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Partial Methylation Studies on Methyl β-D-Glucopyranoside and some Derivatives

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The partial methylation of methyl β-D-glucopyranoside, unsubstituted and substituted in the 4-*O*-position with benzyl or tetrahydropyranyl (two stereoisomers) has been studied. The results are discussed in connection with the similar partial methylation of cellulose.

In previous communications from this Department, summarised in Ref.[1], studies on the distribution of substituents in some partially etherified celluloses have been reported. The differences in reactivity observed at the various positions (2, 3, 6) of a glucose residue in a cellulose molecule could be due to electronic and steric effects, the latter either from substituents in the same glucose residue or from adjacent glucose residues. Effects from other cellulose chains in heterogeneous reactions seem to be negligible, as the observed relative reactivities at the various positions were about the same in homogeneous and heterogeneous reactions[2]. In order to throw some light upon these questions the partial methylations of cellulose,[2] amylose,[3] xylan,[4] methyl 4,6-*O*-benzylidene-β-D-glucoside[3] and methyl 4,6-*O*-ethylidene-β-D-glucoside[3] were studied (Table 1).

The suggestion that the low reactivity at the 3-position in cellulose[5] was due to steric hindrance from the —CH_2OH group at C-5 was ruled out when it was observed that esparto xylan also showed this low reactivity at C-3. It has been proposed[6] also that a strong hydrogen bond between the C-3

Table 1. Relative reactivities, at C-2, C-3 and C-6, of cellulose and some model substances towards methylation with methyl sulphate and sodium hydroxide.

	k_2	k_3	k_6	Ref.
Cellulose	3.5	1	2	2
Amylose	6	1	7	3
Xylan	2.5	1	—	4
Methyl 4,6-*O*-benzylidene-β-D-glucoside	1.3	1	—	3
Methyl 4,6-*O*-ethylidene-β-D-glucoside	1	1	—	3

hydroxyl and the ring oxygen in the contiguous glucose residue could contribute to this effect. This could be studied by the methylation of suitable model substances — the two acetals in Table 1 are probably not good models for the glucose residues in cellulose.

In the present communication, the synthesis of methyl 4-*O*-benzyl-β-D-glucoside and the partial methylation of this substance and of methyl 4-*O*-(2-tetrahydropyranyl)-β-D-glucoside (two stereoisomers)[7] and methyl β-D-glucopyranoside with dimethyl sulphate in sodium hydroxide is reported.

The benzyl derivative was prepared by benzylation of methyl 2,3,6-tri-*O*-acetyl-β-D-glucopyranoside, using the method described by Croon and Lindberg[8]. The product was then deacetylated and fractionated on a cellulose column. In this substance, as in the tetrahydropyranyl derivatives, the sub-

Table 2. Composition of the hydrolysate of partially methylated methyl 4-*O*-benzyl-β-D-glucoside ($k_2:k_3:k_6 = 1.9:1:2.8$).

Substance*	D.S. 0.72			D.S. 0.81		
	Exptl.	Calc.^{I}	Calc.^{II}**	Exptl.	Calc.^{I}	Calc.^{II}**
S_0	44.3	44.9	44.9	40.2	40.3	40.3
S_2	14.9	13.1	13.9	13.4	12.7	14.1
S_3	5.5	6.9	6.9	6.0	7.0	7.0
S_6	20.7	21.4	21.4	22.0	22.9	22.9
S_{23}	3.1	3.0	2.1	4.7	3.9	2.5
S_{26}	7.1	6.3	6.7	7.3	7.2	8.0
S_{36}	2.8	3.2	3.2	4.3	4.0	4.0
S_{236}	1.6	1.4	1.0	2.2	2.2	1.4

* S_0 = glucose; S_2 = 2-*O*-methyl-glucose, *etc.*
** Calc.^{II} without allowing for adjacent group effects at C-2 and C-3.

Table 3. Composition of the hydrolysates of the partially methylated isomers of methyl 4-*O*-(2-tetrahydropyranyl)-β-D-glucoside.

	(+)-isomer($k_2:k_3:k_6 = 3.3:1:3.9$)						(−)-isomer($k_2:k_3:k_6 = 3.1:1:3.7$)		
Substance	D.S. 0.62			D.S. 0.98			D.S. 1.15		
	Exptl.	Calc.^{I}	Calc.^{II}*	Exptl.	Calc.^{I}	Calc.^{II}*	Exptl.	Calc.^{I}	Calc.^{II}*
S_0	48.1	47.7	47.7	31.2	31.6	31.6	22.7	22.8	22.8
S_2	18.6	16.1	16.7	17.2	17.2	18.5	17.6	16.6	18.3
S_3	1.9	4.5	4.5	2.9	4.8	4.8	3.2	4.7	4.8
S_6	21.9	20.0	20.0	23.4	23.2	23.2	24.3	23.1	23.1
S_{23}	2.3	2.2	1.6	5.6	4.0	2.8	4.0	5.6	3.8
S_{26}	4.6	6.7	7.0	10.8	12.6	13.6	17.0	16.8	18.5
S_{36}	1.8	1.9	1.9	4.9	3.5	3.5	5.7	4.8	4.8
S_{236}	0.8	0.9	0.7	4.1	3.0	2.1	5.7	5.6	3.9

* Calc.^{II} without allowing for adjacent group effects at C-2 and C-3.

stituent in 4-position is easily removed under mild conditions by catalytic hydrogenation and acid hydrolysis, respectively. Partial methylation, removal of the 4-*O*-substituent and acid hydrolysis produces the same mixture of glucose and methyl ethers as was obtained from methyl cellulose. The method used by Croon and Lindberg [9] for the fractionation of this mixture was slightly modified, the mono-*O*-methyl glucoses being separated by electrophoresis in germanate buffer [10].

The methylations were performed with methyl sulphate in 18.9 % sodium hydroxide. The recovery of glucose and methylated glucoses was not quantitative, the average losses being 20—30 %. A careful check of each of the stages in the procedure showed that no one of the individual stages involved significant losses but that an accumulation of losses in the complete working-up operation resulted in this somewhat low recovery. There is no indication, however, that one or some of the components should be selectively removed during this procedure but rather that their relative proportions were uneffected.

The distributions of substituents calculated assuming the relative rate constants which gave the best agreement with the observed values, together with the experimental distributions, are given in Tables 2 and 3. The calculations were performed with and without the special assumption that the rate constant for substitution at C-3 is doubled when the position at C-2 is substituted. The agreement is better with this assumption, as was previously observed also for cellulose and other substances [1].

The complete analyses of partially methylated methyl β-D-glucopyranoside should involve the separation and determination of 16 components. Conditions were therefore chosen whereby the proportion of di- tri- and tetra-*O*-methyl glucoses were low. The monomethyl ether fraction was isolated by chromatography on thick filter paper and was quantitatively separated by paper electrophoreses in germanate buffer [10]. The relative rates at the various positions were then estimated from the proportions of these isomers. The results from the methylations of the model substances are summarised in Table 4.

As was observed for cellulose, all substances have lower reactivities in the 3- than in the 2- or 6-position. It therefore seems unnecessary to ascribe the difference in the case of cellulose to any special effect as, for example, hydrogen bonding between the C-3 hydroxyl and the ring oxygen in the adjacent glucose residue. It is more probable that the higher reactivities in the 2- and 6-positions are due to the greater acidity of the C-2 hydroxyl [11] and the lower steric requirements of the primary C-6 hydroxyl, respectively. The rates,

Table 4. Relative rates for the methylation of methyl β-D-glucopyranoside, some 4-*O*-substituted derivatives of it and cellulose with dimethyl sulphate in 18.9 % sodium hydroxide.

Substance	k_2	k_3	k_4	k_6
Methyl β-D-glucopyranoside	4	1	0.5	4
Methyl 4-*O*-benzyl-β-D-glucopyranoside	2	1	—	3
Methyl 4-*O*-(2-tetrahydropyranyl)-β-D-glucopyranoside (+ and −)	3	1	—	4
Cellulose	3.5	1	—	2

given in Table 4, are relative and not absolute, and it can not therefore be decided whether the differences between the substances are due to activations of some positions or to deactivation of others. It seems possible, however, that the lower reactivity of the 6-position of cellulose, as compared with the model substances, may be due to some steric hindrance at this position in the cellulose molecule.

The differences observed between the two 4-*O*-(2-tetrahydropyranyl)-derivatives are within the experimental errors but the differences between the other model substances are probably significant. Considering the complexity of the systems involved an attempt to interpret these rather small differences would hardly be justified.

EXPERIMENTAL

*Methyl 4-O-benzyl-β-*D*-glucoside.* Methyl 2,3,6-tri-*O*-acetyl-β-D-glucopyranoside [12] (6 g) was dissolved in dimethylformamide (60 ml) and benzyl bromide (24 ml), the solvents being dried and distilled before use. Silver oxide (24 g) was added over 1 h with stirring and the reaction left stirring overnight at room temperature. The product was worked up as described previously [8] — the dried chloroform extract was concentrated and high boiling liquids removed at 80° and reduced pressure (1 mm Hg). The residue was deacetylated with sodium methoxide in methanol and the products separated between hexane and water. The aqueous phase was deionised and concentrated, then fractionated on a cellulose column using water-saturated butanol as the eluant. The first optically active fractions contained the glucoside in about 15 % yield. Crystallisation from ethanol-hexane yielded the pure, hygroscopic substance, m.p. 58—68°, $[\alpha]_D^{25} -14°$ (water, *c* 1.0). (Found: C 58.9; H 7.29. $C_{14}H_{20}O_6$ requires C 59.1; H 7.09). The product had an R_F-value of 0.83 in butan-1-ol-ethanol-water (10:3:5) and could be detected with the periodate-benzidine spray reagent.

Acetylation in acetic anhydride and pyridine yielded methyl 2,3,6-tri-*O*-acetyl-4-*O*-benzyl-β-D-glucoside, m.p. 86.5—87.5°, $[\alpha]_D^{25} -25°$ (chloroform, *c* 2.0) after crystallisation from aqueous ethanol. (Found: C 58.8; H 6.43; O 34.8. $C_{20}H_{26}O_9$ requires C 58.5; H 6.39; O 35.1).

Methylations. A sample of a glucoside (0.5—1.5 g) was dissolved in 18.9 % aqueous sodium hydroxide (80—100 ml). Dimethyl sulphate (2—10 ml) was added over 45 min with stirring under an atmosphere of nitrogen. The stirring was continued for 4 h. The reaction mixture was then neutralised with 6 N sulphuric acid, the sodium sulphate precipitated with ethanol (400 ml) and the solution concentrated.

Removal of 4-O-substituent and hydrolysis. The methylated methyl 4-*O*-benzyl-β-glucoside was dissolved in methanol (20 ml), palladium on carbon catalyst (20 mg) was added and the mixture kept under hydrogen with shaking until the hydrogen uptake was constant. After filtration and concentration, the product was treated as below.

The methylated glucoside was dissolved in 1.8 N sulphuric acid (50—100 ml) and kept at 95° for 4 h. Most of the sulphate ions were removed by treatment with barium carbonate, remaining salts were removed by ion exchange and the solutions were concentrated.

Analytical procedure. The hydrolysis products were fractionated on a carbon-Celite column as described by Croon and Lindberg [9]. The monomethyl ethers, which are not separated well, were taken together and separated by paper electrophoresis in germanate buffer [10] (pH 10, 1000 V, 40°, 3 h). They were then estimated quantitatively by elution and hypoiodite titration [13].

The latter procedure was checked with standard samples, and although the absolute values were up to 10 % low, the relative analyses were within 5 %.

The procedure for the product obtained from partially methylated methyl β-D-glucopyranoside was somewhat different. The mixture was fractionated by chromatography on thick filter paper (butan-1-ol—ethanol—water, 10:3:5) giving glucose (79 %), mono-*O*-methylglucoses (16 %), di-*O*-methylglucoses (4 %) and higher ethers (approx. 1 %).

The proportions of the mono-*O*-methyl glucoses was determined by electrophoresis in germanate buffer as described above and found to be 43:11:5:41 for 2-, 3-, 4- and 6-*O*-methyl-D-glucose, respectively. The figures represent average values from 3 determinations.

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