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DISTRIBUTION OF SUBSTITUENTS IN *O*-ETHYL-*O*-(2-HYDROXYETHYL)CELLULOSE

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ABSTRACT

The distribution of substituents in six *O*-ethyl-*O*-(2-hydroxyethyl)celluloses has been investigated by methylation analysis. The samples were prepared under conditions analogous to those used industrially. An analysis of the results, under simplified assumptions, indicates that the distribution of substituents in the greater part of each sample is fairly similar to that expected for a homogeneous reaction. There was, however, a considerable discrepancy between the percentage of (CH_2CH_2O) residues determined by analysis and the value calculated from the composition of the hydrolysate. The former value was much higher, indicating that glucose ethers with a high degree of hydroxyethylation have been overlooked in the g.l.c. analysis.

INTRODUCTION

Ethyl(hydroxyethyl)cellulose [*O*-ethyl-*O*-(2-hydroxyethyl)cellulose] is a non-ionic cellulose ether used as a thickener, adhesive, and emulsifier. For a better understanding of its physical properties in solution, it is desirable to determine the distribution of the two types of ether substituents. (Hydroxyethyl)cellulose [*O*-(2-hydroxyethyl)cellulose] is an intermediate in the preparation of ethyl(hydroxyethyl)cellulose and, as a first step in such studies, the distribution of substituents in some (hydroxyethyl)celluloses was investigated[1]. This was done by methylation of the (hydroxyethyl)cellulose, hydrolysis to a mixture of glucose ethers, and reduction and acetylation of these to the alditol acetates. The mixture of partially etherified, acetylated glucitols was analysed by g.l.c. and the individual components were identified by g.l.c.–m.s. We now report similar studies of ethyl(hydroxyethyl)-cellulose.

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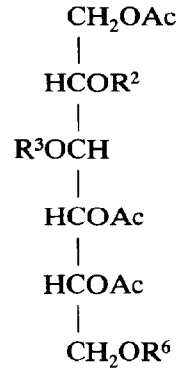
METHODS

Six samples of ethyl(hydroxyethyl)cellulose, EHEC 1, 2, 3, 4, 5, and 6, were prepared under conditions similar to those used in the technical process, that is treatment of "alkali cellulose" with a mixture of ethylene oxide and ethyl chloride. During the first step, at 43°, hydroxyethylation predominates and ethylation is insignificant. When it was assumed that the ethylene oxide had been consumed (1–2 h), the temperature was raised to 105° in order to start the ethylation reaction.

As in the investigation of (hydroxyethyl)cellulose[1], the sample of ethyl-(hydroxyethyl)cellulose was first fully methylated and then hydrolysed to a mixture of glucose ethers. These were reduced with sodium borohydride and acetylated. The resulting glucitol derivatives (**1**) were identified by g.l.c.–m.s., and their molar proportions were determined by g.l.c., using a flame-ionisation detector and molar response factors[2].



$R = (CH_2CH_2O)_nCH_3$ or $(CH_2CH_2O)_nC_2H_5$
$n = 0, 1, 2, 3 \ldots$

1

The fragmentation of the glucitol ethers on e.i.-mass spectrometry was analogous to that discussed for the glucitol ethers obtained from the (hydroxyethyl)cellulose, and the identification of the individual components followed the same principles. The presence of an ethyl instead of a methyl group gave an increase of 14 m.u. and did not complicate the identification. A serious complication, however, was the great number of ethers obtained. For $(n_2 + n_3 + n_6) = 0, 1, 2, 3$, and 4, the theoretical number of these ethers is 8, 24, 48, 80, and 120. However, at most, 48 or the 160 possible glucitol derivatives for which $(n_2 + n_3 + n_6) \leq 3$ were identified. Derivatives with $(n_2 + n_3 + n_6) = 4$ were not observed. Seven such ethers were obtained from a (hydroxyethyl)cellulose (HEC 3.3)[1], which was further ethylated to give sample EHEC 5. It is thus obvious that a number of ethers were overlooked, either because they occurred in too low amounts or because of overlapping with other components in g.l.c. One example of overlapping was actually observed. The 6-*O*-(2-methoxyethyl)- and 2-*O*-(2-ethoxyethyl)-glucitol de-

rivatives were not separated but were identified from the mass spectrum given by the mixture. However, it was not possible to determine their proportions; in the calculations discussed below, it is assumed that the mixture contained only the major component, namely, the 6-*O*-(2-methoxyethyl)glucitol derivative.

As several minor components have been overlooked, the number of substituents per glucosyl residue, as determined from the composition of the hydrolysate of the ethyl(hydroxyethyl)cellulose, is too low. The relative reactivity in the least reactive 3-position will also be underestimated.

RESULTS

The glucitol ethers observed, their retention times, and their molar percentages are given in Table I. The molar percentages are calculated from the responses of the flame-ionisation detector and the relative molar response factor[2]. The factor for 1,4,5-tri-*O*-acetyl-2,3,6-tri-*O*-methyl-D-glucitol is 0.74, and 0.10 is added for each ethyl group or (CH_2CH_2O) residue in **1**. In Table I, H_2E_3 stands for an ether in which $R^2 = CH_2CH_2OCH_3$ and $R^3 = C_2H_5$, $H_{66}E_6$ for an ether in which $R^6 = (CH_2CH_2O)_2C_2H_5$, *etc.*

The average numbers of (CH_2CH_2O) residues (MS) and of ethyl groups (DS) per glucosyl residue in the ethyl(hydroxyethyl)cellulose can be calculated from the composition of the hydrolysate as given in Table I. These values, and the corresponding values determined by analysis, are given in Table II, which also contains the relative amounts of ethylene oxide and ethyl chloride charged in the preparation of the different samples. For comparison, the corresponding values[1] for the (hydroxyethyl)cellulose studied previously are also given.

For the HEC samples, the agreement between the calculated MS values and those determined analytically is reasonably good. The same is true for the DS values of all EHEC samples. The analytical MS values for the EHEC samples, however, are very much higher than those calculated from the composition of the hydrolysate. A possible explanation for this discrepancy may be that, during the synthesis of the EHEC samples, all of the ethylene oxide had not been consumed when the temperature was raised in order to start the ethylation reaction. This ethylene oxide may then react to give long chains of oligo(ethylene glycol) linked to glucosyl residues. These structures will contribute to the ether group analysis, but the corresponding glucitol derivatives will, most probably, escape detection in g.l.c.

The results in Table I could be used for a simple kinetic analysis, as was done for the (hydroxyethyl)cellulose. The same assumptions are made, namely, that all glycosyl residues in the "alkali cellulose" are equally accessible and that the relative reactivities at the 2-, 3-, and 6-positions and at the introduced hydroxyethyl groups are constant throughout the reaction and not affected by substituents in adjacent positions. It is further assumed that hydroxyethylation is complete and all ethylene

TABLE I

GLUCOSE ETHERS IN HYDROLYSATES OF FULLY METHYLATED ETHYL(HYDROXYETHYL)CELLULOSES

Ether		T[a]	*Mole %*					
H	*E*		*EHEC 1*	*EHEC 2*	*EHEC 3*	*EHEC 4*	*EHEC 5*	*EHEC 6*
0	0	1.00	31.5	10.7	22.5	21.7	19.0	18.6
0	3	1.05	2.6	1.9	2.0	1.3	1.4	1.8
0	2	1.07	10.6	8.4	7.9	8.2	6.0	11.1
0	6	1.12	8.4	5.9	5.0	5.4	4.6	7.0
0	23	1.14	1.9	3.5	1.6	0.9		
0	36	1.20	1.3	1.8	0.8	0.8		0.9
0	26	1.22	3.5	6.4	2.4	2.3	1.5	3.0
0	236	1.27	1.0	3.0	0.5	0.5		1.4
2	0	1.70	3.4	1.5	4.3	4.1	3.7	3.9
3	2	1.74	0.4	0.4		0.6		0.6
2	3	1.76	1.9	1.9	2.4	2.1	1.9	2.9
6	0[b]	1.81	6.0	3.1	7.7	7.3	7.3	6.5
2	6	1.85	1.3	1.0	2.6	1.2	3.3	2.4
6	3	1.87	0.8	0.7	1.7	1.4	1.5	0.8
6	2	1.91	5.3	5.7	7.6	6.2	5.1	3.6
2	23	1.94	0.5	1.2		0.5		0.8
6	23	1.97	0.7	1.3	1.6	0.8		0.7
6	6	2.00	3.0	5.0	3.5	3.1	2.9	3.6
2	36	2.05	0.8	1.6	1.1	0.8	0.8	1.0
6	36	2.07	0.6			0.6		0.8
2	236	2.09		1.3				0.6
6	26	2.11	1.9	5.4	3.3	1.9	2.3	2.6
6	236	2.16	0.6	1.3		0.3		
23	0	2.41	0.5			0.3	1.5	1.0
26	0	2.60	1.3	0.9	2.2	1.1	2.7	2.0
26	3	2.64	0.6		0.7	0.8	1.2	
22	0	2.67	0.9	0.7	1.3	2.2	2.0	0.8
22	6	2.70		0.7	0.7	1.0		1.1
26	2	2.72	0.4	1.1	1.7	1.7	1.2	1.4
23	2	2.74				0.6		
26	6	2.77	0.6	2.0	1.0	0.8	1.5	2.5
66	0	2.81	2.8	4.1	6.3	5.9	6.9	5.8
26	36	2.83	0.3			1.2		
22	2	2.85	0.9	1.3	2.6	1.2	1.2	1.5
66	2	2.90	1.0	1.6	2.0	2.6	4.3	2.5
36	23	2.94	0.3			0.4		0.6
26	26	2.96	0.3	1.0		0.6	1.1	1.0
26	236	3.00	0.4	0.6		0.5		
66	6	3.04	1.0	3.8	1.3	1.8	2.2	3.1
66	36	3.12		1.2				0.6
66	26	3.14	0.7	1.7	1.7	1.0	1.6	1.5
66	236	3.18		1.6				
236	0	3.28					2.1	
226	0	3.55				1.2	2.4	
266	0	3.58				2.1	1.7	
666	0	3.80		2.6		1.0	3.2	
666	2	3.90					0.9	
666	6	4.04		2.1			1.0	

[a]Retention time relative to 1,4,5-tri-*O*-acetyl-2,4,6-tri-*O*-methyl-D-glucitol in g.l.c.: Hewlett–Packard Ultra 2 (cross-linked 5% phenyl methyl silicone) fused silica, capillary column (25 m × 0.20 mm i.d.). Temperature programme: 2 min at 150°, →230° at 3°/min, and hold at 230° for 20 min. The retention time for the reference substance was 6.40 min. [b]Contaminated by H_2E_2.

TABLE II

RELATIVE AMOUNTS OF ETHERIFYING AGENTS AND EXTENT OF SUBSTITUTION FOR DIFFERENT HEC AND EHEC SAMPLES

Sample	C_2H_4O[a]	C_2H_5Cl[a]	*MS*[b] *(found)*	*MS*[c] *(calc.)*	*DS*[d] *(found)*	*DS*[e] *(calc. 1)*	*DS*[f] *(calc. 2)*
HEC[g] 1.3	1.33	0	0.54	0.51	0	0	0
HEC 2.3	2.36	0	1.12	0.94	0	0	0
HEC 3.3	3.33	0	1.69	1.49	0	0	0
EHEC 1	1.33	1.0	0.79	0.44	0.66	0.71	0.63
EHEC 2	1.7	1.3	1.51	0.90	1.25	1.17	1.17
EHEC 3	1.8	0.8	1.72	0.81	0.75	0.70	0.63
EHEC 4	2.36	1.0	1.64	0.94	0.68	0.68	0.59
EHEC 5	3.33	1.0	2.77	1.18	0.73	0.55	0.47
EHEC 6	4.3	0.9	3.54	0.82	0.85	0.79	0.79

[a]Mole of etherifying agent per glucosyl residue in the "alkali cellulose". [b]Number of (CH_2CH_2O) groups per glucosyl residue, from analysis. [c]Number of (CH_2CH_2O) groups per glucosyl residue, calculated from the values in Table I. [d]Number of ethyl groups per glucosyl residue, from analysis. [e]Number of ethyl groups per glucosyl residue, calculated from the values in Table I. [f]Number of ethyl groups per glucosyl residue, estimated from the relative proportions of non-hydroxylated ethers in Table I. [g]Values for the HEC samples taken from ref. 1.

oxide consumed before the ethylation starts. These assumptions involve considerable over-simplifications. Thus, the reactivities in different positions depend upon the alkali concentration, which is constant during the hydroxyethylation but decreases during the ethylation. The number of minor components, and probably also of highly etherified components which have escaped detection, also involves a source of error, as discussed above. For these reasons, the calculated values for the relative reactivities in different positions of the glucosyl residues are not very accurate and definitely less so than the corresponding values for the (hydroxyethyl)cellulose.

As previously, S_2 is defined as the fraction of the glucosyl residues in the ethyl(hydroxyethyl)cellulose which contains one or several (CH_2CH_2O) residues in the 2-positions, but no such residues in any other position, *etc.*

$S_2 = H_2 + H_{22} + H_{222} + \ldots$, in which H_2 includes all H_2E_{xyz} derivatives for which x = 0 or 2, y = 0 or 3, and z = 0 or 6, *etc.*; $S_{23} = H_{23} + H_{223} \ldots$, *etc.*

The relative rates for hydroxyethylation at the 2-, 3- and 6-positions and at the introduced hydroxyethyl groups are defined as k_2, k_3, k_6, and k_H. As the relative rates are assumed to be constant throughout the reaction, the hydroxylation may be treated as a first-order reaction and the "time", t in kt, reflects the degree of substitution achieved in each experiment. The values for k_2t, k_3t, and k_6t are calculated from

$$S_2 + S_{23} + S_{26} + S_{236} = (1 - e^{-k_2t}), \text{ etc.}$$

For k_Ht, the equation for two consecutive first-order reactions gives

$$H_6 + H_{26} + H_{236} = k_6(e^{-k_6t} - e^{-k_Ht})/(k_H - k_6).$$

TABLE III

RELATIVE RATE CONSTANTS FOR THE REACTION AT DIFFERENT POSITIONS DURING THE HYDROXYETHYLATION REACTION

Sample	*MS (calc.)*	k_2t	k_3t	k_6t	k_Ht	$k_2:k_3:k_6:k_H$
HEC 1.3	0.51	0.182	0.042	0.235	0.47	1:0.23:1.40:2.6
HEC 2.3	0.94	0.300	0.086	0.445	0.83	1:0.29:1.48:2.7
HEC 3.3	1.49	0.393	0.164	0.675	1.13	1:0.42:1.72:2.9
EHEC 1	0.44	0.152	0.012	0.337	0.42	1:0.08:2.22:2.8
EHEC 2	0.90	0.184	0.004	0.631	1.00	1:0.02:3.43:5.4
EHEC 3	0.81	0.242	0.020	0.541	0.58	1:0.08:2.23:2.4
EHEC 4	0.94	0.274	0.019	0.585	0.76	1:0.07:2.13:2.8
EHEC 5	1.18	0.333	0.037	0.757	1.18	1:0.11:2.27:3.5
EHEC 6	0.82	0.254	0.022	0.504	0.80	1:0.09:1.98:3.1

The value for k_Ht is calculated only for the 6-position because of the much lower degree of substitution in the other positions.

The values calculated under these assumptions are given in Table III, which also gives the corresponding values for the three (hydroxyethyl)celluloses previously investigated. If the assumptions upon which the calculations are based are justified, and all experiments were performed with the same "alkali cellulose", the relative rate constants, assuming $k_2 = 1$, should be the same in all nine experiments. The values for k_3 are consistently lower for the ethyl(hydroxyethyl)celluloses than for the (hydroxyethyl)celluloses, and this is most probably due to the fact that a high percentage of the ethers substituted in the 3-position escaped detection. However, the other differences, both between the hydroxyethyl- and the ethyl(hydroxyethyl)-cellulose and within the latter group, are also considerable and indicate that the assumptions upon which the calculations are based involve an over-simplification, and possibly also that the conditions for preparation of the ethyl(hydroxyethyl)celluloses were not strictly reproducible.

From the values in Table III and using the same assumptions as above, it is also possible to calculate the relative rates for the ethylation reaction. However, this was feasible only for the non-hydroxylated glucosyl residues, and the values for the rate constants, k_{2E}, k_{3E}, and k_{6E}, are summarized in Table IV. For EHEC 5, the percentage of non-hydroxylated ethers was too low and three ethylated glucitol derivatives were not found, so that a calculation was considered meaningless. The relative reactivity at a hydroxyethyl group was determined from the H_6E ethers. It is less accurate than the other values, but indicates that the hydroxyl in an introduced hydroxyethyl group has approximately the same reactivity as the HO-2. As seen from Table IV, there is reasonably good agreement between the calculated relative reactivities for the four different samples. The experimental errors are also smaller than in the similar calculations for the hydroxyethylation reaction, as the former calculations are based upon the relative proportions of 8 derivatives only, and these were all observed and well separated from each other by g.l.c.

TABLE IV

RELATIVE RATES FOR ETHYLATION AT DIFFERENT POSITIONS DURING THE ETHYLATION OF (HYDROXYETHYL)CELLULOSE

Sample	*DS (calc.)*	$k_{2E}t$	$k_{3E}t$	$k_{6E}t$	$k_{HE}t$	$k_{2E}:k_{3E}:k_{6E}:k_H$
EHEC 1	0.71	0.33	0.12	0.27	0.39	1:0.37:0.82:1.2
EHEC 2	1.17	0.72	0.28	0.52	0.74	1:0.39:0.72:1.0
EHEC 3	0.70	0.34	0.12	0.23	0.41	1:0.35:0.68:1.2
EHEC 4	0.68	0.34	0.09	0.25	0.31	1:0.26:0.74:0.9
EHEC 6	0.79	0.50	0.15	0.27	0.81	1:0.30:0.54:1.0

A comparison of the distribution of the (CH_2CH_2O) groups actually found (from Table I) and that calculated from the *kt* values given in Table III has been carried out. As the results are very similar to those obtained in our investigation of (hydroxyethyl)cellulose, they are not reported. They confirm, however, that the assumption that all glucosyl residues in the "alkali cellulose" are equally accessible seems to be reasonable.

A similar calculation has also been performed for the ethylation reaction, using the k_Et values given in Table IV. The calculation concerns the non-hydroxyethylated glucosyl residues only. As discussed above, the calculation is based upon rather crude approximations, but, nevertheless, there is a reasonably good agreement between the calculated and the observed values. This indicates that all glucosyl residues, and most probably also the hydroxyethylated residues, are approximately equally accessible in the ethylation reaction. This situation is almost certainly due to the initial hydroxyethylation of the "alkali cellulose", which opened up the structure of the initially more-ordered regions.

The DS, calculated for the non-hydroxylated residues only ($DS_{calc.2}$ in Table II), is also similar to that calculated for the whole sample, again demonstrating the absence of inaccessible regions in the "alkali cellulose" after the hydroxyethylation reaction. Such regions exist in the original "alkali cellulose", but ethylene oxide is obviously small enough to penetrate regions of different accessibility with approximately the same ease.

The discrepancy between the analysis of the (CH_2CH_2O) residues and the MS values determined from the composition of the hydrolysates indicates a significant systematic error. As discussed above, it seems probable that a fraction consisting of highly hydroxylated glucitol derivatives escaped detection by g.l.c. The analyses and calculations reported in this communication are therefore representative for the major part of the EHEC samples, but not for the whole material.

EXPERIMENTAL

The experimental procedures, including preparation of samples, methylation analysis, g.l.c., and g.l.c.–m.s., were the same as in the investigation of (hydroxyethyl)cellulose[1].

ACKNOWLEDGMENT

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