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DISTRIBUTION OF SUBSTITUENTS IN *O*-(2-HYDROXYETHYL)CELLULOSE: A ^{13}C-N.M.R. APPROACH

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ABSTRACT

O-(2-Hydroxyethyl)cellulose was converted into a mixture of the corresponding D-glucitol derivatives by hydrolysis followed by reduction of the sugars with $NaBH_4$. On the basis of the spectra of individual *O*-(2-hydroxyethyl)-D-glucitols, the ^{13}C-n.m.r. spectrum of this mixture was assigned to the extent that permitted quantitative analysis in terms of monomer composition of the polymer. The monomer mole-fractions conform to a statistical, kinetic model that assumes that the reactivity of the 3-hydroxyl group of the D-glucosyl residues of cellulose depends on the state of substitution at O-2. The relative rate-constants of the hydroxyl groups in the (hydroxyethyl)ation reaction are k_2:k_3:k_3':k_6:k_x = 6.0:1.0:4.0:11.1:34.6, indicating that the reactivity of OH-3 increases fourfold upon (hydroxyethyl)ation of OH-2.

INTRODUCTION

Recent analyses of the ^{13}C-n.m.r. spectra of hydrolyzed or methanolyzed cellulose ethers have led to the determination of the degrees of positional substitution of *O*-(2-hydroxypropyl)cellulose[1,2] and, in favorable cases, *e.g.*, *O*-(carboxymethyl)cellulose (CMC)[3], *O*-methylcellulose[4], and *O*-ethylcellulose[5], to the detailed monomer compositions. Hydrolysis (or methanolysis) of a cellulose ether yields a mixture of 16 monosaccharide species, which includes the α and β anomers of the eight monomers (unsubstituted D-glucose, three mono-, three di-, and a tri-substituted D-glucose). In the process of making *O*-(2-hydroxyethyl)cellulose (HEC), however, the pendent 2-hydroxyethyl group also reacts, leading to oxyethylene side-chains of different lengths. Thus, the number of monomers increases substantially. The situation is further complicated by the non-stoichiometric formation of cyclic acetals when a single 2-hydroxyethyl group is attached at O-2 of D-glucose[1]. Substantial simplification can be achieved by reducing the hydrolysis mixture to the corresponding mixture of D-glucitol derivatives.

We now present the assignments of the ^{13}C-n.m.r. spectra of 2-, 3-, and 6-*O*-(2-hydroxyethyl)-D-glucitol. These assignments are then used to obtain partial assignment of the spectrum of the product of hydrolysis of HEC and the reduction

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thereof. Quantitative analysis of the latter spectrum yields the monomer composition of the polymer. The results permit a meaningful evaluation of theoretical models describing the distribution of substituents in HEC.

A simple theoretical model describing the distribution of substituents in HEC[6] assumes, *inter alia*, that the *relative* rate constants of reaction of the hydroxyl groups remain unchanged throughout the process and that substitution within a given D-glucosyl unit does not affect the reactivity of the remaining hydroxyl groups. According to this model, four relative rate constants (k_2, k_3, k_6, and k_x) are needed for a complete description of HEC. At least four independent observable quantities are needed for their determination. An additional fifth quantity is needed, however, in order to test the applicability of the model. The analytical data sets of Wirick[7] and Glass *et al.*[8], each of which contains only three observables, are adequately described by the model[6]. (Other relevant work on HEC is also discussed in ref. 6.) Recent studies of *O*-methylcellulose[4] and *O*-ethylcellulose[5] have shown that the reactivity of OH-3 depends on the state of substitution at C-2. Such a possibility in regard to HEC has not been considered previously, probably due to the lack of suitable data.

RESULTS AND DISCUSSION

Spectra. — The ^{13}C chemical-shift data for D-glucitol and its *O*-(2-hydroxyethyl) derivatives are summarized in Table I. The assignments for the parent D-glucitol were taken from the literature[9,10]. The assignments for the derivatives are based

TABLE I

CARBON-13 CHEMICAL SHIFTS (IN P.P.M.) OF D-GLUCITOL AND SOME OF ITS O-(2-HYDROXYETHYL) DERIVATIVES IN Me_2-SO-d_6

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-2'*[a]	*C-1'*[a]
D-Glucitol	64.11	75.32	70.44	73.89	73.04	65.01	—	—
2-HE-D-glucitol	62.21	84.57	70.33	72.97	72.70	65.15	62.21	73.64
3-HE-D-glucitol	64.15	74.45	80.71	73.08	72.98	65.19	62.66	75.38
6-HE-D-glucitol	64.20	75.27	70.40	73.86	71.46	74.65[b]	61.93	74.10[b]

[a] Primed numerals refer to hydroxyethyl substituents. [b] Assignments are interchangeable.

TABLE II

EFFECTS OF (HYDROXYETHYL)ATION ON THE CARBON-13 CHEMICAL SHIFTS OF D-GLUCITOL

Position	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*
2	−1.90	9.25	−0.11	−0.92	−0.34	0.14
3	0.04	−0.87	10.27	−0.81	−0.06	0.18
4	−0.09	−0.05	−0.04	−0.03	−1.58	9.64

on the expected substituent effects (large downfield shifts for carbon atoms bearing a substituent, and small upfield shifts for vicinal ones) and the results of attached-proton-test[11] experiments. The substituent effects of (hydroxyethyl)ation on the ^{13}C chemical shifts of D-glucitol are summarized in Table II.

Inspection of the data in Tables I and II leads to the following expectations regarding the spectrum of the mixture of D-glucitol derivatives obtained from HEC. Substituted atoms C-2 and C-3 should be outstanding in the low-field end of the spectrum. Multiple resonances are expected for these carbon atoms, depending on the state of substitution at other carbon atoms. At the high-field end should be the unsubstituted C-6 (at ~65 p.p.m.) and C-1 (at ~64 p.p.m.). The resonance of C-1, vicinal to a substituted C-2, is expected to be farther upfield (at ~62 p.p.m.), possibly overlapping with that of C-2 of the hydroxyethyl group. The other resonances are grouped together in the range 70–76 p.p.m. At the high-field end of this band, at ~70.5 p.p.m., the resonances of unsubstituted C-3 should be resolved. The data indicate that the effect of substitution of C-2 on the chemical shift of C-3 is rather small. This finding should not be surprising because, contrary to the case of D-glucopyranoses, D-glucitol is a rather flexible molecule, and the unpredictable effects of conformational changes[9,10] that may accompany substitution are superimposed on the usual substituent effects.

The ^{13}C-n.m.r. spectrum of the mixture of D-glucitol derivatives obtained by borohydride reduction of hydrolyzed HEC is shown in Fig. 1. The expectations discussed in the preceeding paragraph are born out well. However, contrary to the

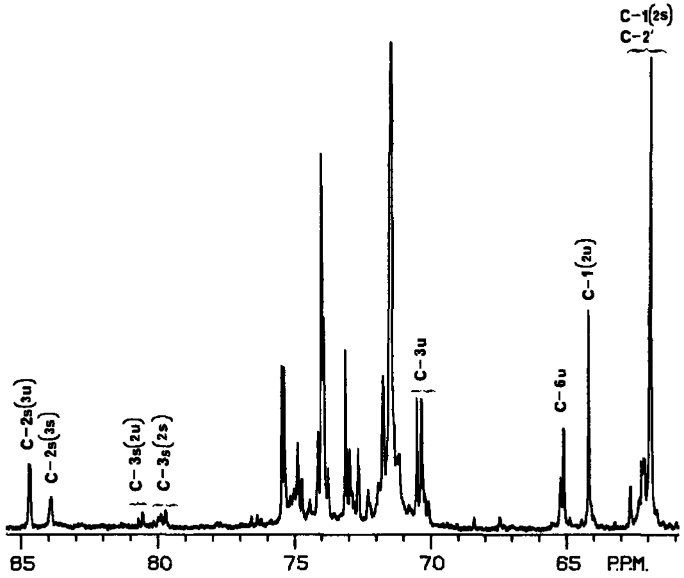

Fig. 1. ^{13}C-N.m.r. spectrum of the mixture of *O*-(2-hydroxyethyl)-D-glucitols obtained by borohydride reduction of hydrolyzed HEC. The letters s and u indicate substituted and unsubstituted, respectively.

sharp and well resolved resonances of the mixture of monosaccharides from CMC[3], *O*-methylcellulose[4], and *O*-ethylcellulose[5], the lines here are broad and not well resolved. This is probably due to the chemical heterogeneity arising from different lengths of the oxyethylene side-chains. Thus, *e.g.*, the chemical shifts of the CH_2 unit of the ethyl group in $CH_3CH_2O(CH_2CH_2O)_nH$ are 66.98, 67.00, and 67.05 p.p.m. for $n = 1, 2,$ and 3, respectively. This uncertainty to the extent of 0.07 p.p.m., is greater than the effect of substitution at C-6 on the chemical shift of C-2. Therefore, the sums of mole fractions $s_2 + s_{26}$, as well as $s_{23} + s_{236}$ cannot be separated. The resolution is better for the resonances of substituted C-3. Owing to the much lower substitution level at this atom (*vide infra*), chain extension here is less probable. The first two peaks (from low to high field), at ~80.7 p.p.m., were assigned to s_3 and s_{36}, respectively. The band (consisting of at least four peaks) between 80.2 and 79.7 p.p.m. has an intensity similar to that of the broad absorption at 83.9 p.p.m., and is assigned to $s_{23} + s_{236}$.

Quantitative analysis. — Integrated intensities were obtained by detailed curve-fitting of the corresponding resonance bands. The following relationships between integrated intensities and mole fractions were used.

$$I(84.6) = a(s_2 + s_{26}) \qquad (1)$$

$$I(83.9) = a(s_{23} + s_{236}) \qquad (2)$$

$$I(80.7) = a\,s_3 \qquad (3)$$

$$I(80.6) = a\,s_{36} \qquad (4)$$

$$I(65.0 - 65.3) = a(1 - x_6) \qquad (5)$$

$$I(79.9 - 80.7) + I(70.0 - 70.6) = a, \qquad (6)$$

where the chemical shifts are given in parentheses, and x_6 is the degree of substitution at C-6. The bands at 84.6 and 83.9 p.p.m. were deconvoluted, so as to give tentative values for s_{26} and s_{236}. The latter were then used to calculate

$$s_6 = x_6 - s_{36} - s_{26} - s_{236}. \qquad (7)$$

Finally, s_0, the mole fraction of unsubstituted D-glucitol, was calculated as

$$s_0 = 1 - (s_2 + s_{26}) - (s_3 + s_{36}) - (s_{23} + s_{236}) - s_6. \qquad (8)$$

A value for the molar substitution, M, was obtained by simple integration of the spectrum.

Monomer composition. — The monomer composition of the HEC sample investigated in this work is summarized in Table III. We shall discuss these results in the framework of the following, first-order kinetic scheme for the reaction of the cellulose hydroxyl groups with ethylene oxide (EO).

$$\text{-C-2-OH} + \text{EO} \xrightarrow{k_2} \text{-C-2-OEOH} \qquad (9)$$

$$\text{-C-2(OH)C-3-OH} + \text{EO} \xrightarrow{k_3} \text{-C-2-(OH)C-3-OEOH} \qquad (10)$$

$$\text{-C-2(OEOH)C-3-OH} + \text{EO} \xrightarrow{k_3'} \text{-C-2(OEOH)C-3-OEOH} \qquad (11)$$

$$\text{-C-6-(OH)} + \text{EO} \xrightarrow{k_6} \text{-C-6-OEOH} \qquad (12)$$

TABLE III

MONOMER COMPOSITION OF HEC (IN MOLE FRACTIONS) AND RELATIVE RATE CONSTANTS OF HYDROXYETHYLATION

Monomers	*Experiment*	*Model I*	*Model II*
s_0	0.258	0.221	0.254
s_2+s_{26}	0.216	0.293	0.216
s_3	0.015	0.053	0.021
s_6	0.330	0.291	0.335
$s_{23}+s_{236}$	0.148	0.071	0.148
s_{36}	0.032	0.071	0.027
Relative rate-constants			
k_2		0.54	0.54
k_3		0.26	0.09
k_3'		—	0.36
k_6		[1.00]	[1.00]
k_x		2.77	3.11
M	2.57		
D	1.13		

$$\text{-C}_i\text{-OEOH} + \text{EO} \xrightarrow{k_x} \text{-C}_i\text{-OEOEOH} \tag{13}$$

The solutions of the first-order rate-equations written according to the kinetic scheme of Eqs. *9–13* give the following expressions for the mole fractions, s_i, of the induvidual monomers[12].

$$s_0 = p_2p_3p_6 \tag{14}$$
$$s_2 = p_6R \tag{15}$$
$$s_3 = p_2p_6x_3 \tag{16}$$
$$s_6 = p_2p_3x_6 \tag{17}$$
$$s_{23} = p_6(x_2 - R) \tag{18}$$
$$s_{26} = x_6\mathrm{R} \tag{19}$$
$$s_{36} = p_2x_3x_6 \tag{20}$$
$$s_{236} = x_6(x_2 - R), \tag{21}$$

where

$$p_i = e^{-Bk_i} \tag{22}$$
$$x_i = 1 - p_i \tag{23}$$
$$R = k_2(p_3' - p_2p_3)/(k_2 + k_3 - k_3'), \tag{24}$$

with k_i being a first-order-rate constant, and B a factor with the dimension of time.

A general expression relating the molar substitution, M, to the relative rate-constants was derived as previously described[6].

$$M = 3Bk_x + D$$
$$- k_x[(1-p_2)/k_2 + (1-p_6)/k_6 + r(1-p_3')/k_3' + (1-r)(1-p_2p_3)/(k_2+k_3)], \tag{25}$$

where

$$r = k_2/(k_2 + k_3 - k_3'), \tag{26}$$

and D is the average degree of substitution. For $k_3 = k_3'$, Eq. 25 reduces properly to the previously given expression[6].

$$M = 3Bk_x + D - k_x\Sigma_i(x_i/k_i) \qquad (27)$$

In order to clarify the situation with the HEC process, it is instructive to separate the general model into two cases: Model I, where $k_3 = k_3'$ and $R = x_2p_3$, *i.e.*, no correlation of the reactivities of OH-2 and OH-3, and Model II, where $k_3 \neq k_3'$.

Model I. Detailed analysis of a series of CMC samples has shown that, within experimental error, there is no correlation between the reactivities of OH-2 and OH-3, and Model I holds[3]. In order to test the confirmity of the experimental data to the model, positional degrees of substitution are calculated as

$$x_2 = s_2 + s_{23} + s_{26} + s_{236} \qquad (28)$$

$$x_3 = s_3 + s_{23} + s_{36} + s_{236} \qquad (29)$$

$$x_6 = s_6 + s_{26} + s_{36} + s_{236} \qquad (30)$$

and values of p_i as

$$p_i = 1 - x_i \qquad (31)$$

Expectation (theoretical) values of s_i are then calculated with the appropriately simplified version of Eqs. *14-21*. The results thus obtained with the data on HEC are summarized in Table III. A plot of experimental *versus* calculated values is shown in Fig. 2. Although the two sets correlate, the scatter of points is substantial. It may be noted that s_0 and s_6 deviate in a similar fashion. A linear-regression analysis yields the relatively low correlation coefficient of 0.881. The standard deviation between experimental and calculated values is substantial: 32.4% of the average value.

Model II. Both *O*-methylcellulose[4] and *O*-ethylcellulose[5] obey Model II. In order to test the conformity of the experimental data to this model, x_2 and x_6 are

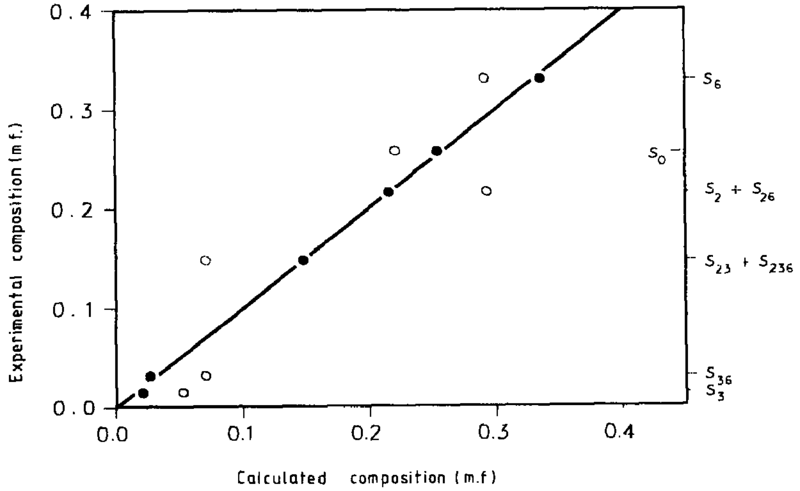

Fig. 2. Experimental *versus* calculated values of the mole fractions of the HEC monomers: Model I, open circles; Model II, filled circles.

calculated with Eqs. *28* and *30*, respectively. The other quantities are obtained as

$$R = s_2 + s_{26} \tag{32}$$

$$p_3 = (1-s_2+s_0+s_6-s_3-s_{36})/2(1-x_2) \tag{33}$$

It should be noted that because the sum $s_0 + s_6$ appears in Eq. *33*, systematic errors in their determination (Eqs. *7* and *8*) will cancel. The results of the calculations according to Model II are summarized in Table III. A plot of experimental *versus* calculated values is shown in Fig. 2. The conformity of the experimental data to this model is almost perfect. Now the correlation coefficient is 0.9994 and the standard deviation is only 2.4% of the average value.

The relative rate-constants of reaction of the cellulose hydroxyl groups with EO are summarized in Table III. The reactivity of OH-3 increases fourfold upon substitution of OH-2. Similar phenomena have been observed with *O*-methylcellulose[4] and *O*-ethylcellulose[5]. In CMC, however, the reactivity of OH-3 is independent of the state of substitution at O-2. The main factor responsible for these phenomena appears to be the involvement of OH-3 in an intramolecular hydrogen-bond. It seems that chloroacetate, the negatively charged reagent in the CMC process, can disrupt this hydrogen bond, whereas the neutral methyl chloride, ethyl chloride, and ethylene oxide cannot.

EXPERIMENTAL

The HEC sample used in this work was prepared by allowing a 5 molar excess of ethylene oxide to react with cellulose in a *tert*-butyl alcohol slurry that contained aqueous sodium hydroxide. The sample was withdrawn after reaction for ~2 h at a final temperature of 80°. The sample was then made neutral with acid, washed with aqueous acetone, and dried at 50° in a convection oven. After hydrolysis with sulfuric acid, the acid was neutralized with barium carbonate, the precipitate was filtered off, and the filtrate was evaporated in a rotary evaporator. The resulting syrup was reduced with $NaBH_4$ by following the procedure of Lee and Perlin[1].

O-(2-Hydroxyethyl) derivatives of D-glucitol were prepared by borohydride reduction[1] of the corresponding D-glucose derivatives. The latter were obtained from V-Labs, Covington, LA.

^{13}C-N.m.r. spectra of Me_2SO-d_6 solutions were recorded at 90.56 MHz, as previously described[3-5].

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