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Distribution of substituents in 2-hydroxypropyl ethers of cyclomaltoheptaose

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ABSTRACT

The distribution of substituents in 2-hydroxypropyl ethers of cyclomaltoheptaose, prepared by alkylation of the carbohydrate with propylene oxide in aqueous sodium hydroxide, was investigated. The samples were fully methylated and hydrolyzed, and the resulting mixture of alkylated sugars analyzed as their alditol acetates by g.l.c.–m.s. High and low alkali concentration favored the formation of 2-hydroxypropyl ethers at O–6 and O–2, respectively; substitution at O–2 increased the reactivity of O–3. The overall extent of substitution had only secondary effects on the relative reactivities of O–6 and O–2, and the 2-hydroxypropyl groups remained unevenly distributed among the glucose residues, even when the overall substitution increased. Only small proportions of the isomeric 2-(1-hydroxypropyl) ethers were formed, and the percentage of oligopropylene glycol ethers was also low.

INTRODUCTION

2-Hydroxypropyl ethers of cyclomaltoheptaose ("β-cyclodextrin") may be used as host molecules for lipophilic compounds, and thus increase their solubility in water[1]. The mixtures of these ethers may be characterized by a combination of ^{1}H n.m.r. and plasma-desorption mass spectrometry[2]. The distributions determined by the latter method were essentially symmetrical but rather wide—thus a sample having an average of 7–8 ether groups per molecule had all the degrees of substitution from 3 to 14 present. Furthermore, mass spectrometry of the samples of hydrolyzed *O*-(2-hydroxyalkyl) cyclomaltoheptaoses revealed an unexpectedly high representation of di- and tri-substituted glucoses[2].

It was of interest to determine the distribution of substituents between the three positions in the α-D-glucopyranosyl residues and how this might be manipulated by changing the reaction conditions during the etherification. It is known from hydroxyethylation of cellulose[3] that strong alkali favors alkylation at O–6, the most accessible position, and that weak alkali favors alkylation at O–2, the most acidic position. As OH-2 and OH-3 in cyclomaltoheptaose[4,5] were found to be much more acidic than OH-6, the basicity of the reaction medium was expected to affect the regioselectivity in the present case as well. We now report such studies on a number of hydroxypropyl ethers of cyclomaltoheptaose prepared under different conditions.

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EXPERIMENTAL

Preparation of the 2-hydroxypropyl ethers in aqueous media (Examples 1–7). — A well established procedure was employed[1,2]. In Examples 1–3 techniques and equipment suitable for the preparation of up to 2 kg of product were used. Furthermore, processes that eliminate toxic oligopropyleneglycols were included. Examples 4–8 were gram-scale laboratory preparations employing (*S*)-propylene oxide. Briefly, cyclomaltoheptaose was dissolved at 60° by stirring in aq. NaOH (for the amounts, see Table I). After cooling to ice-bath temperature, the clear solution was treated with propylene oxide, which was added dropwise while stirring. After overnight stirring at 0–5°, the solution was kept for 3 h at room temperature, carefully made neutral with H_2SO_4 (10%, pH 7.0–7.5), and evaporated under diminished pressure (45°). Thereafter the product (except for Example 4) was extracted from the insoluble Na_2SO_4 by EtOH (95%), the extracts were evaporated, and after dissolution in water they were dialyzed briefly ($\sim$3 h) against distilled water. The retained fraction was freeze-dried; in Examples 1–3 the preparations were additionally extracted with acetone to remove oligopropylene glycols; products of Examples 4–7 were used directly.

TABLE I

Summary of preparative conditions of hydroxypropyl ethers of cyclomaltoheptaose

	Examples						
	1	*2*	*3*	*4*	*5*	*6*	*7*
Sodium hydroxide solution used as a solvent (%)	16.9%	17.5%	5.7%	1.5%	4.8%	17%	30%
Final reaction mixture (%)							
sodium hydroxide	10.4%	10.5%	2.9%	1.1%	2.7%	10.3%	23.4%
cyclomaltoheptaose (anhydrous)	29.6%	21.3%	28.6%	15.1%	23.0%	21.3%	11.6%
propylene oxide	4.0%	15.4%	14.4%	10.9%	16.6%	15.4%	8.4%
Final reaction mixture (molar ratio)							
Sodium hydroxide–cyclomaltoheptaose	10.0	13.9	2.9	2.1	3.4	13.8	57.2
Propylene oxide–cyclomaltoheptaose	2.6	14.1	9.8	14.3	14.3	14.3	14.1

Direct preparation of permethylated 2-hydroxypropyl ethers in dimethyl sulfoxide (Example 8). — Sodium hydride (5.5 g, 80% dispersion in mineral oil, 0.31 mol) was added to Me_2SO (65 mL) and left to react at 60° under argon with stirring for 1 h. The anhydrous solution of cyclomaltoheptaose (10 g, 9 mmol) in Me_2SO (65 mL) was then added, followed by the slow addition of (*S*)-propylene oxide (2.05 g, 35 mmol) in Me_2SO (10 mL). After 15 h at room temperature, MeI (26 mL) was added dropwise while cooling by ice bath. After one day of stirring at room temperature the reaction was terminated by the addition of water (100 mL) and the product extracted with $CHCl_3$ (2 × 150 mL). Chloroform extracts were washed with water (100 mL), saturated NaCl, and evaporated. The residue was partitioned between water (20 mL) and Et_2O (2 × 100 mL). Ethereal extracts were washed with water (20 mL), dried (Na_2SO_4) filtered through Al_2O_3 (8 g), and evaporated to yield a pale-yellow syrup (10.2 g).

Permethylation of 2-hydroxypropyl ethers. — A process similar to that just described was adopted, using dry 2-hydroxypropyl ethers in place of β-cyclodextrin and omitting the addition of propylene oxide.

Analyses of permethylated derivatives. — The permethylated product (3 mg) was dissolved in M aq. CF_3CO_2H (0.5 mL), kept in a screw-cap tube overnight at 100° and evaporated by flushing with air. The residue and $NaBH_4$ (10 mg) were dissolved in M aq. ammonia (0.5 mL) and kept for 1 h at room temperature. The solution was acidified with 50% AcOH (2 drops) and evaporated. Boric acid was removed by evaporating first 1:9 acetic acid–methanol (5 mL) and then methanol (25 mL) from the product. The residue was treated with Ac_2O and C_5H_5N (2:1, 0.5 mL) for 30 min at 100°, the solution was concentrated, and the residue partitioned between $CHCl_3$ and water (2:1, 6 mL). The $CHCl_3$ phase was evaporated and the residue analyzed by g.l.c. and g.l.c.–m.s.

G.l.c. was performed on a Hewlett–Packard 5830 A instrument fitted with a flame-ionization detector, with hydrogen as the carrier gas. G.l.c.–m.s. was performed on a Hewlett–Packard 5790-5970 system with helium as the carrier gas. A Hewlett–Packard Ultra 2 (cross-linked 5% phenyl methyl silicone) fused silica, capillary column (25 m, 0.20 mm i.d.) was used. Temperature program: 8 min at 185°, → 250° at 5° per min, 250° for 10 min.

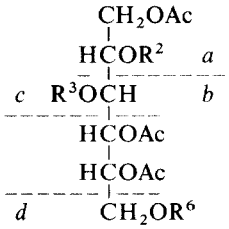
RESULTS AND DISCUSSION

Samples of 2-hydroxypropyl ethers of cyclomaltoheptaose were prepared by treating the oligosaccharide with propylene oxide in aq. sodium hydroxide. For one sample, sodium methylsulfinylmethanide in dimethyl sulfoxide was used as promotor. The reaction conditions are summarized in Table I. In order to determine the distribution of substituents between the different positions in the α-D-glucopyranosyl residues, each sample was successively permethylated, hydrolyzed, and the resulting glucose ethers analyzed, as their alditol acetates, by g.l.c. Their molar proportions were determined by g.l.c., using a flame-ionization detector and relative molar-response factors[6]. The same technique has been used previously for *O*-(2-hydroxyethyl)cellulose[7] and for *O*-(2-hydroxypropyl)guaran[8].

Etherification with propylene oxide is relatively a more complicated reaction than the corresponding reaction with ethylene oxide. When racemic propylene oxide is used, diastereomeric ethers are formed. As observed previously[8], the diastereomeric ethers of this type do not separate well on g.l.c. The same observation was made here and only one pair, the 3-*O*-(2-methoxypropyl)-D-glucitol derivatives, was partially separated. In order to fully address this complication, three samples (Examples 1–3, Table I) were prepared using racemic propylene oxide while the remaining samples (Examples 4–9) were prepared using (*S*)-propylene oxide.

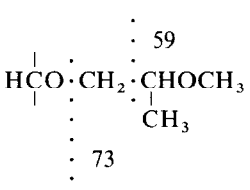
Another complication is that the oxirane ring in propylene oxide can be opened either by attack on C-1, which is the predominating reaction and gives a 2-hydroxypropyl ether, or on C-2, giving a 2-(1-hydroxypropyl) ether. Small quantities of two derivatives of the latter type were observed in the present study and others, because of their low concentrations, could have escaped detection.

The secondary hydroxyl group in a 2-hydroxypropyl group should not be very reactive, and alkylation in this position may consequently not be very important. This is in contradistinction to the hydroxyethylation reaction, in which oligomeric ether groups are readily formed. Small proportions of such derivatives were, however, observed.



1

R=$(CH_2CHO)_nCH_3$ (n_2, n_3, n_6 = 0, 1, 2, or 3; CH3 branch)



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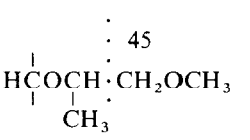

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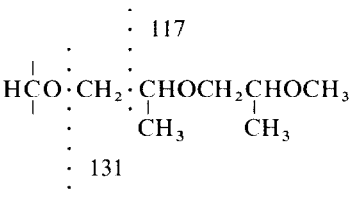

4

The fragmentation of the acetylated D-glucitol ethers (**1**) on electron impact follows established principles[9]. The ions *a* (m/z = 117 + n_2·58) and *b* (m/z = 233 + n_{3+6}·58) are of diagnostic value. From ion *c* (m/z = 161 + n_{2+3}·58), although not very strong, and the stronger secondary fragment, (*c* - 60), it could often be decided whether a substituent is located on O 3 or O 6. Ion *d*, (45 + n_6·58) is weak and of little value, unless n_6 = 0. The ions of m/z = 59 and 73 are very strong, and formed as indicated in

partial structure (**2**). A 2-(1-methoxypropyl) ether (**3**) does not give $m/z = 59$, but instead $m/z = 45$. An *O*-methyldipropylene glycol group (**4**) gives the fragments $m/z = 117$ and 131, of which the latter has diagnostic value. The mutual order of the derivatives on g.l.c. was the same as that observed for the corresponding 2-methoxyethyl ethers[7]. The percentages of the different ethers were also in agreement with the identifications, as a high or low reactivity in a different position should influence these percentages in a consistent manner.

The results of the analyses are summarized in Table II. In some analyses undermethylation, especially in the 3-position, was observed. The products, however, were identified from their mass spectra, and the molar percentages added to those of the corresponding fully methylated components. Two 2-(1-methoxypropyl) ethers were observed, namely S_2' and S_6', with this group in the 2- and the 6-position of a glucosyl residue, respectively. The yields of these ethers were 2–4% of the corresponding 1-(2-hydroxypropyl) ethers, and reflect the relative reactivities at the C-1 and C-2 positions of propylene oxide, respectively. Other 2-(1-hydroxypropyl) ethers, escaped detection because of their low concentration.

TABLE II

Glucose ethers in hydrolysates of fully methylated 2-hydroxypropyl ethers of cyclomaltoheptaose[a] and the respective relative reactivities of hydroxylgroups in cyclomaltoheptaose

Ether[b]	*T*[c]	*Examples (mole %)*							
		1	*2*	*3*	*4*	*5*	*6*	*7*	*8*
S_0	1.00	77.8	43.9	39.3	74.4	43.0	45.1	53.2	65.5
$S_{2'}$	1.77					0.6			
S_3	1.85	2.4[d]	5.2[d]	5.4[d]	4.8	6.6	3.0	1.4	0.9
S_2	1.92	5.2	10.9	30.3	14.6	23.6	8.4	3.1	2.3
$S_{6'}$	1.96						0.6	0.5	
S_6	2.02	12.5	23.2	3.8	2.6	7.3	28.1	33.0	23.3
S_{23}	2.54	0.6	2.2	14.3	2.2	9.6	2.8	0.7	
S_{36}	2.67	0.3	3.8	1.4	0.5	1.6	2.2	0.9	
S_{26}	2.73	0.9	7.7	3.7	0.9	5.2	6.4	1.9	1.8
S_{66}	2.96						0.3	4.7	6.0
S_{236}	3.21	0.1	1.3	1.7		2.4	2.3	0.7	
S_{226}	3.41						0.2	0.2	
S_{266}	3.48						0.5	0.4	
S_{666}	3.75							0.2	
Relative reactivity									
k_3/k_2		0.43	0.40	0.15	0.36	0.27	0.28	0.41	0.17
k_6/k_2		2.1	1.5	0.12	0.08	0.32	2.2	7.6	8.3

[a] For some samples, undermethylated products were also identified. The molar percentages of these components are included in those of the corresponding fully methylated derivatives. [b] Subscript: 2 connotes a $MeOCHMeCH_2$- substituent at postition 2 in glucose, 22 connotes a $MeOCHMeCH_2OCHMeCH_2$- substituent in the same position, e.t.c. In S_2' and S_6' the corresponding group is $MeOCH_2CHMe$-. [c] 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 on g.l.c. (see Experimental). [d] Partial separation of the diastereomers was observed.

The relative reactivities at the three different positions in the α-D-glucopyranosyl groups may be determined from the molar percentages of the ethers. In studies on cellulose ethers it has been observed that the reactivity at O–3 is often considerably enhanced when O–2 is alkylated, but that the reactivities at O–2 and O–6 are virtually unaffected by etherification in other positions[10,11]. Spurlin[12] has given equations for determining the relative reactivities from the distribution of the substituents, and these were used to calculate the values given in Table II. The value for k_3/k_2 concerns the relative reactivity at O–3 when O–2 is not alkylated, and is calculated from the molar percentages of ethers not substituted in the latter position. Further calculations indicate that the reactivity at O–3 is considerably enhanced when O–2 becomes alkylated, but the values are inaccurate and are not reported. The reactivity at the hydroxyl groups introduced on 2-hydroxypropylation is low and has not been calculated. From the results given in Table II, it is evident that the relative reactivities at O–2 and O–3 are rather independent of the alkali concentration during the etherification. The relative reactivity of O–6 versus O–2, however, varies from ~ 1:5 at low alkali concentration to 7:1 at high alkali concentration. For the reaction promoted by sodium methylsulfinylmethanide in dimethyl sulfoxide, the alkylation in the 6-position is even more favored.

In conclusion, it is possible to obtain a degree of regioselectivity in the reaction of cyclomaltoheptaose with propylene oxide by varying the alkali concentration during the reaction. High alkali concentration favors alkylation at O–6 and low alkali concentration at O–2. It remains to be seen if 2-hydroxypropyl ethers having the same degree of substitution but with different distribution of these substituents will have different properties as host molecules for lipophiles. Modified cyclodextrins have been used as enzyme models (compare *e.g.*, ref. 13–15). Selective alkylations at either O–2 or O–6 may also be a convenient first step in the introduction of a reactive group in such a molecule.

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