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^{13}C-N.M.R.-SPECTRAL AND RELATED STUDIES ON THE DISTRIBUTION OF SUBSTITUENTS IN *O*-(2-HYDROXYPROPYL)CELLULOSE*

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ABSTRACT

Information about the degree of substitution at individual oxygen atoms of *O*-(2-hydroxypropyl)cellulose, and the total molar substitution, was obtained from ^{13}C-n.m.r. spectra of the intact polymer and of its hydrolyzate. On the basis of their $^{13}CH_3$ chemical-shifts, *O*-(2-hydroxypropyl) (HOPr) substituents occurring singly, or as terminal units of substituent chains, were readily distinguished from inner HOPr units of chains. Differentiation between monomeric HOPr units and longer chains located at O-2 of D-glucosyl residues was effected by the transformation of appropriately substituted sugars in the hydrolyzate into 1,2-cyclic acetals incorporating a 2-*O*-(2-hydroxypropyl) group. Similarly, the pattern of substitution at O-6 of D-glucosyl residues was determined, through selective degradation, from the identity of HOPr derivatives of ethylene glycol, representing C-5 and C-6 of the residues. Overall, it was found that, although O-2 and O-6 are more readily substituted than O-3, the rate at which each, initially introduced, HOPr substituent is converted into a dimeric structure is not materially affected by its location. Also described are the synthesis and the n.m.r. spectra of several HOPr derivatives of D-glucose, and of simple alkanols that served as model compounds.

INTRODUCTION

Nuclear magnetic resonance spectroscopy has been extensively employed[1–4] for the chemical characterization of derivatives of cellulose. In continuation of a study[2] on the ^{13}C-n.m.r. spectroscopy of cellulose ethers, an investigation has been carried out on (2-hydroxypropyl)cellulose (HOPrcel), which is prepared commercially[5] by a base-catalyzed reaction between cellulose and propylene oxide (methyloxirane). Information presented here augments earlier ^{1}H-n.m.r. data[1] by giving degrees of substitution (d.s.) at O-2, O-3, and O-6 of the D-glucosyl residues in the polymer, as well as an independent measure of the total content of 2-hydroxypropyl (HOPr) groups. Moreover, the characteristics of the propagation of side chains [poly(propy-

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lene glycol) residues] at individual positions are described. That is, although it is well known[6] that the three hydroxyl groups of a D-glucosyl residue may differ notably in reactivity, it has not been evident that, in subsequent, chain-extending reactions with propylene oxide, such differences are transmitted, in part or at all, to individual HOPr substituents at O-2, O-3, or O-6. Two approaches have been devised in order to examine this question.

As an aid in the analysis of ^{13}C-n.m.r. spectra of HOPrcel, several reference compounds were synthesized, and the spectroscopic study also encompasses hydrolyzates of HOPrcel. and other degradation products.

RESULTS AND DISCUSSION

^{13}C-N.m.r. spectra of reference compounds. — ^{13}C-Chemical-shift characteristics of the HOPr group as an ether substituent were examined with HOPr derivatives of simple alkanols, as well as of D-glucose. These compounds included examples containing not only a single ether group (**1**), but several in which substitution had been extended to include two HOPr units (**2**). It may be noted that, as the latter derivatives comprise mixtures of four diastereoisomers [(*RR*), (*SS*), (*RS*), and (*SR*)], two pairs of which are enantiomeric, two individual signals were observed for a number of the ^{13}C nuclei.

(*a*) *2-Hydroxypropyl derivatives of alkanols.* — Methylene carbon atoms (C-1) of HOPr ethers of methanol, ethanol, and the other alkanols produce their signals between δ 79.3 and 68.7 (see Table I). When the HOPr group is attached to the primary position, in the methyl (**3**) or ethyl (**4**) ether, the C-1 chemical shift is δ 79.3

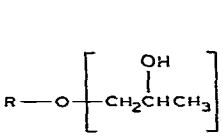
TABLE I

^{13}C-CHEMICAL SHIFTS OF 2-HYDROXYPROPYL ETHERS OF ALKANOLS[a]

Alkanol	*Ether*	*C-1*[b]	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*Alkanol-C*
Methanol	3	79.3	67.3	20.4				60.0 (CH_3)
	7	77.3	76.3[c]	17.4	75.6	68.0	20.1	59.0 (CH_3)
			76.1		75.4	67.7		
Ethanol	4	76.9	67.5	20.2				68.2 (CH_2)
								15.8 (CH_3)
	8	75.1	76.6	17.3	75.5	68.2	19.8	68.3 (CH_2)
			76.3		75.2	67.8		15.7 (CH_2)
2-Propanol	5	74.9	67.6	20.7				73.7 (CH)
								23.1 [$(CH_3)_2$]
	9	73.1	77.1	17.9	76.0	68.1	20.2	74.0 (CH)
			76.5		75.6	67.8		22.9 [$(CH_3)_2$]
tert-Butyl alcohol	6	68.7	68.2	20.4				75.6 ($C_{quat.}$)
								28.5 [$(CH_3)_3$]

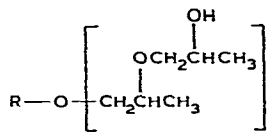
[a]In D_2O solution. [b]Numbered carbon atoms refer to 2-hydroxypropyl substituent(s). [c]This pair (and the other pairs) of signals represents pairs of diastereoisomers.

or 76.9, respectively, whereas attachment to a secondary (as in **5**) or tertiary position (as in **6**) results in a C-1 chemical-shift of δ 74.9 or 68.7, respectively. This high sensitivity to the nature of the alkyl (R) component of **1** may be attributed to a balance between well known[7] influences, *i.e.*, inductive deshielding (β-effect) accompanied by an increase in shielding due to nonbonded interactions (γ-effect). Hence, as the chemical shift of the C-1 signal of 1,2-propanediol is δ 68.7, the inductive effect of a 1-*O*-methyl substituent (in **3**) amounts to $\sim$10 p.p.m. For the other substituents (in **4–6**), inductive deshielding would be progressively offset as the steric factor increases.



HOPr

1



dHOPr

2

3 R = Me
4 R = Et
5 R = Me_2CH
6 R = Me_3C

7 R = Me
8 R = Et
9 R = Me_2CH

With the introduction of a second HOPr group (as in **7–9**), the C-2 signal is shifted downfield (β-effect) by $\sim$9 p.p.m. The C-1 resonance is displaced upfield by 1.8–2.0 p.p.m., *i.e.*, for **7–9** as compared with **3–5**, ascribable to a γ-effect by the second HOPr unit. As discussed later, this source of upfield displacement helps greatly in the analysis of the spectrum of HOPrcel itself.

(*b*) *2-Hydroxypropyl derivatives of* D-*glucose.* — Assignments of ^{13}C-chemical shifts for HOPr derivatives of D-glucose were readily made by reference to data[2,8–10] for α,β-D-glucose, various alkyl ethers thereof, and the simpler model-compounds.

For 6-*O*-(2-hydroxypropyl)-α,β-D-glucose (**10**), C-6 resonates $\sim$9 p.p.m. to low field of C-6 of α- or β-D-glucose, whereas C-5 of **10** is more shielded, by 1.1 p.p.m. (see Table II). The addition of a second HOPr unit to **10**, giving **12**, had a barely detectable effect on the C-4 and C-6 signals, comparable to that of the CH_2 resonance for **8**. Whereas these two signals were coincident, at δ 71.4, in the spectrum of **10**, one appeared at δ 71.5 in the spectrum of the α anomer of **12**, and at δ 71.6 in that of its β anomer. By introducing a deuterium atom into the 12-methyl group, affording **13**, the two CH_3 signals (C-9 at δ 17.1, and C-12 at δ 19.7) were unequivocally differentiated, because the C-12 signal then appeared as a triplet ($^1J_{C,D}$ 19.5 Hz). This confirmed the corresponding assignments ascribed to the CH_3 signals of **12**, based on anticipated shielding-effects, and served as a ready basis for distinguishing between inner and terminal substituent units in HOPrcel, as shown later.

Deuterium-isotope shifts observed by comparing the spectra of **10** and **12** with those of their monodeuterio analogs, **11** and **13**, were upfield, as generally observed[11], amounting to 0.26–0.28, 0.05–0.11, and 0.04–0.05 p.p.m., for the α-, β-, and γ-carbon atoms, respectively.

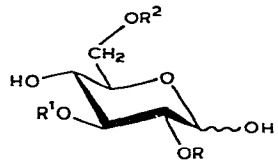
TABLE II

^{13}C-CHEMICAL SHIFTS OF MONO-*O*-(2-HYDROXYPROPYL)-D-GLUCOSES, AND RELATED DERIVATIVES[a]

Compound	*Anomer*	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-7*	*C-8*	*C-9*	*C-10*	*C-11*	*C-12*
D-Glucose	α	93.5	72.9	74.2	71.1	72.9	62.1						
	β	97.3	75.6	77.2	71.0	77.4	62.2						
2-*O*-(2-Hydroxypropyl)-D-glucose (**15**)	α	91.4	81.5[b]	73.6	71.0	72.7	62.1	79.1	68.3	19.4			
			81.2					78.8	67.8				
	β	97.3	84.5	76.8	71.0	77.3	62.2	77.0	68.3	19.4			
		97.2	84.2					76.8	68.0				
3-*O*-(2-Hydroxypropyl)-D-glucose (**14**)	α	93.6	72.8	83.7	70.8	73.0	62.0	79.3	68.3	19.4			
			72.7					79.2	68.2				
	β	97.3	75.3	86.5	70.8	77.3	62.2	79.3	68.3	19.4			
				86.4				79.2	68.2				
6-*O*-(2-Hydroxypropyl)-D-glucose (**10**)	α	93.6	72.9	74.2	71.4	71.8	71.4	77.8	67.6	19.6			
									67.5				
	β	97.4	75.6	77.2	71.4	76.2	71.4	77.8	67.6	19.6			
									67.5				
6-*O*-[2-(2-Hydroxypropoxy)-propyl]-D-glucose (**12**)	α	93.5	73.0	74.3	71.5	71.8	71.5	75.3	76.5	17.2	76.0	68.1	19.7
								75.1	76.2	17.1	75.6	67.8	
	β	97.4	75.6	77.3	71.4	76.2	71.6	75.3	76.5	17.2	76.0	68.1	19.7
								75.2	76.2	17.1	75.6	67.8	

[a]In D_2O solution. [b]This pair (and each of the other pairs) of signals represents a pair of diastereoisomers.

Monosubstitution, at O-3 (to give **14**), produced the expected, strong downfield-shift for C-3, and upfield shifts of ~0.3 p.p.m. for C-2 and C-4 (see Table II). Two signals that were 0.1 p.p.m. apart were observed for C-3 of the β anomer of **14**, and for C-2 of the α anomer. Whereas the chemical shifts of the pair of C-8 signals correspond to that of the methine carbon atom of the isopropyl ether **5**, the C-7 pair of resonances was, unaccountably, 4.2 p.p.m. downfield of the position expected.



10 R = R^1 = H, R^2 = HOPr
11 R = R^1 = H, R^2 = HOPr-9-^{2}H
12 R = R^1 = H, R^2 = dHOPr
13 R = R^1 = H, R^2 = dHOPr-12-^{2}H
14 R = R^2 = H, R^1 = HOPr
15 R^1 = R^2 = H, R = HOPr

Typical, downfield shifts were observed for C-2 of 2-*O*-(2-hydroxypropyl)-α,β-D-glucose (**15**), relative to α- and β-D-glucose (see Table II). Also, as found with other 2-*O*-alkyl derivatives, C-1 of the β anomer of **15** exhibited no upfield shift, whereas the C-1 signal of the α anomer was 2.1 p.p.m. upfield of that α-D-glucose. It appears, perhaps fortuitously, that this difference in C-1 chemical-shifts between the α and β anomers is matched, although in the reverse order, by a difference of 2.1 p.p.m. in the chemical shifts for the C-7 atoms. Diastereoisomeric influences were evident in the pairs of signals observed for C-1 of the β anomer, as well as for C-2, C-7, and C-8 of both anomers (see Table II).

(*c*) *^{13}C-Substituent effects, and chemical shifts predicted for multiple substitution.* — Substituent effects taken from the data in Table II are summarized in Table III; also included in Table III are ^{13}C-chemical shifts, predicted empirically from the substituent effects, for the carbon atoms of di- and tri-*O*-(2-hydroxypropyl)-D-glucoses, as well as for the carbon atoms of the β anomer when linked glycosidically through O-1 and O-4. ^{13}C-Chemical shifts anticipated for HOPr substituents are listed in Table IV. As may be seen, these values are helpful in the analysis of the ^{13}C-n.m.r. spectra of HOPrcel and hydrolyzates thereof.

Analysis of ^{13}C-n.m.r. spectra of (2-hydroxypropyl)cellulose. — ^{13}C-N.m.r. spectra of HOPrcel (Klucel E) recorded at 22.6 and 100 MHz (see Fig. 1) are dominated by signals for CH_3, CH_2, and CH of the HOPr substituents. That is, because the substituents have a high mobility relative to the cellulosic matrix, their ^{13}C-nuclei produce resonances much narrower than those of the D-glucosyl residues. The latter signals are barely discernible at 22.6 MHz, and, although they remain very broad at 100 MHz, individual peaks are sufficiently separated to permit a partial

TABLE III

SUBSTITUENT EFFECTS, AND CALCULATED ^{13}C-CHEMICAL SHIFTS FOR *O*-(2-HYDROXYPROPYL)-D-GLUCOSES AND -CELLULOSE

Atom	*δ*	*Effect of substitution*[a] *of* D-*glucose at*					*Cumulative substituent effect, and (calc. ^{13}C-chemical shift) for*			
							HOPr[b]*-β-*D-*glucose*		*HOPr*[b]*-cellulose*	
		O-1	*O-2*	*O-3*	*O-4*	*O-6*	*2,6*	*2,3,6*	*1,2,4,6*	*1,2,3,4,6*
	β-D-Glucose									
C-1	97.3	+6.7	0	0	+0.1	+0.1	+0.1 (97.4)	+0.1 (97.4)	+6.9 (104.2)	+6.9 (104.2)
C-2	75.6	−0.7	+8.8	−0.3	+0.2	0	+8.8 (84.4)	+8.5 (84.1)	+8.3 (83.9)	+8.0 (83.6)
C-3	77.2	+0.1	−0.6	+9.0	−1.2	−0.2	−0.8 (76.4)	+8.2 (85.4)	−1.9 (74.3)	+7.1 (84.3)
C-4	71.0	+0.2	0	−0.2	+9.2	+0.4	+0.4 (71.4)	+0.2 (71.2)	+9.8 (80.8)	+9.6 (80.6)
C-5	77.4	+0.2	+0.1	+0.1	−1.0	−1.0	−0.9 (76.5)	−0.8 (76.6)	−1.7 (75.7)	−1.6 (75.8)
C-6	62.2	+0.1	0	0	+0.6	+9.2	+9.2 (71.4)	+9.2 (71.4)	+9.9 (72.1)	+9.9 (72.1)
	α-D-Glucose						HOPr-α-D-glucose			
C-1	93.5		−2.1	+0.1		+0.1	−2.0 (91.5)	−1.9 (91.6)		
C-2	72.9		+8.5	−0.2		0	+8.5 (81.4)	+8.3 (81.2)		
C-3	74.2		−0.6	+9.5		0	−0.6 (73.6)	+8.9 (83.1)		
C-4	71.1		−0.1	−0.3		+0.3	+0.2 (71.3)	−0.1 (71.0)		
C-5	72.9		−0.2	+0.1		−1.1	−1.3 (71.6)	−1.2 (71.7)		
C-6	62.1		0	−0.1		+9.3	+9.3 (71.4)	+9.2 (71.3)		

[a]By glycoside formation at O-1 and O-4, or with a 2-, 3-, or 6-*O*-(2-hydroxypropyl) group. [b]*O*-(2-Hydroxypropyl).

analysis, based on the information provided by the spectra of the model compounds.

Most readily accessible from Fig. 1 is a measure of the extent to which the propagation of substituent chains occurred during the reaction of cellulose with propylene oxide. This is given by the relative intensities of the two CH_3 signals, at δ 19.8 and 17.5. It may be noted that corresponding information has not been available[1] from ^1H-n.m.r. spectra of HOPrcel. As shown with reference compounds **10** and **12**, the CH_3 signal of the inner unit of a dimeric substituent is ~2.4 p.p.m. upfield

TABLE IV

^{13}C-CHEMICAL SHIFT OF *O*-(2-HYDROXYPROPYL) SUBSTITUENTS[a]

Position	*C-7*	*C-8*	*C-9*	*C-10*	*C-11*	*C-12*
2	79.0(α) 76.8(β)	68.1	19.4			
3	79.2	68.3	19.4			
6	77.8	67.6	19.6			
6 (dimeric)	75.2	76.4	17.2	75.8	68.0	19.7

[a]Expected for *O*-(2-hydroxypropyl)-α,β,D,glucose or -cellulose, based on data in Tables I and II.

of that of the terminal unit, or of an individual, HOPr substituent. Integration of the pairs of CH_3 signals* in the 22.6- and 100-MHz spectra in Fig. 1 gave a value of 1:1.7 ($\pm$0.2) for the ratio of inner (I) units to terminal *plus* individual units (end units, E). That it is valid to compare these two different signals directly, as a measure

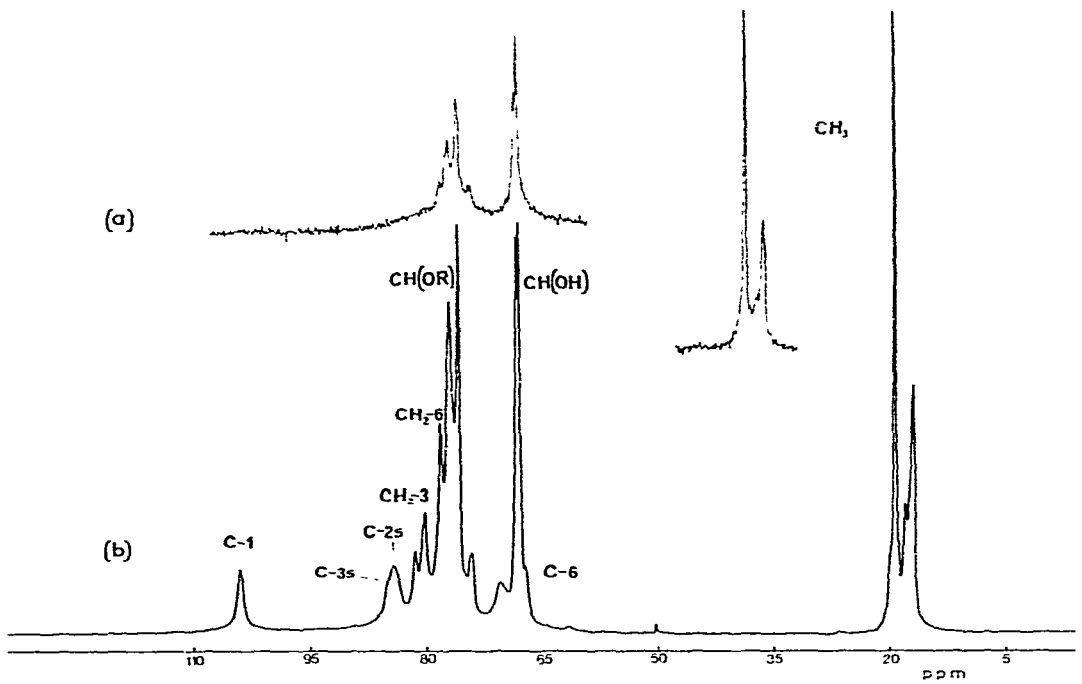


Fig. 1. ^{13}C-N.m.r. spectra of *O*-(2-hydroxypropyl)cellulose in D_2O at 30°, acquired at (a) 22.6 MHz, and (b) 100 MHz. [Signals designated by "s" are due to carbon atoms bearing ether substituents. Signal of internal standard (CH_3OD) is at δ 50.4.]

*The minor peak at δ 18.4 was taken as a component of the upfield methyl resonance.

of the degree of substituent side-chain extension in HOPrcel, received support later, from an examination of hydrolyzates of HOPrcel, and related experiments.

Based on the model studies, signals due to methylene carbon atoms (C-7), at δ 79.7, 77.6, and 76.6 (see Fig. 1b), appear to be related to HOPr substituents appended to O-3, O-6, and O-2 (β), respectively, although the last signal is probably augmented by that of methine carbon atoms (C-11) of extended chains. As the peak at δ 79.7 is only about half as strong as that at δ 77.6, substitution on O-3 of the HOPrcel is proportionately less than on O-6.

Despite the fact that the resonances due to carbon atoms of the D-glucosyl residues are weak, relative to those of the HOPr carbon atoms**, and much broader, they are clearly informative in several respects. Most obvious is the fact that there is only a very weak signal at δ 61.5 (see Fig. 1b), due to an unsubstituted, primary carbon atom (C-6), which shows that almost all of the primary positions in the polymer must bear at least one substituent unit. Consequently, the reciprocal signal for C-6 that bears the (2-hydroxypropyl)oxy unit(s), at δ 70.1, is found to be comparatively strong.

Overlapping signals at δ 84.4 and 83.6 (see Fig. 1b) are attributed, respectively, to C-3 and C-2 adjacent to HOPr substituents. Evidently, because the C-3 shoulder is much weaker, the degree of substitution at O-3 is substantially lower than at O-2. Hence, the latter, like O-6, must be almost fully substituted. Also consistent with this evaluation is the fact that the combined area of the C-2, C-3 peaks is $\sim$1.5 times that of the anomeric (C-1) signal, at δ 103.2. As all of these D-glucose carbon atoms are expected to relax at approximately the same rate, a direct comparison of their peak intensities is justified.

In summary, it appears that the d.s. at O-2 and O-6 is 0.9–1.0, and, perhaps, 0.5 at O-3, or a total d.s. of $\sim$2.5. Taking the value of 1 : 1.7 for the ratio I : E, the overall molar substitution (mol. subst.) was estimated to be $[(1/1.7 \times 2.5) + 2.5] = 4.0$. These results were found in good agreement with a more-definitive analysis of an acid hydrolyzate of HOPrcel, in which errors inherent in the poor resolution and low sensitivity of the polymer spectrum were minimized.

^{13}C-N.m.r. spectrum of an acid hydrolyzate of HOPrcel. — As found with other cellulose derivatives[2], a hydrolyzate of HOPrcel afforded a ^{13}C-n.m.r. spectrum (see Fig. 2) far superior in signal dispersion to that of the intact polymer. Hydrolysis with 3M sulfuric acid at 95° effected almost complete hydrolysis to the monosaccharide level, judging from the virtual elimination of the glycosidic C-1 signal at δ 103.2; also, there was no indication that the HOPr substituent groups were altered by this treatment***.

**This disproportionately strong response by the methyl carbon atoms was observed over a range of pulse-sequence conditions employed, in attempting to find optimum experimental parameters[12].

***This statement must be qualified by the fact that the spectrum contains unidentified, minor signals (δ 42–25) not observed in the polymer spectrum (see Fig. 1).

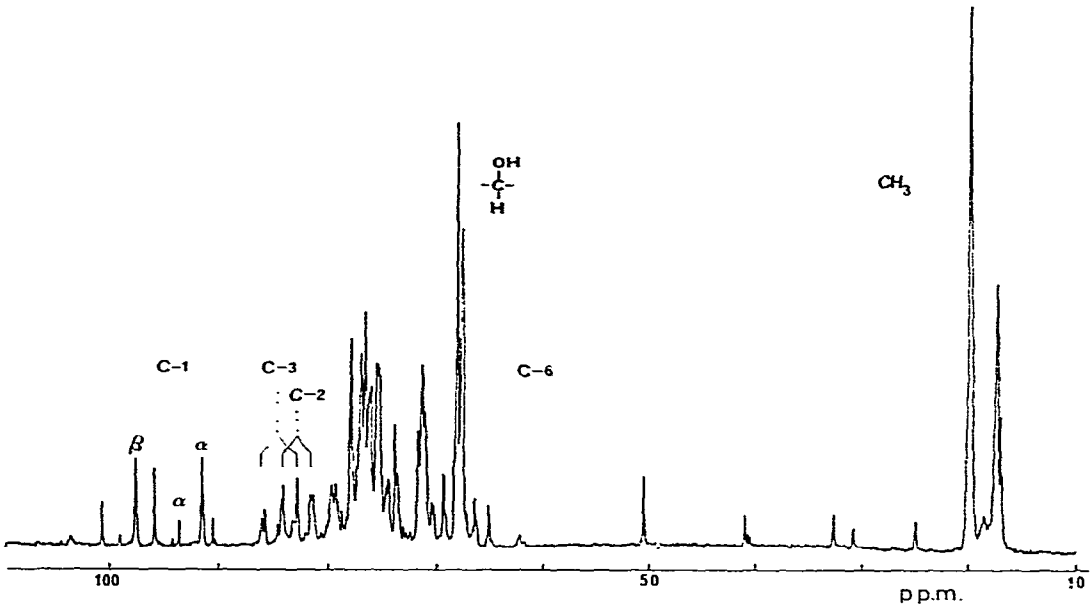


Fig. 2. ^{13}C-N.m.r. spectrum (100 MHz) of acid hydrolyzate of *O*-(2-hydroxypropyl)cellulose in D_2O at 30°. [Signals designated by "α-" or "β-" are those of aldose anomers, and by "s", of carbon atoms bearing ether substituents. Signal of internal standard (CH_3OD) is at δ 50.4. The origin of minor signals between δ 42 and 25, is unknown.]

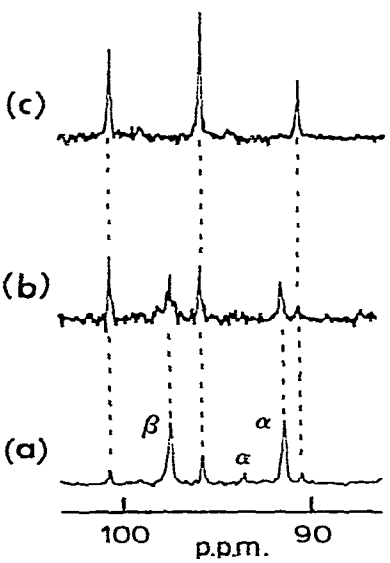


Fig. 3. Partial, ^{13}C-n.m.r. spectra (22.6 MHz) in D_2O at 30°, illustrating the anomeric region of (a) acid-hydrolyzate of *O*-(2-hydroxypropyl)cellulose; (b) following the formation of 1,2-cyclic acetals involving 2-*O*-(2-hydroxypropyl) substituents; (c) 1,2-cyclic acetal fraction, isolated chromatographically. [Signals designated by "α-" or "β-" are those of C-1 of aldoses.]

Signals at δ 97.5 and 91.4 are attributable to C-1 of β- and α-aldoses, respectively. As already seen (see Tables II and III), the upfield signal corresponds to α-D-glucose substituted at O-2, whereas, in the absence of the substituent, C-1 resonates at δ 93.5. Consequently, the minor signal at δ 93.5 (see Fig. 3), being less than one-tenth the intensity of that at δ 91.4, confirms that substitution at O-2 is almost complete (d.s. ~0.95).

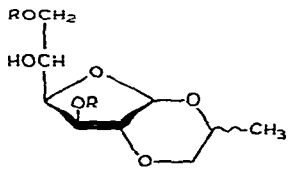
Other signals, at δ 100.6, 99.0, 95.7, and 90.4, are attributed to anomeric carbon atoms of cyclic products formed[13], during the hydrolysis, from residues of the polymer bearing a monomeric 2-*O*-(2-hydroxypropyl) group. The significance of these products for characterization of the hydrolyzate is discussed in the next section.

On the basis of ^{13}C-chemical shifts predicted for D-glucoses substituted in various ways (see Table III), the signals at δ 85.9, 84.0, 82.7, and 81.3 may be assigned to C-3 (β), C-2 (β), C-3 (α), and C-2 (α), respectively. As already observed in the spectrum of the intact polymer, the C-3 peaks are less intense than those of C-2. A d.s. value of 0.6 for O-3 was given by a comparison of the C-3(β) and C-1(β) signals. The presence of only a minute C-6 signal (at δ 62.2) shows that the primary position is almost fully derivatized (d.s. ~0.95).

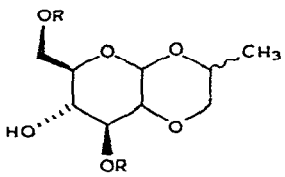
The CH_3 signals at δ 17.3–18.4 and δ 19.8, representing inner- and end-unit methyl carbon atoms, respectively, have relative intensities of 1 : 1.6, which is close to the I : E ratio estimated for the intact polymer. The same value was obtained for the hydrolyzate when the spectrum of its solution in acetone containing a relaxation reagent, chromium tris(acetylacetonate)[14] was recorded, indicating that differences between the dynamic properties of the CH_3 groups of end- and inner-units did not materially distort the ratio measurements made.

Differentiation between mono-O-substitution, and chain-extension at O-2. — In acidic media, a molecule of D-glucose (or appropriate derivative) bearing a 2-*O*-(2-hydroxypropyl) substituent (as in **15**) can give rise[13] to 1,2-cyclic acetals (*e.g.*, **16** and **17**) through intramolecular attack on C-1 by the hydroxyl group of the substituent. The formation of acetals is much more favored under anhydrous conditions. Consequently, when the hydrolyzate was dissolved in chloroform containing 0.1% of hydrogen chloride, there was a marked increase in the proportion of the mixed acetals. This change is illustrated in Fig. 3 by the anomeric region of the ^{13}C-n.m.r. spectrum of the hydrolyzate (*a*) initially, and (*b*) following the cyclization step. By reducing the remaining aldoses with borohydride, followed by column chromatography, the relatively nonpolar, cyclic products were isolated. As may be seen in Fig. 3c, these products served to confirm the anomeric signals attributed (in Fig. 3a and 3b) to the cyclic acetals.

Based on the behavior of model compounds[13], it was assumed that an essentially quantitative cyclization reaction occurred in the acidic chloroform solution. Furthermore, cyclization was regarded as unlikely when the substituent was dimeric (or longer), for this would require formation of (at least) 9-membered-ring acetals; the latter, in any event, should be recognizably different from the 6-membered-ring type



16 R = H, HOPr, or dHOPr



17 R = H, HOPr, or dHOPr

(**16** and **17**) already characterized. Accordingly, the intensities of the C-1 signals of the acetals, relative to those of the aldoses in Fig. 3b, were taken as a measure of the D-glucosyl residues in the HOPrcel bearing a single HOPr substituent at O-2, as compared with those bearing two or more such substituents; this amounted to a ratio of ~1:1.

Values of d.s. and mol. subst., and rates of chain extension for HOPrcel. — The respective d.s. values for O-2, O-3, and O-6 are x, y, and z*, and additional substitution on an HOPr unit at each of these positions is x_1, y_1, and z_1, respectively. From the measurements of relative intensities of ^{13}C signals: $x = 0.95$, $y = 0.6$, $z = 0.95$, and $(x + y + z)/(x_1 + y_1 + z_1) = 1.6$ (mean value); therefore, d.s. $= x + y + z = 2.5$, and the number of HOPr units present in extended substituents is $(x_1 + y_1 + z_1) = 2.5/1.6 = 1.6$. Hence, mol. subst. $= 2.5 + 1.6 = 4.1$. This result is in excellent agreement with the mol. subst. value of 4.2 obtained[1] for Klucel E by ^1H-n.m.r. measurements; also the d.s. value coincides with that given[1] by proton integrals of an isocyanate derivative of HOPrcel.

Were the rate of reaction of propylene oxide with the hydroxyl groups of the 2.5 substituents (introduced initially) independent of their positions, chain extension should have involved (1.6/2.5) = 0.6 of the hydroxyl groups at each position. As this is close to the value of ~0.5 found for O-2, it appears that, once a HOPr substituent is in place on the D-glucosyl residue, its reactivity towards a second molecule of propylene oxide is not materially affected by its location on the residue. This possibility is substantiated by the results of a different experiment, described later.

^{13}C-N.m.r. spectrum of the reduced hydrolyzate of HOPrcel. — Additional data, which supplemented the ^{13}C-n.m.r. analysis of HOPrcel and its hydrolyzate, were obtained through borohydride reduction of the hydrolyzate. This minimized some of the complexity inherent in the spectrum of the anomeric mixture. Also, suitable reference data were readily accessible from alditols obtained by borohydride reduction of the aldose model compounds. Using ^{13}C-chemical shifts for D-glucitol[15], and appropriate α-, β-, and γ-substituent effects, as earlier, good agreement was found between observed and calculated values for alditols **18** and **19**, prepared from the 6- and 2-*O*-substituted D-glucose derivatives, **12** and **15**, respectively (see Table V). ^{13}C-Chemical shifts expected for the 2,6-di- and 2,3,6-tri-*O*-substituted D-glucitols

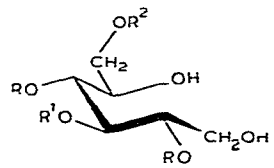
*These are representative of end-units, that is, either single, HOPr substituents, or ends of chains.

TABLE V

^{13}C-CHEMICAL SHIFTS OF *O*-(2-HYDROXYPROPYL)ALDITOLS[a]

Compound		*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-7*	*C-8*	*C-9*	*C-10*	*C-11*	*C-12*
D-Glucitol[b]		63.8	74.3	71.0	72.6	72.5	64.2						
18 (2-mono)	*obs.*	61.7	83.7[c] 83.3	70.7	72.5	72.1	64.4	77.5 77.1	68.3 68.1	19.6			
	calc.	62.8	83.3	70.0	72.9	72.5	64.2	74.9	67.6	20.7			
19 (6-mono)	*obs.*	63.9	74.4	71.1	72.7	71.1	73.7	75.9	76.7 76.4	17.1	75.4 75.2	68.2 67.8	19.7
	calc.	63.8	74.3	71.0	72.9	71.5	73.2	75.1	76.6 76.3	17.3	75.5 75.2	68.2 67.8	19.8
20 (2,6-di)	*calc.*	62.8	83.9	70.8	72.6	70.7	73.9						
21 (2,3,6-tri)	*calc.*	63.1	82.9	79.8	71.6	71.0	73.9						

[a]Observed values are for measurements on D_2O solutions. Calculated values are based on substituent effects listed in Table III (average values: β-effect, +9 p.p.m.; γ-effect, −1 p.p.m.; δ-effect, +0.3 p.p.m.), and chemical-shift data in Tables I and II. [b]Assignments are based on ref. 15. [c]This pair (and each of the other pairs) of signals represents diastereoisomeric species.



18 R^1 = R^2 = H, R = HOPr
19 R = R^1 = H, R^2 = HOPr
20 R^1 = H, R = R^2 = HOPr or dHOPr
21 R = R^1 = R^2 = HOPr or dHOPr

(**20** and **21**) are also included in Table V, together with values for monomeric and dimeric HOPr substituents.

Signals found in the anomeric region of the ^{13}C-n.m.r. spectrum of the reduction product (see Fig. 4a) are due mainly to those of the cyclic acetals. These components were removed by column chromatography, to eliminate interference by their signals with those of the alditols: this may be seen on comparing Fig. 4a with the spectrum of the purified alditol mixture (Fig. 4b). In these spectra, the anomeric carbon atoms of the original aldoses are represented by the signal at δ 61.9. When deuterium was introduced at C-1 with borodeuteride, this signal virtually disappeared, again confirming that very few residues in the polymer had escaped derivatization at O-6. Consequently, there is an appropriately strong signal at δ 73.9 which, according to the results in Table V, is attributable to C-6 bearing substituted O-6. Resonances

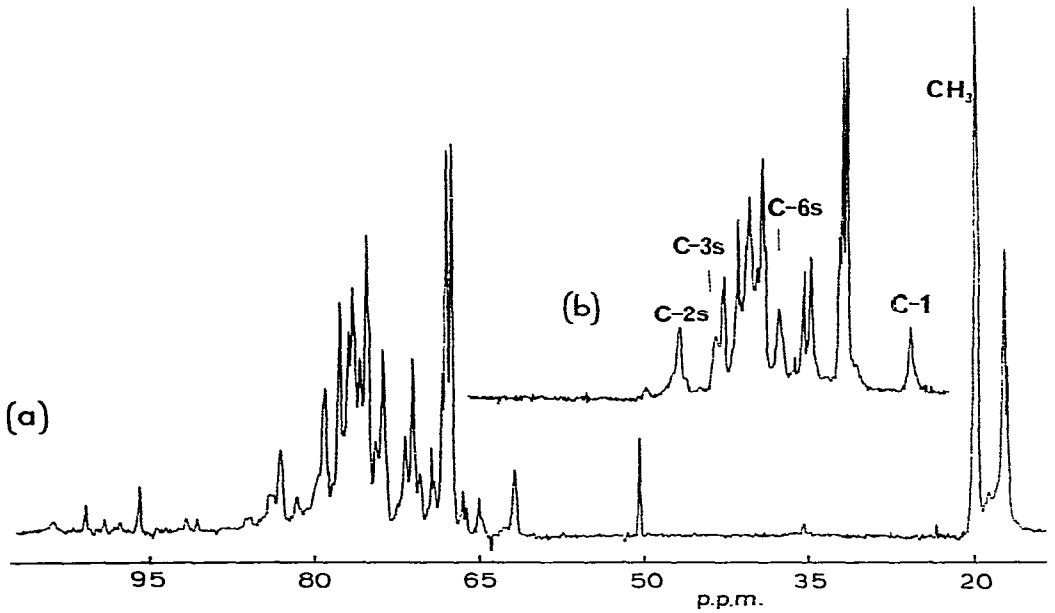
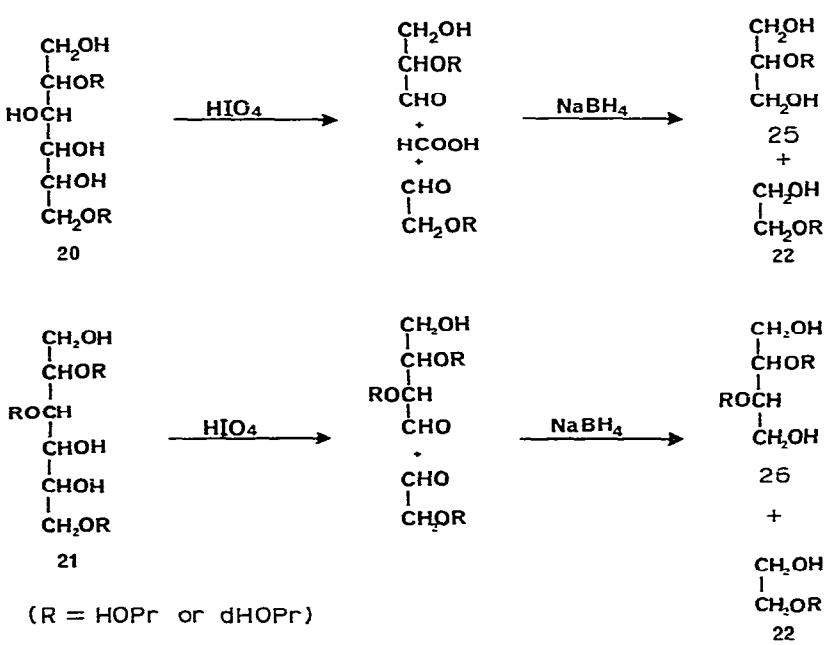


Fig. 4. ^{13}C-N.m.r. spectra (22.6 MHz) in D_2O at 30°, of (a) product obtained by borohydride reduction of hydrolyzate; (b) region of δ 100–60, after removal of 1,2-cyclic acetal components by chromatography. [Signal of internal standard (CH_3OD) is at δ 50.4.]

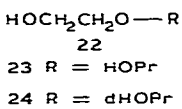


SCHEME 1

at δ 83.0 and 79.8 correspond to those expected (see Table V) for *O*-substituted C-2 and C-3, respectively. Although the latter signal is partly obscured by HOPr methine signals, it is noticeably weaker than the C-2 signal, as expected from the observations on HOPrcel and its hydrolyzate. Consistent, also, is the ratio of I:E substituents, as given by the CH_3 signals at δ 17.4 and 19.8, which is 1:1.6.

Chain extension of HOPr substituents. — Consideration has already been given to the chain length of HOPr substituents. Specifically, it was found that ~50% of the HOPr substituents at O-2 are themselves substituted. Information about the degree of chain extension at O-6 was obtained in the following way.

Each of the alditols described in the previous section is characterized by a 4,5-diol grouping when O-2, O-3, and O-6 are substituted, as in **21**, and by a 3,4,5-triol grouping when only O-2 and O-6 are substituted (as in **20**). Hence, by periodate oxidation of the alditol derivatives, followed by reduction (see Scheme 1), structures **20** and **21** should afford substituted ethylene glycol (**22**), representing C-5 and C-6

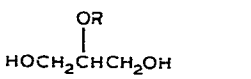


22

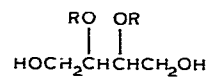
23 R = HOPr

24 R = dHOPr

of D-glucosyl residues in HOPrcel. Depending on the mol. subst. value at O-6, **22** should constitute a mixture of singly- and longer-chain-substituted species, *i.e.* **23** and **24**. Additional products of the degradation should be the corresponding glyceritol (**25**) and tetritol (**26**) derivatives, representing carbon atoms 1 to 3, and 1 to 4, respectively.



25 R = HOPr or dHOPr



26 R = HOPr or dHOPr

The products obtained according to Scheme 1 were partially separated by column chromatography into three fractions. Of these, the most mobile material (12% of the total) consisted almost exclusively of 1-*O*-(2-hydroxypropyl)-1,2-ethanediol (**23**), as shown by its ^{13}C-n.m.r. spectrum (see Fig. 5). Hence, it gave five principal signals, the chemical shifts of which were wholly consistent with structure **23**. The minor product was **24**; a further quantity of **24**, estimated at ~10%, was present in a second fraction*. The total yield of **23** was ~0.5 mol per mol.

This isolation of **23** clearly demonstrated that substitution by a single HOPr unit at O-6 of D-glucosyl residues in the HOPrcel occurs at close to the level expected for uniform rates of chain extension of HOPr substituents attached initially to a

*The second fraction appeared to consist mainly of **25**; that is, its ^{13}C-n.m.r. spectrum contained a prominent signal at δ 81.7 attributable to C-2 of glyceritol derivative **25**, additional evidence that some residues in HOPrcel were unsubstituted at O-3.

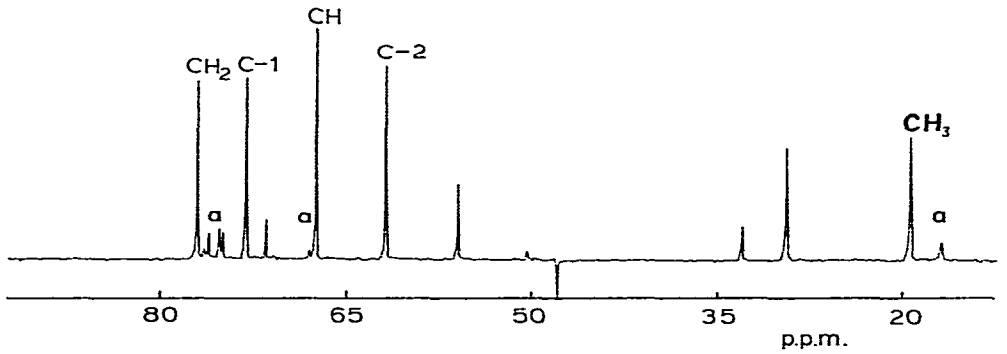
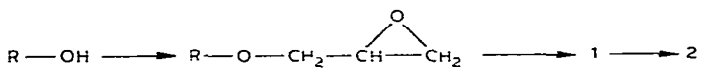


Fig. 5. ^{13}C-N.m.r. spectrum (22.6 MHz) in D_2O at 30° of isolated fraction consisting mainly of 1-*O*-(2-hydroxypropyl)-1,2-ethanediol (**23**). [Signals of the ethylene glycol carbon atoms are designated C-1 and C-2. Minor signals, designated "a", are attributed to ethylene glycol having a dimeric substituent unit (**24**). The origin of the other signals is unknown.]

D-glucosyl residue. Consequently, these rates are similar at O-2 and O-6 and, hence, also at O-3, and indicate that the overall, mol. subst. value (4.1) is comprised of individual mol. subst. values of 1.5–1.6 at O-2 and O-6, and of 0.9–1.0 at O-3.

Synthesis of model compounds. — 2-Hydroxypropyl ethers (**3**–**6**) of simple alkanols were synthesized by the reaction between a given alkanol and propylene oxide at the reflux temperature in the presence of sodium hydroxide, as reported[16] for the ethyl derivative **4**.

Each of the *O*-(2-hydroxypropyl)-D-glucoses (**10**, **14**, and **15**) was synthesized by the following general scheme: an appropriately protected D-glucose derivative (**27**) was allowed to react with 1-chloro-2,3-epoxypropane (epichlorohydrin)[17] in the presence of sodium hydride and imidazole, giving the *O*-(2,3-epoxypropyl) derivative (**28**), which, on hydrogenolysis with lithium aluminum hydride, afforded the corresponding *O*-(2-hydroxypropyl) compound (**1**).



27 28

For the introduction of a second *O*-(2-hydroxypropyl) unit onto **1**, giving **2**, the same sequence of reactions was employed. By using lithium aluminum deuteride instead of the hydride for the hydrogenolysis step, a monodeuterio analog [*e.g.*, of **1**, R-O-CH_2-CH(OH)-CH_2D] was obtained.

1,2:3,5-Di-*O*-methylene-α-D-glucofuranose served as the starting compound for the synthesis of 6-*O*-(2-hydroxypropyl)-α,β-D-glucose (**10**), 6-*O*-[2-(2-hydroxypropoxy)propyl]-α,β-D-glucose (**12**), and the C-12 deuterio analog (**13**) of the latter.

The 3-*O*-(2-hydroxypropyl) derivative (**14**) was synthesized by substitution at O-3 of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, and the 2-*O*-substituted sugar (**15**) was obtained from methyl 3,5,6-tri-*O*-benzyl-α,β-D-glucofuranoside, as reported elsewhere[13].

EXPERIMENTAL

General methods. — Solutions were usually evaporated below 40° under diminished pressure. Column chromatography was performed by the procedure of Still *et al.*[18], with silica gel 60 (Merck: 40–63 μm). Mass spectra were recorded with an LKB 9000 spectrometer at an ionization potential of 70 eV, or, by chemical ionization (isobutane), with an HP 5980 A spectrometer. N.m.r. spectra (^1H and ^{13}C) were recorded with a Bruker WH-90, Varian XL-200, or Bruker WH-400 spectrometer. For the ^{13}C spectra, the pulse widths used ranged from 3.3–5.0 μs, and repetition times from 0.5–6.0 s, and the signal intensities were obtained from the computer print-out, as well as from measurements of the areas of scale-expanded signals. Chemical shifts (δ) are reported with reference to tetramethylsilane, taking δ 50.4 as the chemical shift of MeOD (added as an internal reference for D_2O solutions).

2-(Hydroxypropyl) derivatives of alkanols (**3–6**). — Representative of these syntheses is that of methyl ether **3**, according to the procedure of Chitwood and Freure[16]. Propylene oxide (44 mL, 0.6 mol) was added to methanol (50 mL, 1.2 mol) and sodium hydroxide (0.2 g), and the mixture was heated under reflux until the temperature remained constant at 85°, cooled, and the base neutralized with sulfuric acid. Compound **3** (20 mL) was collected by distillation at 122–123°. The residue (5 mL) appeared to consist principally of the dimeric species (**7**).

The ^1H-n.m.r. data for **3** ($CDCl_3$): δ 3.97 (m, 1 H, H-2), 3.40 (s, 3 H, OCH_3), 3.38 (dd, 1 H, H-1), 3.21 (dd, 1 H, H-1'), 2.86 (bs, 1 H, OH), and 0.94 (d, 3 H, H-3); $J_{2,3}$ 6.37, $J_{1,1'}$ 8.45, $J_{1,2}$ 7.99, and $J_{1',2}$ 3.20 Hz. The ^1H-n.m.r. data for **7** ($CDCl_3$): δ 4.0–3.8 (m, 2 H, H-5), 3.39 (s, 3 H, OCH_3), 3.38 (s, 3 H, OCH_3), 3.7–3.1 (m, 10 H), 3.04 (bs, 2 H, 2 OH), and 1.2–1.1 (m, 12 H). The ^{13}C-n.m.r. data for **3** and **7** ($CDCl_3$) are given in Table I.

Products **4** (15 mL) and **8** (5 mL) were isolated from the reaction of ethanol (34 mL, 0.6 mol) and propylene oxide (20 mL, 0.3 mol) by fractional distillation at 131° and 174°, respectively. The ^1H-n.m.r. data for **4** ($CDCl_3$): δ 3.96 (m, 1 H, CH), 3.56 (dd, 2 H, CH_3CH_2), 3.41 (dd, 1 H, CH_2CH), 3.27 (dd, 1 H, CH_2CH), 2.86 (bs, 1 H, OH), 1.22 (t, 3 H, CH_3CH_2), and 1.15 (d, 3 H, $CHCH_3$); $J_{1,1'}$ 9.0, $J_{1,2}$ 8.1, $J_{1',2}$ 3.2, $J_{2,3}$ 6.37, and $J_{CH_2CH_3}$ 6.97 Hz. The ^1H-n.m.r. data for **8** ($CDCl_3$): δ 4.0–3.9 (m, 1 H, H-5), 3.8–3.1 (m, 7 H), 1.22 (t, 3 H, CH_2CH_3), and 1.12 (d, 6 H, H-6); $J_{2,3} = J_{5,6} = 7.0$ and $J_{CH_2CH_3}$ 7.0 Hz. The ^{13}C-n.m.r. data for **4** and **8** ($CDCl_3$) are given in Table I.

Product **5** (10 mL) was isolated from the reaction between 2-propanol (44 mL, 0.6 mol) and propylene oxide (20 mL, 0.3 mol) by distillation at 138°; the residue (7 mL) appeared to be mainly **9**. The ^1H-n.m.r. data for **5** ($CDCl_3$) were: δ 3.93 (m,

1 H, H-2), 3.61 (m, 1 H, CH_3CH), 3.41 (dd, 1 H, H-1), 3.21 (dd, 1 H, H-1'), 1.17 [d, 6 H, $(CH_3)_2CH$], and 1.14 (d, 3 H, H-3); $J_{1,1'}$ 9.3, $J_{1,2}$ 3.4, $J_{1',2}$ 7.9, $J_{2,3}$ 6.4, and $J_{CH(CH_3)_2}$ 6.1 Hz. The ^{13}C-n.m.r. data ($CDCl_3$) for **5** and **9** are given in Table I.

Ether **6** was obtained from the reaction between *tert*-butyl alcohol (40 mL) and propylene oxide (15 mL) following a reflux period of 72 h. The ^{13}C-n.m.r. data for **6** are given in Table I.

6-O-(2,3-Epoxypropyl)-1,2:3,5-di-O-methylene-α-D-glucofuranose. — To a solution of 1,2:3,5-di-*O*-methylene-α-D-glucofuranose (2.0 g) in dry oxolane (20 mL) were added sodium hydride (1.0 g), imidazole (20 mg), and epichlorohydrin (20 mL; Aldrich). After 24 h, when t.l.c. showed that the reaction was complete, the suspension was filtered, the filtrate evaporated, and the residue purified by column chromatography (eluant, 1:2 ethyl acetate–petroleum ether), to afford a syrup (2.4 g, 92%); $[\alpha]_D$ +34.3° (*c* 5.4, MeOH); ^{1}H-n.m.r. data ($CDCl_3$): δ 6.01 (d, 1 H, H-1), 4.92 (dd, 2 H, CH_2), 4.46 (d, 1 H, H-2), 4.34 (d, 1 H), 4.2–3.8 (m, 8 H), 4.04 (d, 2 H, CH_2), 3.7–3.3 (m, 2 H), 3.3–3.1 (m, 1 H), 2.80 (dd, 1 H), and 2.57 (dd, 1 H), $J_{1,2}$ 3.6 Hz; ^{13}C-n.m.r. data ($CDCl_3$): δ 104.3 (C-1), 96.5 (C-13), 88.0 (C-14), 83.7 (C-2), 76.7 (C-4), 75.9 (C-3), 72.3 (C-5,7), 71.55, 71.51 (C-6), 50.2 (C-8), and 43.8 (C-9).

Anal. Calc. for $C_{11}H_{16}O_7$: mol. wt., 260. Found (chemical ionization): *m/z* 261 (MH^+, 95%).

6-O-(2-Hydroxypropyl)-1,2:3,5-di-O-methylene-α-D-glucofuranose, and its C-11-^{2}H analog. — A solution of the 2,3-epoxypropyl derivative (0.52 g) in diethyl ether (10 mL) was added dropwise to a suspension of lithium aluminum hydride (20 mg) in diethyl ether (20 mL); 2 h later, the suspension was filtered, and the filtrate evaporated, to give a syrupy product that was purified by column chromatography (eluant, 2:1 ethyl acetate–petroleum ether); yield 0.50 g (96%); $[\alpha]_D$ +34.7° (*c* 5.8, MeOH); ^{1}H-n.m.r. data ($CDCl_3$): δ 6.00 (d, 1 H, H-1), 5.03 (d, 2 H), 4.91 (dd, 2 H), 4.46 (d, 1 H, H-2), 4.32 (d, 1 H), 4.2–3.6 (m, 5 H), 3.6–3.2 (m, 2 H), 2.5 (bs, 1 H, OH), and 1.16 (d, 3 H, CH_3); $J_{1,2}$ 3.7, $J_{8,9}$ 6.2 Hz; ^{13}C-n.m.r. data ($CDCl_3$): δ 104.4 (C-1), 96.5 (C-13), 88.0 (C-14), 83.7 (C-2), 77.4 (C-7), 76.6 (C-4), 76.0 (C-3), 71.8 (C-5), 71.6 (C-6), 66.4 (C-8), and 18.9 (C-9).

Anal. Calc. for $C_{11}H_{18}O_7$: mol. wt., 262. Found (chemical ionization): *m/z* 263 (MH^+, 100%).

The monodeuterio analog, prepared with lithium aluminum deuteride instead of the hydride, differed in that, in the ^{1}H-n.m.r. spectrum, the C-11 methyl signal was appropriately lessened in intensity, and it appeared as a triplet (δ 19.47, 18.61, 17.75) in the ^{13}C-n.m.r. spectrum.

Anal. (for the mono-*O*-trimethylsilyl derivative): Calc. for $C_{14}H_{25}DO_7Si$: mol. wt. 335. Found: *m/z* 320 ($M - CH_3$, 0.7%).

6-O-[2-(2-Hydroxypropoxy)propyl]-1,2:3,5-di-O-methylene-α-D-glucofuranose, and its C-14-^{2}H analog. — The 6-*O*-(2-hydroxypropyl) derivative (0.36 g), when allowed to react with epichlorohydrin for 3 days, gave the corresponding 2-(2,3-epoxypropoxy)propyl derivative, which was purified by column chromatography (eluant, 1:2 ethyl acetate–petroleum ether); yield 0.32 g (84%), $[\alpha]_D$ +26.5° (*c* 0.9,

MeOH). Hydrogenolysis with lithium aluminum hydride (or deuteride) afforded the title compounds; yield 0.33 g (93%); $[\alpha]_D$ +26.2° (*c* 1.4, MeOH); ^{1}H-n.m.r. data ($CDCl_3$): δ 5.90 (d, 1 H, H-1), 5.02 (d, 2 H), 4.92 (dd, 2 H), 4.45 (d, 1 H), 4.35 (d, 1 H, H-2), 4.2–3.1 (m, 10 H), 2.78 (bs, 1 H, OH), 1.14 (d, 3 H, CH_3), and 1.12 [dd, 3 H, CH_3 (terminal)], $J_{1,2}$ 3.6 Hz; ^{13}C-n.m.r. data ($CDCl_3$): δ 104.3 (C-1), 96.5 (C-13), 88.9 (C-14), 83.8 (C-2), 76.7 (C-4), 76.0 (C-3), 75.79, 75.53 (C-8), 75.36, 75.26 (C-10), 75.09, 74.66 (C-7), 72.5 (C-5), 71.5 (C-6), 66.79, 66.30 (C-11), 18.67 (C-12), and 17.05, 16.83 (C-9). The analog, deuterated at C-14, exhibited an appropriate, 2-H doublet at δ 1.12, and a ^{13}C-triplet (δ 19.24, 18.38, and 17.52).

Anal. Calc. for $C_{14}H_{22}D_2O_8$: mol. wt. 322. Found (e.i.): *m/z* 322 (94%).

6-O-(2-Hydroxypropyl)-D-glucose (**10**), *6-O-[2-(2-hydroxypropoxy)propyl]-D-glucose* (**12**), *and monodeuterio analogs* **11** *and* **13**. — A solution of each di-*O*-methylene derivative (0.2–0.4 g) in water (30 mL) containing Amberlite IR-120 (H^+) ion-exchange resin was heated under reflux for 48 h, the suspension was filtered, and the filtrate lyophilized. Each product was a syrup, recovered in 90–98% yield. The ^{13}C-n.m.r. data are given in Table II.

3-O-(2-Hydroxypropyl)-D-glucose (**14**). — This was prepared from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose *via* the 3-*O*-(2,3-epoxypropyl) and 3-*O*-(2-hydroxypropyl) derivatives, as described by Wing *et al.*[17]. Hydrolytic removal of the *O*-isopropylidene groups of the last derivative (as for **12**) afforded compound **14** as a syrup, $[\alpha]_D$ +15.5° (*c* 2.2, MeOH). The ^{13}C-n.m.r. data are reported in Table II.

Hydrolysis of O-(2-hydroxypropyl)cellulose. — *O*-(2-Hydroxypropyl)cellulose (Klucel E, Hercules; 1.0 g) was dissolved in 3M sulfuric acid (50 mL) by stirring, and the solution was heated for 8 h at 95°. (A gel formed when the temperature reached 40°, and this dissolved gradually.) The acid was neutralized with barium carbonate, methanol (50 mL) was introduced, the suspension was filtered through Celite, and the filtrate was evaporated. Methanol was added to the residue, suspended matter was centrifuged off, and the solution was evaporated (yield, 0.92 g). A solution of the syrupy hydrolyzate in D_2O gave the ^{13}C-n.m.r. spectrum shown in Fig. 2.

Formation, and isolation, of cyclic acetals from hydrolysis products. — A solution of the hydrolyzate (0.8 g) in chloroform (60 mL) containing conc. hydrochloric acid (0.2 mL) was stirred for 10 h, the acid neutralized with barium carbonate, the suspension filtered, the filtrate evaporated, and the residue examined by ^{13}C-n.m.r. spectroscopy (see Fig. 3). Sodium borohydride (0.9 g) was added to a solution of the residue (0.7 g) in water (50 mL); after 48 h, the base was neutralized with Amberlite IR-120 (H^+) ion-exchange resin, the suspension was filtered, and the filtrate was evaporated. Methanol was added, and the methyl borate formed was distilled off (three successive treatments). Column chromatography of the product with 1:1:4 ethyl acetate–petroleum ether–acetone afforded mixtures of cyclized products in the early fractions, and mixtures of alditols in subsequent fractions. The ^{13}C-n.m.r. spectra of these products are shown in Fig. 3.

Selective degradation of alditol derivatives by periodate oxidation–borohydride reduction. — A portion of the hydrolyzate was reduced with sodium borohydride,

and the product was fractionated chromatographically, as described in the preceding section. The alditol fraction (1.0 g) and periodic acid (1.2 g) were dissolved in water (50 mL), the solution was kept in the dark for 48 h, the acid neutralized with Dowex-1 (HCO_3^-) ion-exchange resin, and the resin filtered off. Sodium borohydride (400 mg) was added to the filtrate, and, after 48 h, the solution was processed as before, giving a syrupy residue (0.85 g). Column chromatography of the product, using 14:1:4:1 acetone–petroleum ether–ethyl acetate–methanol as the eluant, yielded three fractions (*a*, 0.085 g; *b*, 0.37 g; and *c*, 0.38 g); the ^{13}C-n.m.r. spectrum of fraction *a* is shown in Fig. 5.

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