acetate—light petroleum, m.p. 111—112°, $[\alpha]_{578}^{21}$ −24° (*c*, 1.0, chloroform). (Found: C 52.9; H 7.06; O 40.1. $C_{16}H_{26}O_9$ requires: C 53.0; H 7.18; O 40.0).

1,6-Anhydro-4-O-isopropyl-2-O-tosyl-β-D-glucopyranose. Carlson [17] has recently reported the synthesis of 1,6-anhydro-4-*O*-methyl-2-*O*-tosyl-β-D-glucopyranose by acidic opening of 1,6:3,4-di-anhydro-2-*O*-tosyl-β-D-galactopyranose in methanol, and a similar reaction, in isopropanol, was now attempted. The di-anhydride (2.5 g) and dry Dowex 50 (H^+) (30 g) in isopropanol (150 ml) was stirred under reflux for 18 h and filtered. Water (100 ml) was added, and the product was extracted with benzene (2 × 100 ml). Concentration of the benzene solution yielded the desired substance (1.0 g) which was crystallised from benzene. This material, m.p. 105—106°, $[\alpha]_{578}^{21}$ −38° (*c*, 2.0, chloroform), was not pure

as revealed by elemental analysis, but on detosylation and hydrolysis, yielded reasonably pure 4-*O*-isopropyl-D-glucose (0.3 g). The yield was, however, considerably lower than that obtained by the somewhat longer route described above.

Fisher synthesis of methyl 6-*O*-isopropyl-D-glucosides

6-*O*-Isopropyl-D-glucose (3.1 g), prepared according to Timell,[4] was subjected to a Fisher synthesis and subsequent separation of the products on an ion exchange column as described for the 4-*O*-isopropyl-D-glucose. The 6-*O*-isopropyl-α-glucopyranoside was eluted first, followed by the β-isomer.

Methyl 6-O-isopropyl-α-D-glucopyranoside (1.58 g), m.p. 76.5—77.5° (from ethanol-water), $[\alpha]_{578}^{21}$ + 130° (*c*, 1.0, water). (Found: C 50.9; H 8.30; O 40.9. $C_{10}H_{20}O_6$ requires: C 51.0; H 8.46; O 40.5).

Methyl 6-O-isopropyl-β-D-glucopyranoside (1.0 g), m.p. 84—85° (from ethyl acetate—light petroleum), $[\alpha]_{578}^{21}$ −24° (*c*, 1.0, water). Timell [4] reports 83.5—84°, $[\alpha]_D^{20}$ −24.1°.

Kinetic determinations

The hydrolyses were carried out in a jacketed polarimeter tube, 10 cm, through which water from a thermostat was circulated. The temperature was determined in the tube with a precision thermometer. All measurements at a given temperature were run in sequence, before the thermostat was readjusted. Optical rotations were determined with a Perkin-Elmer Model 141 photoelectrical polarimeter, connected to a recorder. No reversion products were observed on chromatographic examination of the hydrolysates (see Overend *et al.*[3]). For each anomeric pair of glucosides, the same final value for the specific optical rotation was obtained.

For all the substances studied, strict first order kinetics were observed and the plot of log *k versus* $1/T$ gave straight lines.

Acknowledgement. The authors thank Dr. K. N. Slessor for valuable discussions.

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Received June 8, 1966.