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Partial Methylation of some Glucose Derivatives

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Methyl 4,6-*O*-ethylidene-β-D-glucopyranoside, methyl 4,6-*O*-benzylidene-β-D-glucopyranoside and amylose have been partially methylated with dimethyl sulphate in alkaline solution and the distribution of the methoxyl groups has been determined by hydrolysis and resolution of the hydrolysate by chromatographic methods. In the first two derivatives the hydroxyl groups at C_2 and C_3 had approximately the same reactivity ($k_2:k_3 = 1:1$ and $k_2:k_3 = 1.3:1$, respectively); for amylose $k_2:k_3:k_6$ equalled 6:1:7. This investigation supports the idea that intrachain hydrogen bonds play an important role in the reactivity of the hydroxyl groups at positions C_2, C_3 and C_6 in cellulose and amylose, but other factors which can influence the results are also pointed out.

Studies on the distribution of substituents in various ethers of cellulose have been reported in previous communications from this Department [1-4]. In these studies, the cellulose ether was hydrolysed to a mixture of glucose and glucose ethers. This mixture was fractionated by chromatographic methods into pure components which were characterized and identified. The technique also allowed for the quantitative determination of all the expected components, except in the case of hydroxyethyl cellulose from which, however, ten separate components were isolated and identified [1]. This method of studying the distribution of substituents should be more accurate than the indirect methods previously used, which were based upon group analyses, such as the determination of glycol groups by periodate oxidation and of primary hydroxyl groups by tosylation-iodination.

For methyl cellulose, prepared with methyl sulphate in a homogeneous medium (triethylbenzylammonium hydroxide as solvent) the results agreed fairly well with those which could be calculated statistically, using the following assumptions [2]:

1. All glucose residues are equally accessible.
2. The relative rate constants for methylation at carbon atoms $C_{(2)}$, $C_{(3)}$ and $C_{(6)}$ of the glucose unit are constant during the reaction.
3. The effect of end groups is negligible.

The values of $k_2 = 3.5$, $k_3 = 1$ and $k_6 = 2$ for the relative rate constants in methylation reactions with methyl sulphate at $C_{(2)}$, $C_{(3)}$ and $C_{(6)}$ gave the best agreement, but there were deviations which could not be explained as experimental errors. A better agreement was obtained if it was assumed that the reactivity at $C_{(3)}$ was doubled when the hydroxyl at $C_{(2)}$ was methylated. This should not be unreasonable, as the $C_{(2)}$-hydroxyl is the most acidic in the glucose residue and, when dissociated, should considerably reduce the acidity of the $C_{(3)}$-hydroxyl.

In order to study this effect and learn more about the factors which influence the relative reactivities of different hydroxyl groups in a glucose residue, the course of the partial methylation of methyl 4,6-*O*-ethylidene-β-D-glucopyranoside, methyl 4,6-*O*-benzylidene-β-D-glucopyranoside and of amylose has now been investigated, using the same technique as used for the cellulose ethers. The relative reactivities of hydroxyl groups of carbohydrates has been summarised by Sugihara [5]. Most of the results discussed by him were, however, obtained before the development of modern chromatographic technique and are probably rather uncertain.

Table 1. Composition of the hydrolysates of the partially methylated ethylidene and benzylidene glucose derivatives

	Ethylidene derivative						Benzylidene derivative	
	Sample I		Sample II		Sample III			
Substance [a]	Found	Calc.[b]	Found	Calc.[b]	Found	Calc.[b]	Found	Calc.[c]
s_0	66.0	65.3	45.0	42.2	28.2	28.6	54.0	51.2
s_2	14.7	15.5	20.4	22.8	23.0	24.9	20.2	23.5
s_3	15.1	15.5	20.4	22.8	25.6	24.9	15.3	17.2
s_{23}	4.1	3.7	14.4	12.2	23.2	21.6	10.4	8.0

[a] s_0 = unsubstituted glucose; s_2 = 2-*O*-methyl-D-glucose, *etc.*
[b] Calculated for homogeneous reaction in alkaline solution, $k_2:k_3 = 1:1$.
[c] Calculated for homogeneous reaction in alkaline solution, $k_2:k_3 = 1.3:1$.

The two cyclic acetals were methylated with methyl sulphate in sodium hydroxide; ethanol was added to the system to keep the products in solution. The results given in Table 1 were quite unexpected and contrary to those from all cellulose ethers studied, the reactivities at $C_{(2)}$ and $C_{(3)}$ being approximately the same. The percentage of 2,3-di-*O*-methyl-D-glucose (s_{23}), however, was in all cases higher than the calculated value, thus supporting the assumption that the reactivity in one of the positions is increased when the other is methylated. The low reactivity at $C_{(3)}$ in cellulose has been attributed to a hydrogen linkage between this hydroxyl and the ring oxygen of the neighbouring glucose residue [6,7]. On the other hand, the higher reactivity at $C_{(2)}$ has been explained as a result of the higher acidity of the hydroxyl at this position [5,8], due to the inductive effect of the two oxygen atoms at $C_{(1)}$. It must, however, be borne in mind that the observed effect, a change in relative reactivity from 3.5:1 to 1:1, corresponds to a quite small difference in the energy of activation, which might equally well have other explanations, *e.g.* a different magnitude of steric hindrance from the bulky groups in the 4-position, or a slight deviation from the chair conformation of the pyranose ring in the cyclic acetals.

Table 2. Composition of the hydrolysate of the partially methylated amylose

Substance	Sample I (D.S. 0.76)			Sample II (D.S. 1.30)		
	Found	Calc.		Found	Calc.	
		a)*	b)**		a)*	b)**
s_0	43.0	40.1	41.4	18.5	15.1	16.3
s_2	16.5	19.2	18.4	16.7	18.8	17.8
s_3	2.6	2.8	2.7	1.6	2.2	2.2
s_6	21.6	23.2	22.9	20.7	23.8	24.0
s_{26}	11.3	11.1	10.2	28.6	29.7	26.5
s_{36}	1.3	1.6	1.5	2.5	3.5	3.3
s_{23}	2.7	1.3	1.8	5.1	2.7	4.0
s_{236}	1.1	0.8	1.0	6.3	4.3	5.9

* Calculated for a homogeneous reaction in alkaline solution $k_2:k_3:k_6 = 6:1:7$. (See the text.)
** As above, but with the further assumption that l_3 is doubled when the position at $C_{(2)}$ becomes methylated.

Amylose was dissolved in 18.9 % sodium hydroxide and methylated with methyl sulphate and the distribution of the methoxyl groups in the methylated product was studied as above. The results are summarised in Table 2. Here also, the percentage of s_{23} is higher than expected according to the direct statistical calculation, and a better agreement between observed and calculated values is obtained if it is assumed that the reactivity at $C_{(3)}$ is doubled when the position at $C_{(2)}$ is methylated [2]. The most interesting result is that the primary hydroxyl group showed the highest reactivity. The relative reactivity at $C_{(3)}$ is even lower than in cellulose. The conformation of the glucose residues in the amylose chain is not definitely known, but in a recent paper Reeves [9] assumed that there is an equilibrium between B1 and 3B (Fig. 1) and that in strongly alkaline solution a conformation approximating that of 3B predominates.

An inspection of a model of the amylose molecule in the 3B-conformation, using the Courtauld atomic models, shows that as in cellulose the atomic distances are favourable for the formation of a strong hydrogen bridge between the $C_{(3)}$-hydroxyl and the oxygen atom in the adjacent glucopyranoside ring. In the cellulose molecule a hydrogen bridge between the hydroxyl group at $C_{(6)}$ and a glycosidic oxygen atom is possible, but in the starch model this is not the case. The results thus favour the opinion that intramolecular hydrogen bridges play an important role in the relative reactivities in the methylation reaction, but for reasons discussed above great care must be used when trying to interpret these rather small effects. A careful study of a greater number of model substances might throw more light upon these questions.

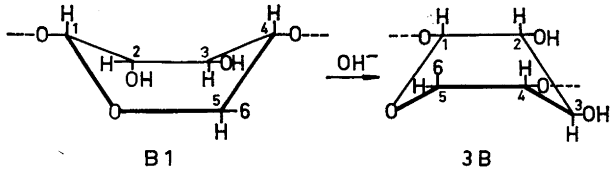

Fig. 1.

EXPERIMENTAL

Methyl 4,6-O-ethylidene-β-D-glucopyranoside (600 mg), prepared according to Helferich [10], was dissolved in 18.9 % sodium hydroxide (60 ml) and methyl sulphate (2 ml) was added during 15 min. After 30 min, traces of the dimethylated compound began to precipitate and, in order to keep the reaction medium homogeneous, ethanol (10 ml) was added. A further quantity (2 ml) of methyl sulphate was added during 30 min. The reaction was carried out for a total time of 4 h. The solution was neutralised with 6 N sulphuric acid and most of the sodium sulphate formed was precipitated with ethanol. The filtered solution was evaporated to 37 ml, and 72 % sulphuric acid was added until the concentration was 8 %. This solution was kept at 100°C for 4 h to remove the ethylidene and the glycosidic methyl groups. The sulphate ions were then removed by treatment with barium carbonate and the solution deionised by ion exchange with IR-120 and IR-4B exchange resins. Evaporation of the deionised solution yielded a light yellow syrup (370 mg) (sample 1 in Table 1). Two other samples were obtained by varying the amount of methyl sulphate and the time of reaction.

Methyl 4,6-O-benzylidene-D-β-glucopyranoside (500 mg), prepared according to Freudenberg, Toepffler and Anderson [11], was dissolved in 18.9 % sodium hydroxide (60 ml) and methyl sulphate (2 ml) was added during 15 min. After addition of ethanol (20 ml), additional methyl sulphate (2 ml) was added dropwise during 30 min. Ethanol (10 ml) was then added and the reaction was allowed to proceed for a total time of 4 h. Neutralisation, precipitation and hydrolysis were performed as above. The hydrolysate (50 ml) was shaken with ether (3 ml) to remove benzaldehyde. The neutralised and deionised solution on evaporation yielded a syrup (295 mg).

Amylose. The pure amylose (1.3 g) was dissolved in 18.9 % sodium hydroxide (60 ml) and methyl sulphate (8 ml) was added during 1 h. After a further 4 h, the solution was neutralised with 6 N sulphuric acid and was dialysed against tap water for a period of 14 days. The partially methylated amylose was recovered by freeze-drying, when a white, fluffy product (1.28 g) was obtained (sample 1 in Table 2). A higher methylated derivative was obtained by methylation of amylose (2 g) with methyl sulphate (20 ml) during 17 h (sample 2 in Table 2).

The amylose derivatives were hydrolysed exactly as previously described for the cellulose ethers [2] by treatment with 72 % sulphuric acid (16.7 ml) for 30 min, and dilution with water to 150 ml, after which the solution was kept at 100°C for 4 h.

All the methylations described above were carried out in an atmosphere of nitrogen.

Analysis of the hydrolysates. The hydrolysates were analysed by separation into pure components by carbon column chromatography, paper electrophoresis and paper chromatography as described in a previous paper [2].

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