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HETEROGENEOUS ETHOXYLATION OF CELLULOSE: INFLUENCE OF ALKALI AND AVAILABLE-WATER CONCENTRATIONS ON SUBSTITUENT DISTRIBUTIONS

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ABSTRACT

O-(2-Hydroxyethyl)cellulose (**1**) as formed by the alkali-catalyzed addition of ethylene oxide to cellulose flock in a slurry process is not uniformly substituted. Most of the ethylene oxide adds to HO-6 in a chain-fashion, so that ~20% of the D-glucose residues remain totally unsubstituted at 2.0 molar substitution. Consequently, an aqueous solution thickened by **1** is highly susceptible to enzymic degradation. Stepwise decrease in concentration of alkali during etherification gives improved stability to enzymic degradation associated with a more-uniform distribution of hydroxyethyl groups between the three hydroxyl groups of the glucose residues in cellulose. The relative reactivities of hydroxyl groups and patterns of substitution were established by matching the distribution patterns from a stochastic computer-model with the distribution of substituents as determined by chemical analyses [namely hydrolysis with sulfuric acid to determine the percentage of unsubstituted glucose residues (u-**2**) and with periodate oxidation for determining the percentage of unsubstituted 2,3-vicinal diol groups per residue]. The reactivities of the three hydroxyl groups at various alkali concentrations in a heterogeneous, slurry-addition process approximate those observed under homogeneous conditions, wherein the reactivities have been determined by tedious chromatographic analyses. In the variable-alkali procedure for addition of ethylene oxide, the amount of water available to the cellulose matrix in the low-alkali (M) sequence is important both for the stability to enzymic degradation and for obtaining gel-free, thickened, aqueous solutions. Optimal stabilities and gel-free solutions are observed at intermediate water: cellulose ratios of 1.10–1.23. At a ratio of 1.23, the stability to enzymic degradation is less sensitive to percentage variations of u-**2** than in **1** prepared at higher or lower water: cellulose ratios. Although the initial degree of degradation between **1** of high molar substitution prepared at 6.8M alkali concentration and a similar product prepared under variable alkali conditions may be related to percentage differences of u-**2**, the

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rate and final degree of degradation do not relate to percentage differences of u-**2**. An adequate interpretation, utilizing known cellulase turnover-rates, is found in stochastic-model projections of the distribution of consecutive **2** residues not substituted at HO-2. The results indicate that (*1*) more-uniform substitution through equalization of hydroxyl reactivities is achieved by lowering the alkali concentration, and (*2*) more-uniform substitution of **2** of the many cellulose-chains being substituted is achieved by employing an optimal amount of "available" water during etherification.

INTRODUCTION

In the preparation of cellulose ethers, a variety of reagents may be substituted at HO-2, HO-3, and HO-6 of each D-glucose residue (**2**). In a heterogeneous slurry-addition technique[1], such preparations are conducted with high alkali-to-cellulose ratios, so that the matrix is swollen to disrupt inter- and intra-molecular hydrogen-bonding (particularly in the crystalline regions), making virtually all hydroxyl groups of **2** available for reaction. The greatest uniformity of substitution is achieved in carboxymethylation, the least in hydroxyethylation. Relative reactivities of the different functional groups under high concentrations of alkali (>4M) have been studied by Croon[2] and co-workers. More-recent reviews[3–5] have also summarized hydroxyl-group reactivities of **2** with various addition reagents. The enzymic degradation of various cellulose ethers has been studied[6], and the rates, based upon reactivity ratio-distribution calculations, have been equated with the percentage of unsubstituted D-glucose residues (% u-**2**).

The mechanism of addition of ethylene oxide is more complex than that of methoxylation or carboxymethylation, because of the generation of additional hydroxyl groups. Ethylene oxide preferentially adds to HO-6 (under high concentrations of alkali), and it has been suggested[7] that a u-**2** adjacent to a 6-O-substituted **2** is less resistant to enzymic attack than a u-**2** adjacent to a 2-*O*-substituted **2**.

The relative reactivities of the hydroxyl groups, $k_2:k_3:k_6:k_x$ (where k_x is the rate of addition to hydroxyl groups generated), in a high-alkali cellulose–ethylene oxide reaction have been estimated[8] to be 3:1:10:20 at molar substitution (mol. subst.) 0.6 and[9] 3:1:10:10 at mol. subst. 1.9–3.7. All samples were made by heterogeneous processes. Subsequently, it was discovered[10,11] that hydroxyethyl and diethylamino[12–14] substituents were more-evenly distributed at lower concentrations of alkali. Recently, n.m.r. studies of aqueous solutions of cellulose ethers have shown promise for directly characterizing hydroxyalkyl-substituted celluloses*.

In assessing the reactivity of hydroxyl groups of **2** toward different reagents, and the uniformity of distribution of a reagent among the u-**2** residues of the many

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*Initial studies of *O*-2-hydroxypropyl-[15] and *O*-2-hydroxyethyl-[16] cellulose estimated molar substitution and degree of substitution. In more-recent investigations[17,18], reactivity ratios for hydroxyethylation have been generalized. The latter studies were subjective and did not display thorough knowledge of prior work.

cellulose-chains, there is a lack of agreement among investigators. This is attributable to the relative inaccuracy of the individual tests applied and probably to differences in reaction conditions. This article uses a computer simulation of a stochastic process to calculate distribution-profiles at various mol. subst. intervals of hydroxyethylation. The distribution profile [% u-**2** and unreacted vicinal diol (% u-vicinal diol) as a function of mol. subst.] for a given simulation is then fitted with experimental data to determine relative ratios of hydroxyl-group reactivity. This combined approach provides a technique superior to prior efforts for determining relative hydroxyl-group reactivities for the following reasons: (*1*) use of a random computer-simulation avoids the approximations necessary in previous mathematical calculations of expected substituent-patterns for given reactivity ratios; (*2*) while % u-**2** data alone do not allow clear differentiation among some reactivity ratios, combined % u-**2** and % u-vicinal diol data are unique for any set of reactivity ratios and allow their determination with a much greater degree of precision; (*3*) the % u-**2** and % u-vicinal diol analyses are much less tedious than previous methods employing degradation, silylation, variations in chromatographic analyses, and mass spectroscopy.

RESULTS AND DISCUSSION

Determination of reactivity ratios. — The viability of using experimental data for both % u-**2** and % u-vicinal diol with the stochastic-model simulation to define the hydroxyl-group reactivities of **2** in the ethylene oxide–alkali-cellulose reaction is illustrated in Fig. 1. In both cellulose and amylose, HO-3 is recognized as the least reactive hydroxyl group. Furthermore, the reactivities of the vicinal 2,3-diols decrease with increasing hydroxide-ion concentration because of complex formation[14]. Nevertheless, the relative reactivities in this study are based on $k_3 = 1$ to avoid fractional relative-rates.

The results of the simulation of three previously reported[8-10] sets of reactivity ratios (all based on $k_3 = 1$), plus slight variations in the k_6 and k_x relative rates (around the actual ratio experimentally selected), are illustrated in Fig. 1. Over the normal mol. subst. range (<3.0), it is essentially impossible (because of the inaccuracy in experimental measurements of u-**2**) to distinguish between most of the relative ratios simulated. Measurement of both % u-**2** and % u-vicinal diol concentrations clearly defines the correct ratio as 5:1:8:12 (previously reported[10] by Ramnäs and Samuelson). Very minor rate-differences (such as 5:1:8:12 *vs.* 5:1:8:10) are distinguished by this technique when the analyses are extended to higher mol. subst. (~4.0) levels.

The fact that the ratio selected for the addition of ethylene oxide to cellulose, at 6.8M sodium hydroxide concentration, is in agreement with a previously reported set[10] may be fortuitous, as none of the previous studies employed similar conditions (except for the use of only slightly different high concentrations of alkali). Reactivity ratios were first determined[8] by analyzing **1** of low mol. subst. (0.6), synthesized at 40–45° at a press-ratio of 2.37. The term "press-ratio" usually refers to a procedure

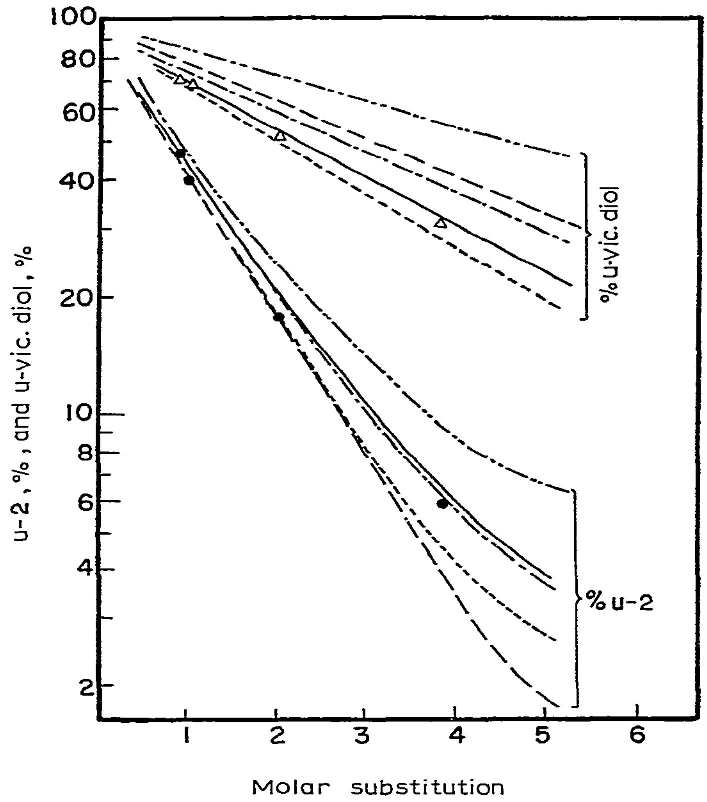

Fig. 1. Stochastic simulation of percentage dependence of unsubstituted glucose residues (u-2) and vicinal diol (u-vic. diol) on molar substitution (hydroxyethylation) of cellulose. △ and ●, experimental % u-vic. diol and % u-2 data, respectively, from *O*-(hydroxyethyl)cellulose (**1**) prepared in 2-methyl-2-propanol dispersant containing 10 wt.% water. Ratios of relative hydroxyl-group reactivity ($k_2:k_3:k_6:k_x$) assumed for high (>4M sodium hydroxide) alkali-catalyzed additions.

Simulation profile	$k_2:k_3:k_6:k_x$
- - - - - - - -	3 : 1 : 10 : 20
—— ——	3 : 1 : 10 : 10
—·—·—·—	5 : 1 : 11 : 15
————————	5 : 1 : 8 : 12
··········	5 : 1 : 8 : 10

wherein ethylene oxide is added to mercerized cellulose in a ribbon-blender–solids-mixing vessel. The second set of relative rates reported[9] did not discuss the conditions for preparation of **1**. The set of reactivity ratios[10] in agreement with this study is associated with the synthesis of **1** from cellulose of very low molecular weight, prepared from hydrolyzed rayon, which was soluble in alkaline aqueous solutions, and the ethoxylations were conducted at 25°. The cotton cellulose of high molecular weight (10^6) used in this study was not soluble in 6.8M alkali and the ethoxylation reactions were conducted at 75°.

The greater sensitivity of % u-vicinal diol (relative to % u-**2**) to narrower relative-rate differences between the hydroxyl groups is illustrated in Fig. 2. Narrower relative-rate differences may be achieved with low (~M) concentrations of alkali, but low levels of alkali are not feasible in the initial stage of a slurry synthesis[1]; there is insufficient alkali to disrupt crystalline regions (~70% in cotton) in the cellulose precursor. Partial hydroxyethylation (to an intermediate mol. subst. of 0.8–1.2) under high concentrations of alkali (6.8M), and subsequent decrease of the catalyst concentration before continuing the hydroxyethylation to mol. subst. 4.0–4.5, is a viable procedure for achieving a more-uniform substitution of hydroxyethyl groups in a heterogeneous-slurry synthesis. This technique may be realized by partial neutralization (that is, as a continuous or stop-and-go procedure) or by a two-stage synthesis. In the latter procedure, the **1** of intermediate mol. subst. is neutralized and extracted while being maintained in a hydrated state.

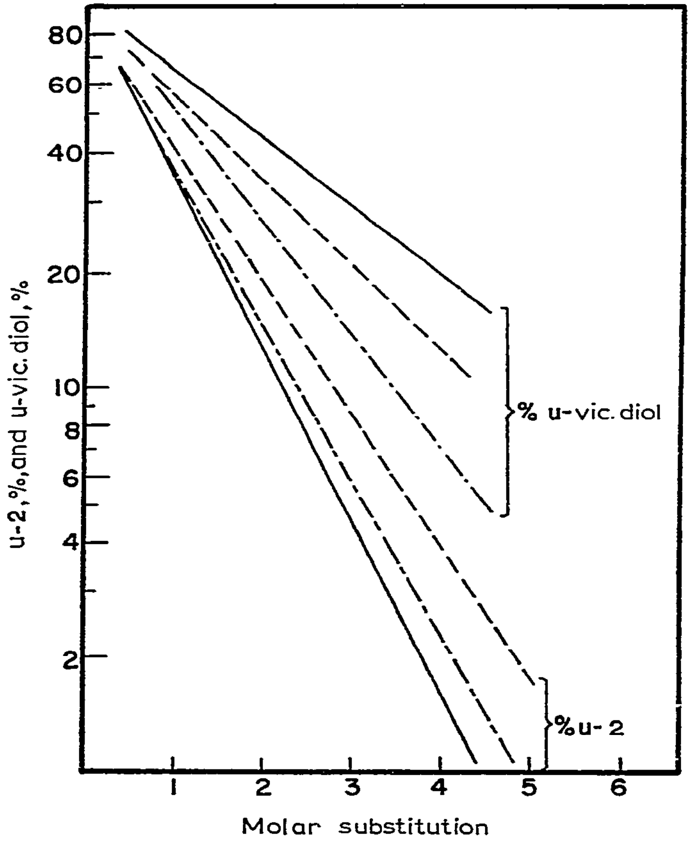

Fig. 2. Stochastic simulation (see Fig. 1). Ratios of relative hydroxyl-group reactivity ($k_2:k_3:k_6:k_x$) assumed for low (~M sodium hydroxide) alkali-catalyzed additions.

Simulation profile	$k_2 : k_3 : k_6 : k_x$
-----	3 : 1 : 3 : 2
------	3 : 1 : 2 : 4
————	3 : 1 : 5 : 4

To reproduce the experimental alkali-decrease techniques, simulation of the ethylene oxide–alkali–cellulose reaction with the 5:1:8:12 ratio for the high-alkali (6.8M) sequence provided distribution profiles for products of intermediate mol. subst. (namely, 0.8, 1.0, or 1.2). Different sets of reactivity ratios were then employed and fitted with the experimental data (% u-2 and % u-vicinal diol) obtained from samples of higher mol. subst. prepared *via* continued hydroxyethylation at low levels of alkali. In both the partial-neutralization and the extracted two-stage reactions, there are insufficient data to define a precise fit with the computer output. Nevertheless, products from both processes delineate a change in the relative hydroxyl reactivities with a decrease in alkali concentration. In the two-stage extraction process

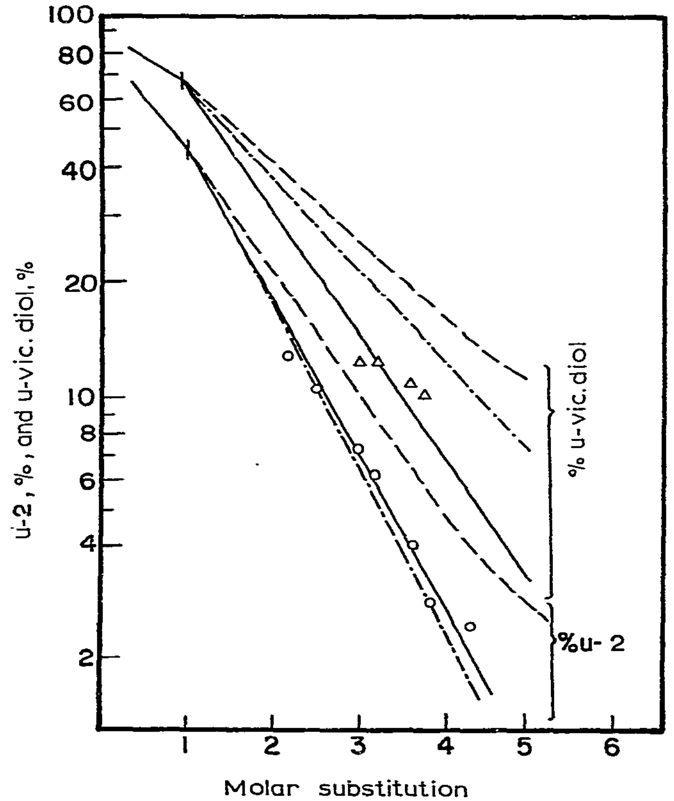

Fig. 3. Stochastic simulation (see Fig. 1). △ and ●, experimental data for % u-vic. diol and % u-2, respectively, from 1 prepared in 2-methyl-2-propanol dispersant containing 10 wt.% water. Ratio of relative hydroxyl-group reactivity of 5:1:8:12 simulated for 6.8M sodium hydroxide, catalyzed addition to a molar substitution level of 1.0; thereafter, narrower relative-ratios are simulated for subsequent low (~M) alkali-catalyzed additions.

Second sequence: *Simulation profile*	$k_2 : k_3 : k_6 : k_x$
- - - - - -	3 : 1 : 3 : 2
— — —	3 : 1 : 2 : 4
————	3 : 1 : 1 : 2

(M alkali in the second sequence), relative reactivities of 3:1:1:2 are indicated (Fig. 3). In the partial-neutralization process [alkali/cellulose wt.% (II) = 0.087, or 1.2M in sodium hydroxide] the mol. subst. (and therefore concentration of alkali) is approximated during the reaction sequence from prior experience; the apparent relative reactivities are 3:1:3:2. These changes in heterogeneous etherification rates are consistent with the observations of other workers[10] in homogeneous derivatization-reactions. The simulated distribution-profiles for the partial-neutralization procedure are recorded in Table I.

Wirick[9] observed that stability to enzymic degradation in solutions thickened by **1** increased with increasing mol. subst., and he related this to a decreasing content of u-**2**. The % u-**2** does decrease with increasing mol. subst. (20.5% at 2.0; 5.7% at 3.9; experimental data from samples prepared in 6.8M alkali) but, in comparison to the effect noted when the concentration of alkali is decreased, the improved stability to enzymic degradation noted as a function of mol. subst. is relatively insignificant. The higher stability to enzymes observed in the **1** of high mol. subst. examined by Wirick is attributable to two factors: (*1*) a lower enzyme concentration [40 *vs.* 1000 p.p.m. (based on polymer) in this study], and (*2*) use of **1** of extremely low molecular weight, and of high mol. subst.

In a two-stage synthesis, the stability to enzymic degradation may be quantitatively related to molar substitution (Eq. *1*):

$$\text{Stability to enzymic degradation} = 24.4(\text{mol. subst.}) - 45.2 \qquad (1),$$

where mol. subst. > 2.0. The correlation coefficient is 0.86. When all other variables in the preparation of **1** by a two-stage, variable alkali concentration are kept constant, a linear relationship (Eq. *2*, correlation coefficient = 0.99) is observed between stability to enzymic degradation and % u-**2**, in the range of 2.5–5.4% u-**2**

$$\text{Stability to enzymic degradation} = 87.9 - 11.1(\%\ \text{u-}\mathbf{2}) \qquad (2).$$

Importance of available water in a heterogeneous synthesis. — In the heterogeneous, variable-alkali-concentration preparation of **1**, the amount of water "available" to swell the alkali-cellulose matrix is important in obtaining **1** having significant stability to enzymic degradation and complete water-solubility. This variable in a slurry process will depend on the amount of total water charged and its solubility in the respective dispersant (Fig. 4).

The importance of the water available to the swollen cellulose matrix and subsequently for stability to enzymic degradation of the final product differs between the first- and second-stage sequences. For example, in the preparation of **1** of intermediate mol. subst. (0.8–1.2), the % u-**2** does not vary with different dispersants [and therefore with varying water concentrations (compare data in Fig. 5 with appropriate values in Fig. 1), and there is no difference attributable to varying the water concentration in the different dispersants]. This agreement (namely, the linearity between log(% u-**2**) and mol. subst. under variable water concentrations in the high-alkali sequence), and the match of the reactivity-ratio set with values

TABLE I

STOCHASTIC-MODEL SIMULATION OF REACTION BETWEEN ALKALI CELLULOSE[a] AND ETHYLENE OXIDE

*Assumed relative reactivity-ratios of HO-2, HO-3, HO-6, and HO-*x *groups*	*Mol. subst.*[b]	*Percent substitution at*							% *u-2*[c]	% *u-vic. diol.*[d]	*Ethylene oxide, distribution of chain-lengths*	*Position of substitution*			*D.s.*[e]
		O-2	*O-3*	*O-6*	*O-2,3*	*O-2,6*	*O-3,6*	*O-2,3,6*				*O-2*	*O-3*	*O-6*	
5:1:8:12	0.50	10.9	1.7	18.7	0.3	4.0	0.6	0.2	63.6	82.3	1	128	25	185	0.42
											2	28	3	47	
	1.00	17.2	3.1	22.7	0.6	7.9	1.9	0.9	45.7	68.4	1	174	44	196	0.67
											2	69	17	97	
											3	21	4	32	
											4	2	0	5	
											5	0	0	4	
3:1:3:2 inserted at mol. subst. = 1.0	1.50	17.4	4.2	23.1	2.6	18.1	4.3	2.2	28.1	51.2	1	273	100	296	1.01
											2	97	27	116	
											3	23	5	45	
											4	10	1	16	
											5	0	0	3	
											6	0	0	1	
	2.00	16.4	4.1	20.5	3.1	26.4	6.4	5.8	17.3	37.8	1	339	145	347	1.30
											2	121	37	149	
											3	43	10	65	

										4	12	2	21	
										5	1	0	8	
										6	1	0	1	
3.00	10.6	2.7	14.6	4.1	37.8	6.5	17.2	6.5	21.1	1	390	200	273	1.76
										2	188	72	234	
										3	85	30	99	
										4	25	3	38	
										5	7	0	12	
										6	2	0	3	
										7	0	0	2	
3.50	8.2	1.8	11.8	5.1	39.9	6.7	23.1	3.4	15.2	1	395	231	346	1.95
										2	211	88	246	
										3	98	41	125	
										4	46	7	53	
										5	10	0	18	
										6	3	0	4	
										7	0	0	1	
										8	0	0	1	
4.00	6.6	1.3	9.5	5.2	39.4	6.0	29.7	2.3	11.8	1	374	238	332	2.08
										2	240	125	261	
										3	122	42	149	
										4	49	14	67	
										5	17	3	29	
										6	4	0	6	
										7	3	0	1	
										8	0	0	1	

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[a]Based on a degree of polymerization = 1000. [b]Molar substitution. [c]% Unsubstituted glucose residues. [d]% Unsubstituted vicinal diol groups. [e]Degree of substitution.

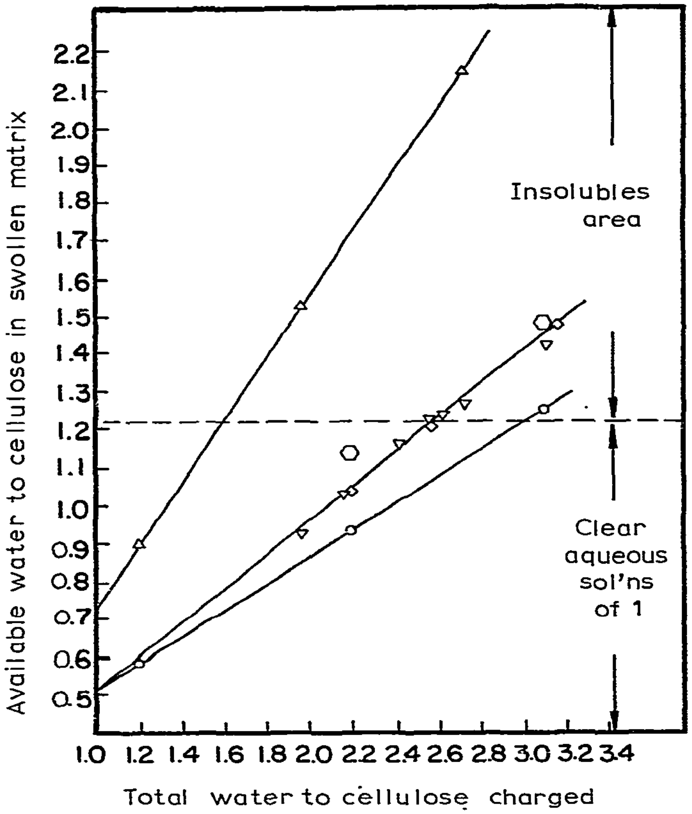

Fig. 4. Dependence of available water ratio on total water:cellulose ratio in various dispersants. Relationships defined under 6.8M sodium hydroxide concentration.

Symbol	*Dispersant*
○	2-propanol
▽	2-methyl-2-propanol
◇	1 : 1 wt.% 2-propanol–butanone
⬡	propanone
△	butanone

obtained from **1** prepared (at 5.4M, 25°) with "solubilized-rayon" cellulose^{10}, suggest that the amount of water available in the high-alkali, first-stage addition is not critical, so long as a threshold amount is present. When 2-methyl-2-propanol is the dispersant, the threshold amount is 6 wt.% (namely, an available-water:cellulose ratio, w/w, of 1.05). If this amount is not present, subsequent **1** products of high mol. subst. possess high concentrations of insolubles, irrespective of the amount of water used in the second-stage sequence. When the threshold amount of water is exceeded in the first-stage sequence, the amount of water in the second-stage sequence is important, and there is an upper, critical water-level in the second sequence.

For example, the stability to enzymic degradation is low when low water-ratios

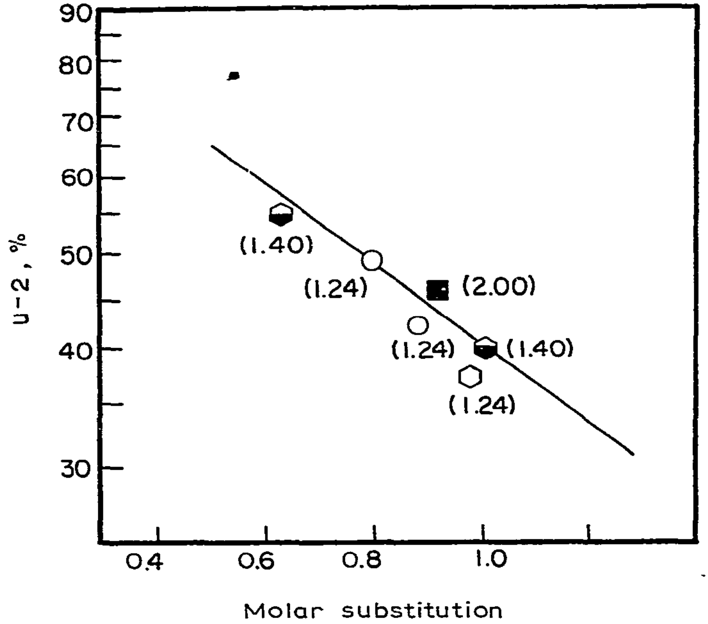

Fig. 5. Dependence of percentage unsubstituted **2** on mol. subst. in 6.8M sodium hydroxide-catalyzed preparation of **1** of intermediate mol. subst.

Symbol	*Dispersant*	*Available water:cellulose ratio*
○	2-propanol	1.24
⬡	propanone	1.24
⬢		1.40
■	butanone	2.00

are used in the low-alkali sequence of the two-stage procedure (Fig. 6). The stability to enzymic degradation increases with increasing water content, and then, at an upper water-level in the second-stage sequence, decreases with the onset of significant levels of insolubles upon dissolution of the **1** of high mol. subst. The parabolic stability to enzymic degradation–second-stage, water-level relationship is illustrated in Figs. 6 and 7 for two first-stage products prepared in 2-methyl-2-propanol containing 9.0 and 7.5% total water (and having mol. subst. 0.86 and 1.15, respectively) in the first sequence.

The parabolic relationship observed when 2-methyl-2-propanol is used as the dispersant in the second stage is also observed with other dispersants. The maximum stability to enzymic degradation is different for each dispersant; the highest (60% retained-viscosity) is observed when 2-methyl-2-propanol is the dispersant, the lowest (30% retained-viscosity) when 2-propanol is the dispersant. The reason(s) for the large difference is not clearly understood. Perhaps the amount of water in the organic phase is critical for maintaining a certain distribution of unreacted oxide and by-products, and in this role, a maximum uniformity of substitution is promoted.

Achieving a certain % u-**2** with the lowest possible mol. subst. is indicative

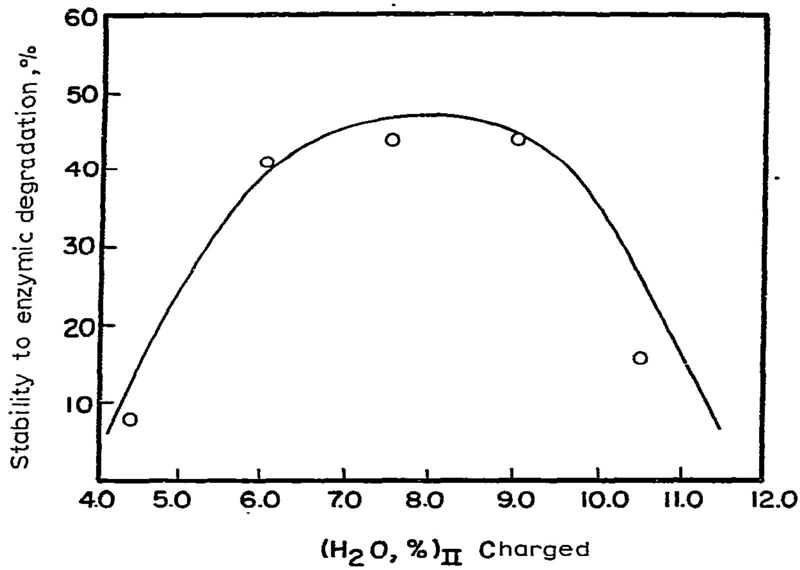

Fig. 6. Stability to enzymic degradation (%), dependence on wt.% of water charged in 2-methyl-2-propanol dispersant in second-sequence ethoxylation catalyzed by M sodium hydroxide to mol. subst. 4.2. Parameters for synthesis of first-sequence 1: 6.8M sodium hydroxide, 9.0 wt.% water in 2-methyl-2-propanol, mol. subst. 0.86.

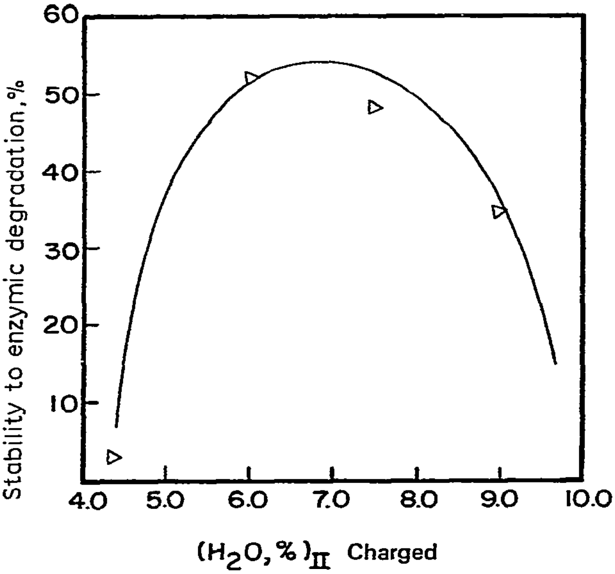

Fig. 7. Stability to enzymic degradation (%), dependence on wt.% of water charged in 2-methyl-2-propanol dispersant in second-sequence ethoxylation catalyzed by M sodium hydroxide to mol. subst. 4.2. Parameters for synthesis of first-sequence 1: 6.8M sodium hydroxide, 7.5 wt.% water in 2-methyl-2-propanol, mol. subst. 1.15.

TABLE II

DISPARITIES IN RELATIONSHIP OF MOLAR SUBSTITUTION, PERCENT UNSUBSTITUTED D-GLUCOSE RESIDUES, AND STABILITY TO ENZYMIC DEGRADATION[a]

Molar substitution of **1**	*u*-**2** *(%)*	*Stability to enzymic degradation (%)*
3.25	2.6	54
3.47	2.4	49
3.77	3.1	44
3.83	3.1	26
3.74	3.1	54
3.85	5.2	16
2.84	5.3	46
3.55	5.4	32

[a] High mol. subst. **1** prepared by partial neutralization technique.

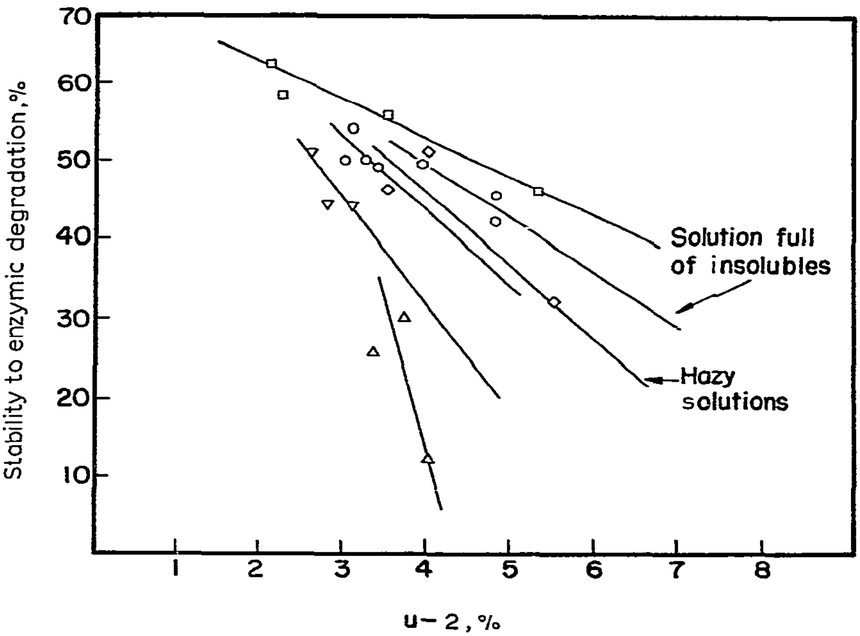

Fig. 8. Stability to enzymic degradation (%), dependence on unsubstituted **2** units (u-**2**, %). *O*-(Hydroxyethyl)cellulose (**1**) prepared in 2-methyl-2-propanol with variable water percentages *via* partial-neutralization syntheses.

Symbol	*Wt.% H_2O in* tert-*BuOH*	*Water : cellulose in aqueous phase*
△	4.3	0.92
▽	6.0	1.04
○	8.0	1.16
□	9.0	1.23
◇	10.0	1.30
o	12.5	1.48

of having achieved the most-random distribution of the unsubstituted residues. The low-alkali sequence does effect more favorable reactivity ratios, and has some positive effect on the disruption of crystal remnants in the **1** of intermediate mol. subst. Disparaties, however, exist between mol. subst., % u-**2** and stability to enzymic degradation (Table II) for **1** of high mol. subst. obtained by the partial-neutralization technique. The most significant variable affecting the disparities is the available water in the second sequence. As stability to enzymic degradation is a function of both the number of u-**2** residues and their distribution, the degree of dependence of stability to enzymic degradation upon u-**2** in a sequence of reactions varying only in available water levels (Fig. 8) may be considered a measure of the evenness of distributions of the u-**2**. A minimum slope is indicated for a water:cellulose ratio of 1.23.

Importance of consecutive, unsubstituted residues. — Finally, additional insight into structural influences on stability to enzymic degradation may be gained from the loss of viscosity in solutions of cellulose ether (Fig. 9) inoculated with *Aspergillus niger* cellulase (1000 p.p.m. based on polymer, 10 p.p.m. based on total solution). There are fewer u-**2** residues (Table III) in the adjusted-alkali-catalyzed ethoxylation

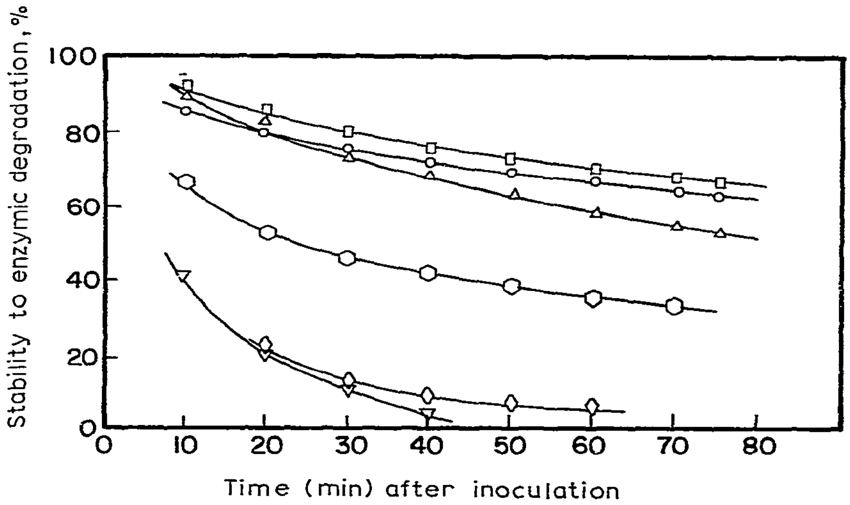

Fig. 9. Stability to enzymic degradation (%), dependence on incubation time (min) for 1 wt.% cellulose ether solutions (inoculated with 1000 p.p.m. of cellulase from *Aspergillus niger*, 30°, pH 5.7).

Symbol	*Cellulose ether*	*Mol. subst./d.s.*	*Total d.s.*
□	*O*-(Hydroxyethyl)cellulose (**1**) *via* 2-stage, extraction synthesis, with optimal process water control	4.6/–	~2.3
○	**1** *via* partial-neutralization synthesis with optimal process-water control	4.6/–	~2.3
△	*O*-(Hydroxyethyl)methylcellulose	1.6/1.3	~2.1
⬡	*O*-(Hydroxyethyl)hydroxypropylmethylcellulose	1.5(0.1 hydroxypropyl)/0.6	~1.5
◇	**1** *via* 6.8M-catalyzed one-stage synthesis	4.2/–	~1.6
▽	**1** *via* 6.8M-catalyzed one-stage synthesis	2.0/–	~1.1

TABLE III

SIMULATION OF CONSECUTIVE SEQUENCE-DISTRIBUTIONS OF UNSUBSTITUTED RESIDUES IN HIGH MOL. SUBST. *O*-HYDROXYETHYLCELLULOSE

[NaOH] during ethoxylation	*Assumed relative reactivity-ratios of HO-2, HO-3, HO-6 and HO-x groups*	*Mol. subst.*	*Degree of subst.*	*Distribution of consecutive residues*	*Unsubstituted 2*		*Unsubstituted at HO-2*		*Total average unsubstituted residues per 1,000*		*Stability at enzymic degradation (40h)*[b] %
					%	*No. per 1,000*	%	*No. per 1,000*	*u-2*	*Non HO-2*	
6.8M	5:1:8:12	4.00	1.58	1	93.8	6.1	39.8	14.9			
				2	6.2	0.4	29.9	11.2			
				3			18.5	6.9			10
				4			7.5	2.8			
				5			2.7	1.0			
				6			1.6	0.6			
									6.5	37.4	
		4.50	1.65	1	96.2	5.1	46.5	15.9			
				2	3.8	0.2	31.6	10.8			
				3			15.8	5.4			
				4			4.7	1.6			
				5			1.5	0.5			
									5.3	34.2	
6.8M to mol. subst. = 1.0, and then M	5:1:8:12, then 3:1:1:2[a]	4.00	2.02	1	90.0	1.8	70.1	8.9			
				2	10.0	0.2	20.5	2.6			
				3			9.4	1.2			
									2.0	12.7	
		4.50	2.13	1	91.2	1.3	73.5	7.2			
				2	8.8	0.2	20.4	2.0			
				3			6.1	0.6			80
									1.5	9.8	

[a] Fig. 3. [b] Fig. 9

product than in the **1** of high mol. subst. synthesized with 6.8M sodium hydroxide. Over a short time-interval, the values of stability to enzymic degradation could be equated with the difference in u-**2** (Eq. *2*), but the rates and final degrees of degradation are not relatable with known[19] turnover rates for cellulase.

The average number of moles of substrate degraded per min per mol of cellulase is dependent upon the number of unsubstituted u-**2** residues in sequence, and reaches a maximum value (454) at five residues[19]. The rate of degradation for two contiguous u-**2** residues is low (that is, 5.6). Similar relative rates for lysozyme acting on oligomers of 2-acetamido-2-deoxy-D-glucose, a close structural analog of cellulose, have also been observed[20]. In view of these observations and the lack of consecutive u-**2** residues (Table III) for the 6.8M-catalyzed high mol. subst. **1**, the rapid rate of degradation (Fig. 9) noted for this product is surprising. A detailed analysis of products from the enzymic degradation of a **1** of low mol. subst. (1.6) led Klop and Kooiman[7] to deduce that a u-**2** residue contiguous with a residue not substituted at HO-2 was enzymically degradable. In support of their deduction, the rate and degree of degradation between the high and the adjusted, alkali-catalyzed **1** is more readily interpretable in terms of the consecutive sequence-distributions, which include non-2-substituted D-glucose residues (Table III). This correlation clearly demonstrates the power of the simulation process. Having established the correct relative-rates for a given or set of given conditions, the detailed structural aspects of a macromolecule are available for definitive correlation with the polymer's performance in subsequent tests. The laborious experimental analyses on complex mixtures[7], and the possible omission of key by-products[10,11] in such analyses are by-passed.

A quantitative understanding of the enzymic degradation of **1** of high mol. subst., however, is not yet possible. For example, the cotton linters used in this study were ~70% crystalline, and 5–10% of this crystallinity (X-ray diffraction analysis[21]) remains in the dried **1** of intermediate mol. subst. (1.0). From the linewidths of the diffraction patterns at one-half intensity, the crystals in the 1.0-mol. subst. products may be estimated to be ~39 Å in size. This result corresponds to five residues of **2**, the optimal consecutive length for rapid enzymic degradation. The final, high-mol. subst. (4.0–4.5) **1** prepared by either catalysis procedure exhibits crystalline diffraction-lines too weak to be quantified. If crystalline units are included in the stochastic simulation, the number of consecutive u-**2** residues (e.g., five) will remain constant (because of their unavailability) throughout the higher ethoxylation range. Possible disruption of these aggregates during dissolution of the dry product in aqueous solution through shear-stress forces would facilitate rapid enzymic degradation, beyond that expected from the sequence profiles listed in Table III. The dramatic influence of the available water (Figs. 6 and 7) on distribution patterns, either alone or through interaction with the other variable already cited, adds additional complexities to a detailed analysis.

The improved stability to enzymic degradation in **1** noted in this investigation, a result of controlling the alkali and available-water concentration, suggests that even greater control of the chaining and uniformity of distribution should be achievable in the addition of ethylene oxide to alkali cellulose. Optimization of the interactions among the synthesis parameters in a Greco–Latin square-designed, statistical series of investigations should effect realization of this projection in future studies.

EXPERIMENTAL

Materials. — Cotton linters were used throughout this study as the source of cellulose. The two preparative procedures employed for **1** were as follows.

Two-stage, extraction synthesis. The two-stage, extraction technique involves essentially two separate reactions. The first sequence is a standard slurry process[1] for **1** in which sufficient alkali is added to swell the cellulose (alkali/cellulose wt.% = 0.37, or 6.8M in sodium hydroxide). After digestion for 0.5 h, sufficient ethylene oxide is added to the flock to give mol. subst. of ~0.8–1.2 when heated for 1 h to 75°. The slurry is then neutralized and the product of low mol. subst. is extracted to remove by-products and salts. The product is recharged with fresh dispersant, water, and a catalytic amount of alkali (alkali/cellulose wt.% = 0.07, M sodium hydroxide). Additional ethylene oxide is added and allowed to react to give a total mol. subst. of 3.5–4.5; after complete neutralization, the final product is extracted.

Partial-neutralization synthesis. This sequence is identical to the foregoing two-stage extraction with one exception; there is no intermediate extraction. Ethylene oxide is added in an amount to produce a product of intermediate mol. subst. After 30 min at 75°, the slurry is cooled, partially made neutral, and then additional ethylene oxide is added. The temperature is raised (75°) and the reaction continued to completion. The reaction may be conducted without cooling by charging all of the ethylene oxide initially and partially neutralizing the mixture at a predetermined time estimated to correspond to the formation of **1** of mol. subst. 0.8–1.2.

With some of the dispersants used in these preparations, it is necessary to add a hydrocarbon or hydrocarbon–ketone mixture to the final matrix before neutralization, to avoid the formation of a paste through solubilization of the **1** of high mol. subst.

Computer-simulation program. — Stochastic modeling of the reaction of ethylene oxide with hydroxyl groups of **2** was conducted on an IBM 370 computer. A stochastic model[22,23] describes a system as a series of individual states wherein the dynamics of change within the system are determined by the probability of change from one state to the next. The simulation is a random process that does not require differential equations or numerical methods of integration. A random-number generator is used in the selection process; this requires the averaging of several simulations for a given reactivity-ratio ($k_2:k_3:k_6:k_x$) set.

For a given simulation, the following input is required: cellulose chain-length (usually 1000), hydroxyl-group reactivity ratios, percent crystallinity, number of **2** sequences involved in a crystal structure, molar substitution at which a change in the hydroxyl-group reactivities is desired, and a new set of reactivity ratios. The latter four sets of input are optional. The last two were used when a change in the alkali concentration was made during preparation of **1**.

The probability, P_a, of ethylene oxide reacting with a given **2** is a random process defined by Eq. *3*.

$$P_a = \frac{\text{Sum of the reactivities of three hydroxyl groups of } \mathbf{2}}{\text{Sum of maximum possible hydroxyl-group reactivities}} \quad (3).$$

The acceptance or rejection of a given **2** involved in this selection process defines the change in the percentage of unsubstituted glucose residues (% u-**2**) with molar substitution (mol. subst.).

The probability, P_s, of ethylene oxide reacting with a given hydroxyl group of **1** (site selection for a given **2**) is defined by Eq. *4* (for the hydroxyl group at C-2).

$$P_s(\text{2-OH}) = \frac{R(\text{2-OH})}{R(\text{2-OH}) + R(\text{3-OH}) + R(\text{6-OH})} \quad (4),$$

where R is the relative reaction-rate proposed for a given hydroxyl position (R_x, if the position has been previously substituted by ethylene oxide).

Determination of unreacted glucose residues (% u-**2**). — Hydrolysis and neutralization of the cellulose ethers was accomplished by an adaptation of ASTM 1915–63 described by Klug[24].

The glucose analysis of Dahlqvist[25] was modified by using 3,3′-diaminobenzidine as color reagent[26], making use of the optimal time and temperature conditions described by Mueller[27], and conducting the reaction in the dark[28].

Determination of reacted 2,3-vicinal diol. — The periodate oxidation of vicinal diols has been shown to be applicable to starch, cellulose[29], galactomannans[30,31], and *O*-(hydroxyethyl)cellulose[32] (**1**). The method applied to **1** was employed with minor variations in conditions to accelerate the analysis and improve the accuracy of the test. The method depends on a higher rate of oxidation of vicinal diols to aldehydes than the subsequent oxidation of the aldehydes and other species. Oxidations were conducted at 45° in buffered (sodium acetate–acetic acid, pH = 4.0–5.0) solutions of sodium metaperiodate. The residual periodate was determined by iodimetric titration at suitable time-periods. In the analysis of materials of high mol. subst., samples of 0.50 g were withdrawn with a spring-loaded syringe (for greater precision in transferring viscous solutions). The titer was always kept >75% of the blank to avoid the complexities in analysis associated with the reaction of iodate ions with sodium iodide.

The periodate oxidation of carbohydrates is not quantitative with many polysaccharides[33–36] because of the spontaneous formation of hemiacetals by reaction of aldehyde groups (liberated from the periodate oxidation) with adjacent, unoxidized, vicinal diols. The possible interference of hemiacetal formation with a quantitative determination of the concentration of unreacted vicinal diol is minimal for the following reasons: (*1*) the oxidations are conducted in buffered, acidic (pH = 4.0–5.0) solutions that shift the equilibrium away from hemiacetal formation; (*2*) in aqueous solution, hydration of the aldehyde groups competes with hemiacetal formation;

(*3*) in cellulose or **1**, a 6- or adduct hydroxyl group is present to compete with contiguous diol groups; and (*4*) the most-definitive stochastic fitting occurs at molar substitutions >3, where the content of u-vicinal diol is <21%. The probability of a significant amount of these u-vicinal diol groups being contiguous for inter-ring hemiacetal formation is low.

Stability to enzymic degradation. — Stability to enzymic degradation was measured as the percent viscosity retained of a 1% aqueous solution of cellulose ether after 75-min incubation with 10-p.p.m. (based on solution; 1000-p.p.m. based on polymer) Cellase 1000 enzyme (Wallerstein) at pH 5.6, 30°.

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