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Note

Distribution of substituents in carboxymethyl ethers of cyclomaltoheptaose

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Cyclomaltoheptaose (β-cyclodextrin, β-CD) is attracting attention with its remarkable properties of molecular encapsulation (for examples see ref 1). Its solubility in water, however, is somewhat limited: only 18 g (0.0158 mol) per liter. Derivatization, e.g., ether formation, leads to substantial increases in solubility. Thus, *O*-(carboxymethyl)-β-cyclodextrins (CMCD's) are highly soluble derivatives. CMCDs are prepared by reacting sodium chloroacetate with β-CD in aqueous NaOH, giving a product that is a mixture of cyclic oligomers of partially carboxymethylated α-D-glucopyranose. The distribution of substituents in *O*-carboxymethyl-β-cyclodextrins is the subject of this report. We show that the monomer composition of these oligomers can be determined from the ^{13}C NMR spectrum of the hydrolyzed material in a way analogous to that used for the analysis of *O*-(carboxymethyl)cellulose [2].

1. Results

In principle the hydrolysis of ethers of the cyclodextrins should produce a mixture of the α and β anomers of eight monosaccharides as observed with cellulose ethers. One of the remarkable findings of this work is that CMCD prepared with a relatively low concentration of NaOH lacks the monosaccharide units that have a substituent at position 6. This is illustrated in Fig. 1 (top), where the absence of these monosaccharides is immediately apparent in the ^{13}C NMR spectrum of the hydrolyzed material. On the other hand, at high NaOH concentration, substitution at position 3 is extremely low. This phenomenon is also depicted in Fig. 1 (bottom), which shows that the ^{13}C resonances of monosaccharides bearing a substituent at position 3 are extremely weak.

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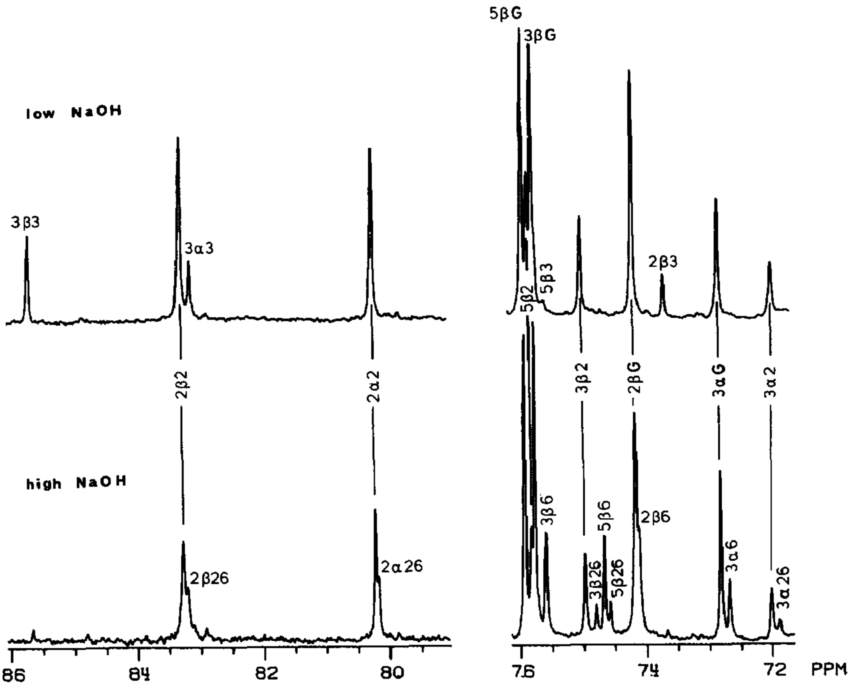

Fig. 1. Portions of the 90.56-MHz ^{13}C NMR spectra of samples A (bottom, high NaOH) and C (top, low NaOH) showing differences in their monomer composition. Sample A has virtually no substitution at position 3, whereas sample C has no substitution at position 6. The symbols used to label the peaks indicate, in sequence, the position number of the carbon atom from which the signal arises, the anomeric configuration of the corresponding sugar molecule, and the position(s) of carboxymethyl substitution.

Table 1
Substituent distribution and relative rate constants of carboxymethylation at different NaOH concentrations

Parameter	[NaOH] (%)		
	A 27	B 10	C 1.5
NaOH/Glc	13.5	4.15	3.1
ds [a]	0.557	0.923	0.412
X_2 [b]	0.275	0.675	0.302
X_3	0.018	0.139	0.110
X_6	0.264	0.109	0
k_2/k_3	17.7	7.51	3.09
k_6/k_3	16.9	0.77	0

[a] Average degree of substitution per glucosyl unit.

[b] Positional degree of substitution.

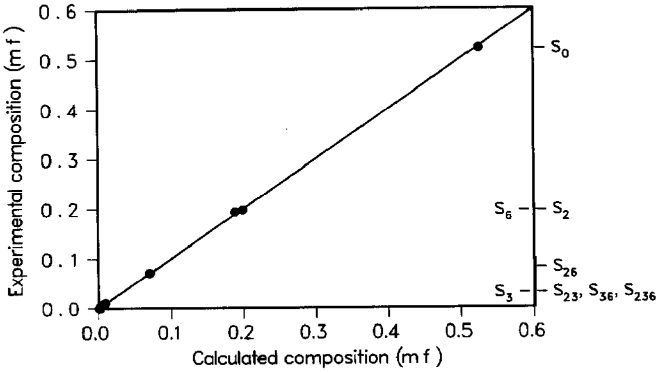

Fig. 2. Experimental mole fractions of monomer units in sample B plotted against values calculated according to Spurlin's model.

The relative abundances (mole fractions) of monomers were obtained from the integrated areas of the corresponding resonances in the ^{13}C NMR spectra. The results were analyzed with Spurlin's statistical/kinetic model [3] as previously described [2] for *O*-(carboxymethyl)cellulose. The model assumes that the relative reactivities of the three hydroxyl groups are independent of the average degree of substitution or of the state of substitution at other positions within the same glucosyl residue. For ether formation it is further assumed that the extent of substitution is governed by the relative rates of reaction in a first-order process. With these assumptions, a set of simple rate equations has been derived [3]. The excellent conformity of our results to Spurlin's model is demonstrated in Fig. 2 with the data for a sample prepared with intermediate concentrations of NaOH and, as a result, containing observable substitution at all three of the positions (hydroxyls) available for derivatization.

The treatment of the data yields the relative rate constants for the reactions of the three hydroxyls. These, along with other pertinent results, are summarized in Table 1.

2. Discussion

The results of this work showing that carboxymethylation of the hydroxyl groups of *β*-CD is preferential and selective depending on the NaOH concentration are in accord with previous findings with *O*-(2-hydroxypropyl) derivatives [4]. At low NaOH concentrations, the highly reactive alkoxide species that undergo alkylation are formed exclusively from the more acidic secondary hydroxyls, whereas at high NaOH concentrations the more accessible primary hydroxyls also become ionized. However, carboxymethylation of OH-6 is still not as extensive as the substitution at that position observed in hydroxypropyl derivatives [4]. This difference is probably due to the lower (and less discriminating) steric demand of the oxiranone carboxymethylating agent that is formed from chloroacetic acid relative to the bulkier propylene oxide. In addition, with the hydroxypropyl derivatives it was found that there is an "interaction" between OH-2 and OH-3: the reactivity of one depending on the substitution state of the other. With CMCD, as the conformity to Spurlin's model (see Fig. 2) indicates, the reactivities of these two positions are independent of their respective states of substitution. This trend is similar to the one observed with cellulose derivatives and may be related to the ionization state of the reactants [5].

The diminished reactivity of OH-3 (at high NaOH concentration) has previously been observed in reactions of cyclodextrins with dialkyl sulfates in the presence of barium hydroxide (Kuhn-Trischler alkylation) [6,7]. The present results suggest that the barium cation may not be responsible for this phenomenon as was previously suspected but not proved [8].

Recent theoretical studies of α-D-glucopyranose and β-maltose have pointed out the greater acidity of OH-2 and OH-3 relative to OH-6, thus predicting the higher reactivity of the former when the latter is not ionized [9]. Also, the modification of the reactivity of OH-3 when position 2 is substituted has been indicated [9].

3. Experimental section

Preparation of O-(carboxymethyl)cyclomaltoheptaose.—In a typical preparation (e.g., sample B), 10 g β-CD, 10 mL water, 27 g chloroacetic acid, and 38 mL of a 40% NaOH solution were stirred for 18 h at room temperature. Methanol was then added to the mixture until it became 70% of the total. The precipitated white solid product was filtered, washed with MeOH, and dried over P_2O_5 in a vacuum desiccator. The yield was 7.8 g. Anal. Found: C, 38.94; H, 5.16; Na, 6.67%. Calcd. for ds = 0.923: C, 39.93; H, 4.67; Na, 8.99%. The observed higher H and lower Na may be due to only partial neutralization of the carboxyl groups.

NMR experiments.—Samples were prepared and analyzed in the same way as previously described for *O*-(carboxymethyl)cellulose [2].

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