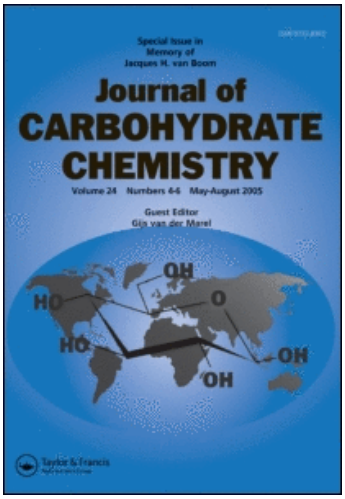

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Distribution of Substituents in Methylcellulose

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DISTRIBUTION OF SUBSTITUENTS IN METHYLCELLULOSE

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ABSTRACT

The distribution of methyl groups in methylcelluloses (DS 1.7) has been determined. The partially methylated monosaccharides obtained on complete hydrolysis of methylcellulose were converted into alditols by reduction. They were identified as their acetates or trimethylsilyl ethers by gas-liquid chromatography - mass spectrometry and quantified by gas-liquid chromatography. In addition, ^{13}C-nuclear magnetic resonance spectra of native and hydrolyzed methylcelluloses as well as the partially methylated alditols obtained by hydrolysis and reduction were analyzed. The main glucose methyl ethers obtained were in decreasing order 2,6-, 2,3,6-, 2-, 6-, and 2,3-. The 2- and 6-positions were occupied by methyl groups in 70.0 and 61.5%, respectively, while the 3-position contained only 37.4%. The GLC-MS method gave a more accurate determination of the distribution of methyl groups in methylcellulose compared to NMR spectroscopy.

INTRODUCTION

O-Methyl groups occur in several natural polysaccharides and are often introduced in order to modify natural polymers. One important example is methylcellulose (MC), which is prepared by treatment of cellulose fibers, obtained from cotton linters or wood pulp, with caustic solution and methylation of the alkali cellulose with methyl chloride. Thus, the original homopolymer is transformed into a heteropolymer containing eight different residues randomly distributed along the chain. Commercial MC has a methoxyl content of 27.5 to 31.5%, which corresponds to a degree of substitution (DS) of about 1.8. It acts as a viscosifier and has also the unusual property of being soluble in cold but not in hot

water. The degree of substitution and the distribution of the methyl groups are important in determining the properties of MC, e.g., solution quality and resistance to enzymatic degradation. Methylcelluloses have many applications which include adhesives, agricultural chemicals, ceramics, cosmetics, glues, inks, paper coatings and pharmaceuticals.[1]

The chemical reactivity of the three hydroxyl groups of the anhydroglucose units in cellulose is of great importance in the manufacture of cellulose derivatives. The distribution of substituents in MC has been analyzed after hydrolysis by quantitative separation of the D-glucose derivatives on a carbon column and further fractionation by paper chromatography and paper electrophoresis.[2, 3, 4] The authors concluded that the reactivities of the hydroxyl groups of cellulose were dependent on the alkylation agent. The proportion of methyl groups in MC prepared by alkali treatment followed by methyl chloride has been shown to be mainly OH-2 > OH-6 >> OH-3.[2, 3, 5] This study now reports the distribution of methyl groups in two commercial MCs. The modified celluloses were hydrolyzed and the resulting partially methylated monosaccharides were reduced to alditols and analyzed as acetates and trimethylsilyl ethers by gas-liquid chromatography - mass spectroscopy (GLC-MS). The ^{13}C-nuclear magnetic resonance (^{13}C NMR) spectra of native and hydrolyzed MC as well as those of the derived alditols were also analyzed.

RESULTS AND DISCUSSION

Two commercial MCs were used in this study. The manufacturers report DS values of 1.70 (A) and 1.65 (B), respectively. O-Methyl group analyses [(28.1% (A) and 27.3% (B))] and C and H analyses [48.01% and 7.01% (A) and 47.83% and 7.11% (B)] were also carried out on these commercial samples. MC samples were hydrolyzed with trifluoroacetic acid of different concentrations and time periods at 100 °C in an ampoule and the hydrolyzate was analyzed by high pressure liquid chromatography (HPLC). Use of 0.67 M trifluoroacetic acid for 16 h at 100 °C resulted in complete hydrolysis and no oligosaccharides were detected. The separation of the partially methylated alditols obtained by total hydrolysis, reduction and acetylation is shown in Figure 1. The components were all well separated and eluted in the order of decreasing substitution of methyl groups. They were identified using GLC-MS by comparison with authentic samples and

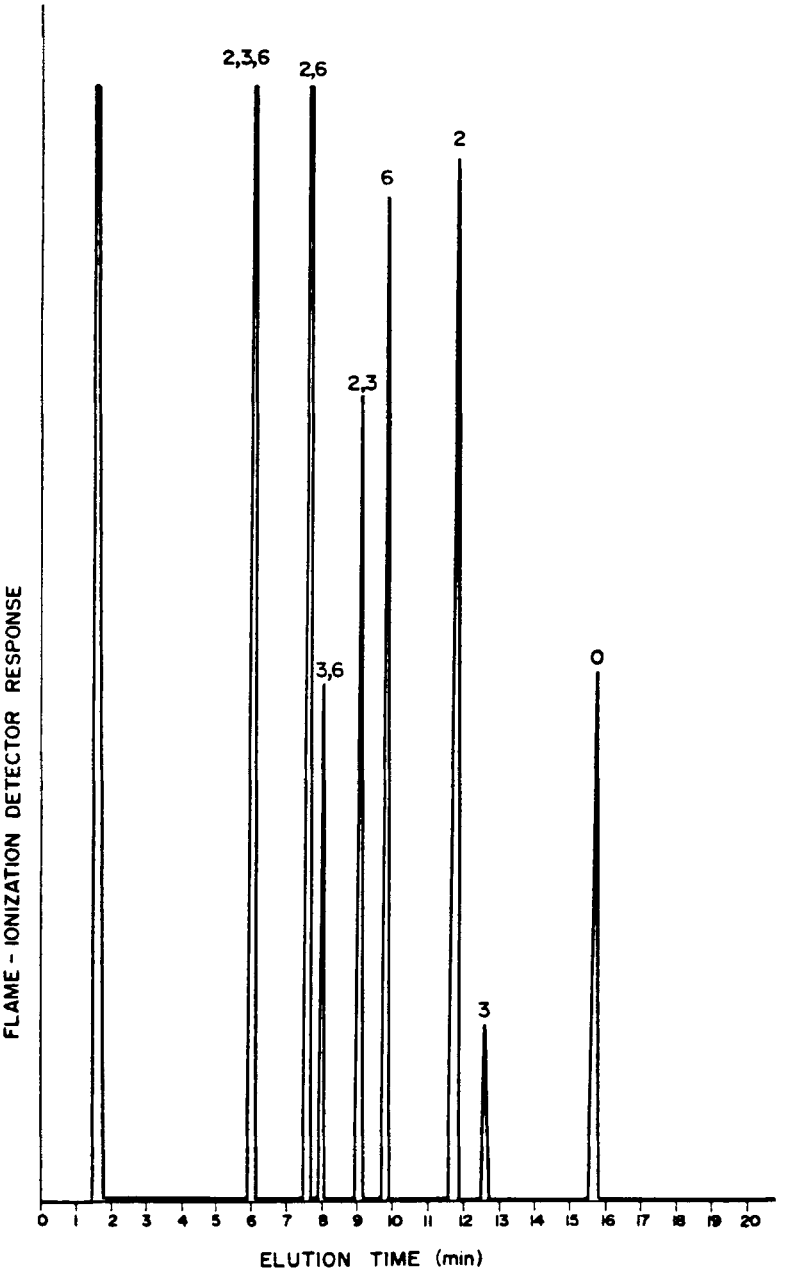

Fig. 1. Capillary GLC chart of partially methylated glucitol acetates obtained from methylcellulose (DS=1.7). The numbers indicate the positions of the methoxyl groups.

Table 1

Glucose Methyl Ethers Obtained on Hydrolysis of Partially Methylated Cellulose of DS 1.70 (A) and 1.65 (B)

Glucose methyl ethers[a]	T[b]	Molar percentage		
		A	B	Calculated
2,3,6	1.00	19.4	19.5	16.3
2,6	1.26	24.6	23.9	27.3
3,6	1.33	5.3	5.2	6.7
2,3	1.50	10.3	8.5	10.2
6	1.63	12.2	12.5	11.2
2	1.96	16.6	16.6	17.1
3	2.09	2.4	2.3	4.2
0	2.62	9.3	11.5	7.0

a. Figures refer to position of methoxyl groups

b. Retention time of the corresponding alditol acetate, relative to that of 1,4,5-tri-O-acetyl-2,3,6-tri-O-methyl-D-glucitol

the molar percentage are presented in Table 1. Similar results were obtained when trimethylsilyl (TMS) ethers of the alditols were analyzed. However, the resolution of the partially methylated alditol trimethylsilyl ethers was less complete than that of the partially methylated alditol acetates. The two MCs showed almost the same distribution of methyl groups.

The percentage of the methyl groups on the individual oxygen atoms was calculated from the values in Table 1, and are presented in Table 2. The high proportion of methyl groups at the 2-postion compared to the 6-position, and especially to the 3-position found here and previously,[5, 6] is surprising. Based upon steric consideration, one would have expected the primary hydroxyl group at the 6-position to be the easiest to substitute in a nucleophilic substitution reaction such as this one. However the 2-hydroxyl group has also been shown to

Table 2

Percent O-Methylation in Position 2, 3 and 6 in the D-Glucose Residues of the Methylcellulose and its DS, Calculated from Table 1

	% O-methyl in position			
	2	3	6	DS
A	70.9	37.4	61.5	1.70
B	68.5	35.5	61.1	1.65

be the most acidic of the hydroxyls due to its proximity to the glucosidic and ring oxygens.[7] A methylcellulose with a lower degree of substitution (1.27) showed an even higher selectivity between the three positions. The 2-, 6- and 3-positions were occupied by methyl groups in 69, 43 and 15%, respectively.[6] The low reactivity of the C-3 hydroxyl groups has been explained by intramolecular hydrogen bonding with the ring oxygens on adjacent anhydroglucose units.[8]

The good agreement between the methoxyl content and the degree of substitution obtained from the analyses (see Table 1) suggests that no hydrolysis of the methyl groups or degradation of the material has occured during the conditions employed. It also indicates that complete hydrolysis of the glucosidic linkages in the partially methylated cellulose has taken place.

This is in contrast to the distribution of other substituents in modified celluloses. A commercial cellulose acetate with a DS of 2.4 showed comparable amounts of O-acetyl groups at the 2- and 3-postion (85%) and a somewhat smaller amount at the 6-position (72%).[9] This difference could be explained by the preparation of the two modified celluloses. The cellulose acetate was prepared by partial hydrolysis of fully acetylated cellulose, while MC was treated with alkali and methyl chloride.

Assuming that there is no influence of end groups, that substitution reaction is of first order with respect to the hydroxyl groups, and there is no influence of substitution on the relative reaction rate constant, it should be possible to calculate the percentages of D-glucose residues methylated at different posi-

tions from the percentage of methylation in each position. Such calculation has been performed using the values from A (Table 2). A good agreement between measured and calculated values was observed indicating that the assumptions above are justified. This suggests that the substitution reaction in preparation of methyl cellulose is of first order and that the relative rate constants of the hydroxylation are not affected by earlier substitution. Similar results have been found for carboxymethyl cellulose,[10] cellulose acetate[9] and ethylcellulose.[11] For preparation of carboxymethyl cellulose, the relative rate constant has been shown to be strongly dependent on reaction conditions, but is equal for cellulose of different origins under constant reaction conditions.[10]

The EI-mass spectra of the resulting partially methylated alditol acetates showed the following main peaks with the intensities in brackets. Only peaks of 10% above and 20% below m/z 120 are shown.

2,3,6-Tri-O-methyl-D-glucitol triacetates:
m/z: 233(19.0), 161(17.1), 143(12.8), 131(32.4), 129(39.5), 117(100.0), 113(88.6), 101(83.8), 99(79.6), 98(22.8), 87(79.5), 85(26.9), 75(23.8), 71(32.9), 43(65.6).

2,6-Di-O-methyl-D-glucitol tetraacetates:
m/z: 159(17.2), 143(21.8), 139(10.0), 129(82.8), 118(23.7), 117(100.0), 115(24.3), 97(20.0), 87(70.3), 58(37.0), 43(71.7).

3,6-Di-O-methyl-D-glucitol tetraacetates:
m/z: 189(20.2), 131(13.9), 129(100.0), 113(44.3), 99(30.5), 87(69.9), 43(29.3).

2,3-Di-O-methyl-D-glucitol tetraacetates:
m/z: 127(19.9), 117(100.0), 101(31.0), 99(21.3), 85(25.2), 43(26.8).

6-Mono-O-methyl-D-glucitol pentaacetates:
m/z: 184(17.8), 170(11.8), 159(22.1), 157(54.2), 147(10.8), 145(30.4), 142(20.5), 140(13.1), 139(49.1), 129(88.4), 128(21.9), 127(20.3), 125(12.8), 117(22.2), 115(100.0), 103(37.2), 99(24.5), 98(31.1), 97(32.8), 87(91.5), 85(26.6), 73(21.2), 43(97.9).

2-Mono-O-methyl-D-glucitol pentaacetates:
m/z: 139(36.1), 129(14.6), 117(100.0), 97(23.0), 43(40.1).

3-Mono-O-methyl-D-glucitol pentaacetates:
m/z: 189(18.0), 129(100.0), 127(31.5), 99(34.7), 87(56.9), 85(38.5), 43(41.3).

D-Glucitol hexaacetates:
m/z: 217(10.7), 187(24.1), 170(23.2), 158(10.4), 157(33.3), 153(10.6), 145(57.9), 139(37.6), 128(43.7), 127(23.6), 116(20.8), 115(100.0), 103(52.3), 97(21.3), 86(20.2), 85(26.9), 43(95.0).

The mass fragmentation of the partially methylated glucitol acetates showed preferential cleavage between adjacent carbons carrying methoxyl groups. Less stable ions were derived by fission between adjacent carbon atoms carrying methoxyl and acetoxyl groups with the former group preferentially carrying the positive charge. Fission between carbon atoms carrying acetoxyl groups resulted in low intensity fragments. The secondary fragments observed may be derived from the primary fragments by single or consecutive elimination of acetic acid(60), ketene(42), methanol(32) and formaldehyde(30). These results follow the same pattern as described by Björndal et al.[12]

The mass fragmentation of the partially methylated alditol trimethylsilyl ethers followed a similar pattern. This is not surprising since close fragmentation analogies have been reported for methyl and TMS derivatives of other species including some carbohydrates.[13, 14]

The mono-, di- and trisubstitution of methoxyl groups were roughly the same for the two methylcelluloses with around 30, 40 and 20%, respectively, with no substitution in 10% of the cellulose residues.

The ^{13}C NMR spectrum of MC (DS=1.7) is shown in Figure 2. O-Alkylation of polysaccharides will promote strong deshielding of the substituted carbinol group resulting in a downfield shift of 9 ppm.[15, 16] The anomeric carbon at 102 ppm is indicative of polymeric β-D-glucose residues. The downfield resonance at 82 ppm is the resonance for the C-2 carbon bonded to a methoxyl group. The resonance at 78 ppm belongs to the C-4 carbon to which the glucosidic linkage is attached. The strong peak at 73 pm belongs to the C-6 carbon bonded to a methoxyl group. The resonances of the unsubstituted C-2, C-3 and C-5 carbons are in the region of 68-78 ppm, while unsubstituted primary carbons (C-6) will be around 60 ppm. The two sharp peaks at 60 and 58 ppm are due to the methoxyl groups and assigned to C-2 and C-6, respectively. The sharpness of the peaks is probably due to long T_2 relaxation times. The methoxyl group from C-3 and unsubstituted C-6 are also in this region, but are not well resolved. The assignments of the carbons are based on earlier published results.[5, 17] The broad resonance peaks and considerable noise in the spectrum are caused by the high viscosity. This could be improved by partial acid or enzymatic hydrolysis of the polysaccharide to reduce the molecular weight and result in less viscous solution. The ^{13}C NMR spectra in general can be improved by raising the sample temperature, but MC has a tendency to gel on heating. The determination of the distribution of methyl groups in methylcellulose using ^{13}C NMR is shown to be difficult not only by bad resolution and identification of the peaks but also with the integration of the peaks.

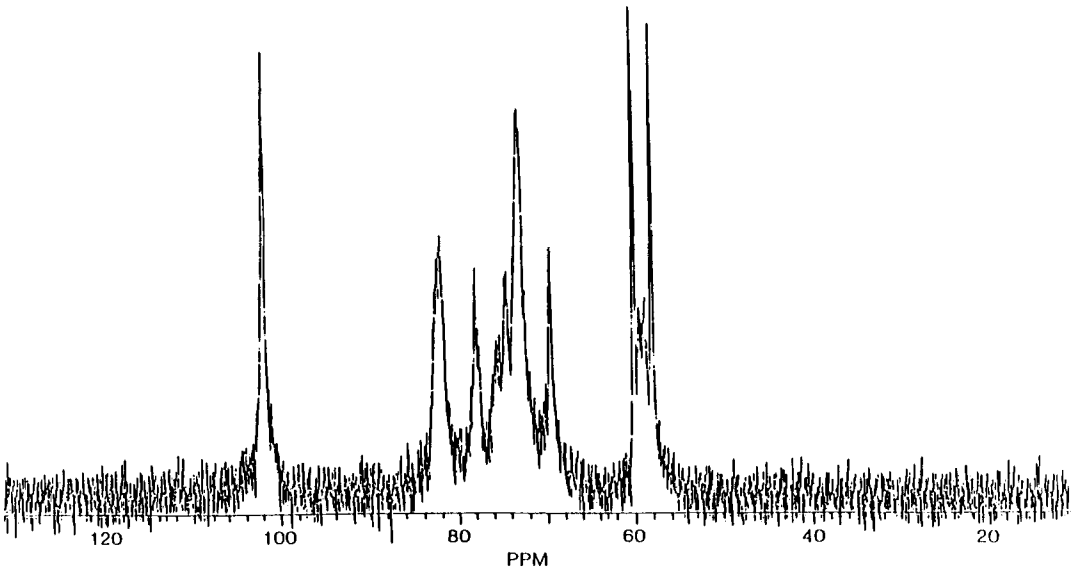

Fig. 2. 400 MHz, ^{13}C NMR spectrum of methylcellulose (DS=1.7) in D_2O, recorded at 21 ^{o}C. Chemical-shift values are relative to internal acetone (δ 31.4).

To improve the resolution of the spectrum, the polysaccharide was hydrolyzed completely with trifluoroaetic acid. The resulting ^{13}C NMR spectrum is shown in Figure 3. Fifty-one resonance peaks were well separated from each other ranging from 60.5 ppm to 99.0 ppm. This indicates that at least 3 additional resonance peaks were not separated and therefore cannot be quantified. The carbon -13 chemical shifts of O-methyl D-glucoses and O-methyl derivatives of methyl D-glucosides obtained from hydrolysis and methanolysis, respectively, have been published by Reuben.[18] The spectrum obtained here is identical to the published spectrum. Reuben's data also showed that the spectrum of methanolyzed MC exhibited considerably better resolution than that of hydrolyzed MC. This was explained by the larger substituent effect in the methyl D-glucoside series. Despite the improved resolution in this spectrum compared to the native one, difficulties remain to determine an accurate distribution of the methyl groups.

In order to avoid complexities associated with α/β mutarotational equilibria of the partially methylated sugars in solution, the hydrolyzed MC was re-

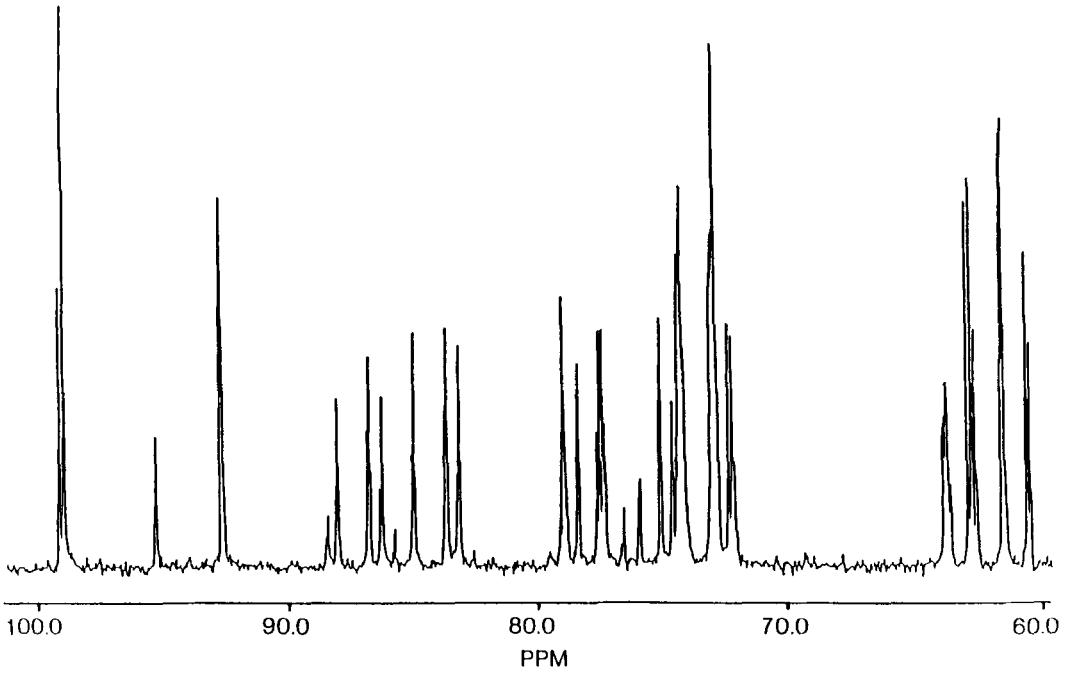

Fig. 3. 400 MHz, ^{13}C NMR spectrum of hydrolysed methylcellulose (DS=1.7) in D_2O, recorded at 21 ^{o}C. Chemical-shift values are relative to internal acetone (δ 31.4).

duced by sodium borohydride and the mixture of partially methylated and non-methylated glucitols were analyzed by ^{13}C NMR spectroscopy and by GLC-MS. The ^{13}C NMR spectrum is shown in Figure 4. Thirty-eight resonance peaks ranging from 51.88 ppm to 85.71 ppm were well separated. This means that 10 additional resonance peaks were not separated and therefore cannot be quantified. Despite fewer resonance peaks in this spectrum compared to the one containing the monosaccharides, it still remains very difficult to determine the location of the methyl groups.

From the results presented in this paper it seems that a complete hydrolysis and characterization by GLC-MS of the obtained glucose ethers will give a more accurate quantitative and qualitative estimation of the distribution of substituents compared to ^{13}C NMR spectroscopy.

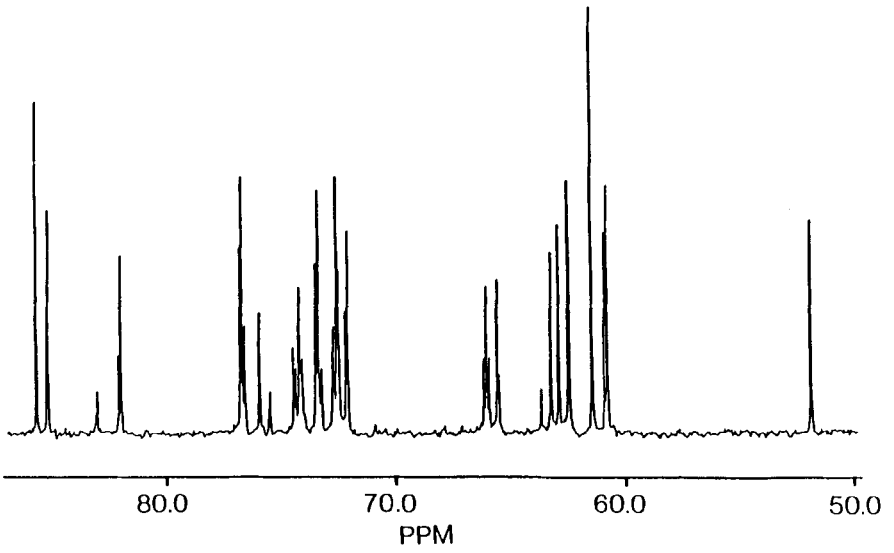

Fig. 4. 400 MHz, ^{13}C NMR spectrum of hydrolysed and reduced methylcellulose (DS=1.7) in D_2O, recorded at 21 °C. Chemical-shift values are relative to internal acetone (δ 31.4).

EXPERIMENTAL

Materials. MCs were obtained from BDH Chemicals, Poole, England (A) and Dow Chemicals, Sarnia, Ontario, Canada (B). The methoxyl contents were determined as described by Hodges et al.[19] The C and H analyses were performed by Canadian Microanalytical Service Ltd., Vancouver, B.C. Concentrations were carried out under diminished pressure at a bath temperature not exceeding 40 °C.

Hydrolysis and analysis of the methyl ethers. MC (5 mg) was hydrolyzed with trifluoroacetic acid (2 mL), using different concentrations and time periods at 100 °C, in an ampoule. The hydrolyzate was concentrated to dryness under a stream of nitrogen gas. The residue was dissolved in water (5 mL) and sodium borohydride (20 mg) was added. After 2 h at room temperature, excess Dowex 50(H^+) was added. The resin was removed by filtration and the filtrate was concentrated to dryness. Boric acid was removed by repeated codistillations with methanol (3 x 5 mL). Part of this residue, dissolved in acetonitrile-water (3:1),

was analyzed on a Supelcosil LC-NH_2 column (25 cm x 4.6 mm) using a Hewlett-Packard 1084A Liquid Chromatography connected to a Hewlett-Packard 79850A LC Terminal. The eluant (acetonitrile-water, 3:1) was monitored with a refractive index detector.

Gas-liquid chromatography - mass spectrometry (GLC-MS). The partially methylated alditols obtained after complete hydrolysis were derivatized in two ways:

(a) Part of the residue was acetylated by treatment with pyridine - acetic anhydride (1:1, 2 mL) for 15 min at 100 ^{o}C. The solution was concentrated to dryness and the resulting partially methylated alditol acetates were dissolved in a small amount of methanol and analyzed by GLC-MS.

(b) Another part was treated with TRI-SIL Z reagent (Pierce Chemical Company, Rockford, IL, USA) at room temperature for 1 h and the resulting partially methylated alditol trimethylsilyl ethers were analyzed by GLC-MS.

GLC was carried out on a Hewlett-Packard 5880 A gas-liquid chromatograph, equipped with flame ionization detectors and connected to an electronic integrator. The separations were performed at 200 ^{o}C isothermal on a fused silica capillary column (DB 1, 15 m x 0.2 mm). Combined GLC-MS was carried out on a Hewlett-Packard 5985 B GC/MS/DS using the above column and an ionization potential of 70 eV.

Nuclear magnetic resonance spectroscopy (NMR). ^{13}C NMR spectra were recorded at a probe temperature of 21 ^{o}C on a Brucker WM-400 instrument operating in the pulsed Fourier transform mode with complete proton decoupling. The chemical shifts are reported in parts per million (ppm) and related to internal acetone (=31.4 ppm). The samples were dissolved in D_2O.

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