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Note

Preparation of carboxymethylcellulose sulfate of high degree of substitution

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Bio-based polyelectrolytes are of growing interest due to their biocompatibility and biological activity, e.g., the heparin-like anti-coagulation activity [1,2], as well as their gel- and symplex-forming tendency [3,4]. These typical properties are dependent on the nature and the degree of substitution (ds) as well as on the distribution of the ionic groups within the sugar units [5,6]. Especially in the case of polyelectrolytes with more than one type of ionic group, interesting properties should be expected but their preparation with high total ds value and especially with uniform distribution of substituents may be quite difficult.

In this context, we wish to report an effective sulfation procedure for the most important ionic cellulose ether, carboxymethylcellulose (CMC). In connection with our studies of homogeneous phase reactions of polyglucan derivatives [7,8], one of the goals of this investigation was to obtain CMC sulfates with both high total ds values and a controlled distribution of substituents.

In order to gain considerable sulfation of carboxy group-containing cellulose derivatives including CMC, an activation of the polyelectrolytes is absolutely necessary [6]. Because of the insolubility and low swelling capacity of CMC in the organic solvents normally used for sulfation reactions, up to now the most effective method for activation is precipitation of an aqueous polyelectrolyte solution by *N*,*N*-dimethylformamide (DMF) and the removal of the water from the swollen gel by repeated distillation under reduced pressure.

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1. Experimental

General procedure.—The degree of sulfation (ds_S) of CMC sulfate (**4–14**) was carried out by a gravimetric method according to Schweiger [9]. The ^{13}C NMR spectra were measured on a Bruker AMX 400 spectrometer operating at 100.62 MHz. The accumulation number was between 10000 and 30000. FTIR spectra were measured on a Bio-Rad FTS 25 PC. The viscosity of the samples was measured in distilled water in the range of concentration from 0.2 to 0.3 g/L with an Ostwald viscometer (Schott) at 32°C.

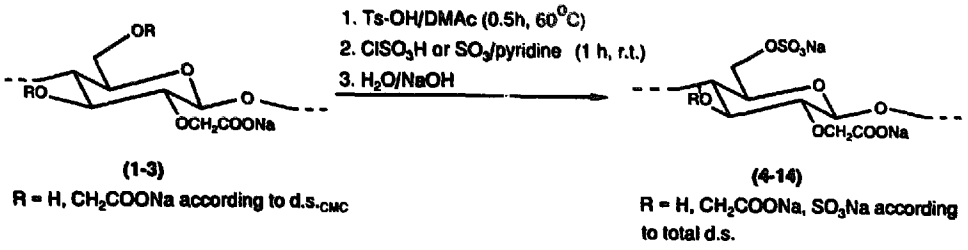
Carboxymethylcellulose sulfates (**4–14**) (*typical procedure*).—For the purpose of activation, 1.66 g (ds_{CMC} 0.76, 7.4 mmol) of the sodium salt of CMC (Fluka) and water-free *p*-toluenesulfonic acid (0.98 g, 5.7 mmol) were slurried in *N,N*-dimethylacetamide (25 mL) for 30 min at 60°C. The highly swollen CMC gel formed was allowed to cool to room temperature and SO_3–pyridine complex (2.38 g, 15 mmol) or chlorosulfonic acid (1.79 g, 15 mmol) was added under stirring. After a reaction time of 1 h at room temperature, the CMC sulfate was isolated by pouring into acetone (150 mL), and the precipitate washed three times with acetone and EtOH. It was then suspended in distilled water and carefully neutralized with 0.5 M aq NaOH, using phenolphthalein as indicator. The dissolved sodium salt of CMC sulfate was precipitated with EtOH, washed twice with aq 80% EtOH (100 mL), and dried under vacuum at 80°C. Yield and ds_S, see Table 1.

2. Results and discussion

The CMC (sodium salt) samples used had ds 0.76 (**1**), 1.73 (**2**), and 1.90 (**3**), respectively. The commercial CMC (**1**) as well as the laboratory-synthesized sample (**2**, synthesized by the standard solvent method in 2-propanol and water [10]) possessed a non-uniform distribution of substituents in the order O-2 > O-6 > O-3. The CMC **3** was synthesized via 6-*O*-triphenylmethylcellulose and possessed a regioselective O-2,3 substitution [11]. For activation, the CMCs were mixed with water-free *p*-toluenesulfonic acid [(TsOH, 0.8 mol per mol carboxymethylated "anhydroglucose" unit (AGU)] and slurried in *N,N*-dimethylacetamide (DMAc) at temperatures ranging from 50 to 70°C [12]. After 30 min, a highly swollen and partly dissolved CMC gel was formed. Besides DMAc, DMF and dimethyl sulfoxide (Me_2SO) are also suitable solvents for the activation procedure. The determination of the swelling ability by adapting the method of Jayme and Rothamel [13] was unsuccessful because the solvent was not removable from the gel by centrifugation up to 3000 rpm.

The gels formed were allowed to react with 1–3 mol of sulfation agent (chlorosulfonic acid, pyridine–SO_3 complex, and $CH_3CO_2SO_3H$, respectively) per mol of modified AGU for 1 h at room temperature. By precipitating into acetone, the unstable acidic sulfate half-esters were obtained. Subsequent neutralization in water led to dissolution of the corresponding water-soluble sodium salts of the CMC sulfates (**4–14**) which were isolated by reprecipitation. A survey of the reaction path is given by Scheme 1.

The results of our sulfation experiments are shown in Table 1. While the sulfation power of $CH_3CO_2SO_3H$ is relatively low, sulfation with $ClSO_3H$ or the SO_3–pyridine complex leads to a high degree of sulfation (ds_S). Using 2 mol of chlorosulfonic acid per mol



Scheme 1.

modified AGU, ds_S values of 1.25 were obtained. In comparison, the sulfation of CMC (ds_{CMC} 0.85) after activation by precipitation of the aqueous CMC solution in DMF and the removal of the water from the swollen gel by repeated distillation yields a ds_S of 0.83 even after a reaction time of 2 h [6]. Without any activation of CMC, practically no sulfation reaction occurs (see Table 1). Starting from commercial CMC (**1**, $\eta_{sp}/c = 276 \times 10^{-2}$ L g^{-1}), CMC sulfates **4–11** and **14** with values of specific viscosity in the range from 266 to 413 have been prepared. We assume that a chain degradation takes place during sulfation, but this degradation was not detectable by viscosity measurements. During purification, the small molecular components of the product were separated. For the two CMC laboratory samples (**2**, $\eta_{sp}/c = 91 \times 10^{-2}$ L g^{-1}; **3**, $\eta_{sp}/c = 37 \times 10^{-2}$ L g^{-1}), small molecular components were separated before sulfation. That is why the subsequent sulfation leads to products with lower specific viscosities.

Table 1
Results of the sulfation of carboxymethylcellulose (CMC **1**, ds_{CMC} 0.76) in *N,N*-dimethylacetamide–*p*-toluenesulfonic acid at room temperature within 1 h

Sulfating agent		CMC sulfate			
Compound	Molar ratio	Sample	ds_S [a]	Yield (%)	η_{sp}/c (L g^{-1} × 10^{-2})
$CH_3CO_2SO_3H$	1	**4**	0.25	81	342
$CH_3CO_2SO_3H$	2	**5**	0.40	88	302
$ClSO_3H$	1	**6**	0.61	65	301
$ClSO_3H$	2	**7**	1.23	64	413
$ClSO_3H$	2	**8** [b]	1.25	69	305
$ClSO_3H$	2	[c]	0.09	83	
$ClSO_3H$	3	**9**	1.48	60	266
SO_3–pyridine	1	**10**	0.57	76	315
SO_3–pyridine	2	**11**	1.28	78	338
SO_3–pyridine	2	**12** [d]	0.94	80	70
SO_3–pyridine	2	**13** [e]	1.06	71	20
SO_3–pyridine	3	**14**	1.48	71	359

[a] Degree of sulfation calculated on basis of sulfur content [13].
[b] Activation for 0.5 h at 60°C and 8 h at room temperature.
[c] Without activation.
[d] CMC **2** (ds_{CMC} 1.72).
[e] CMC **3** (ds_{CMC} 1.90).

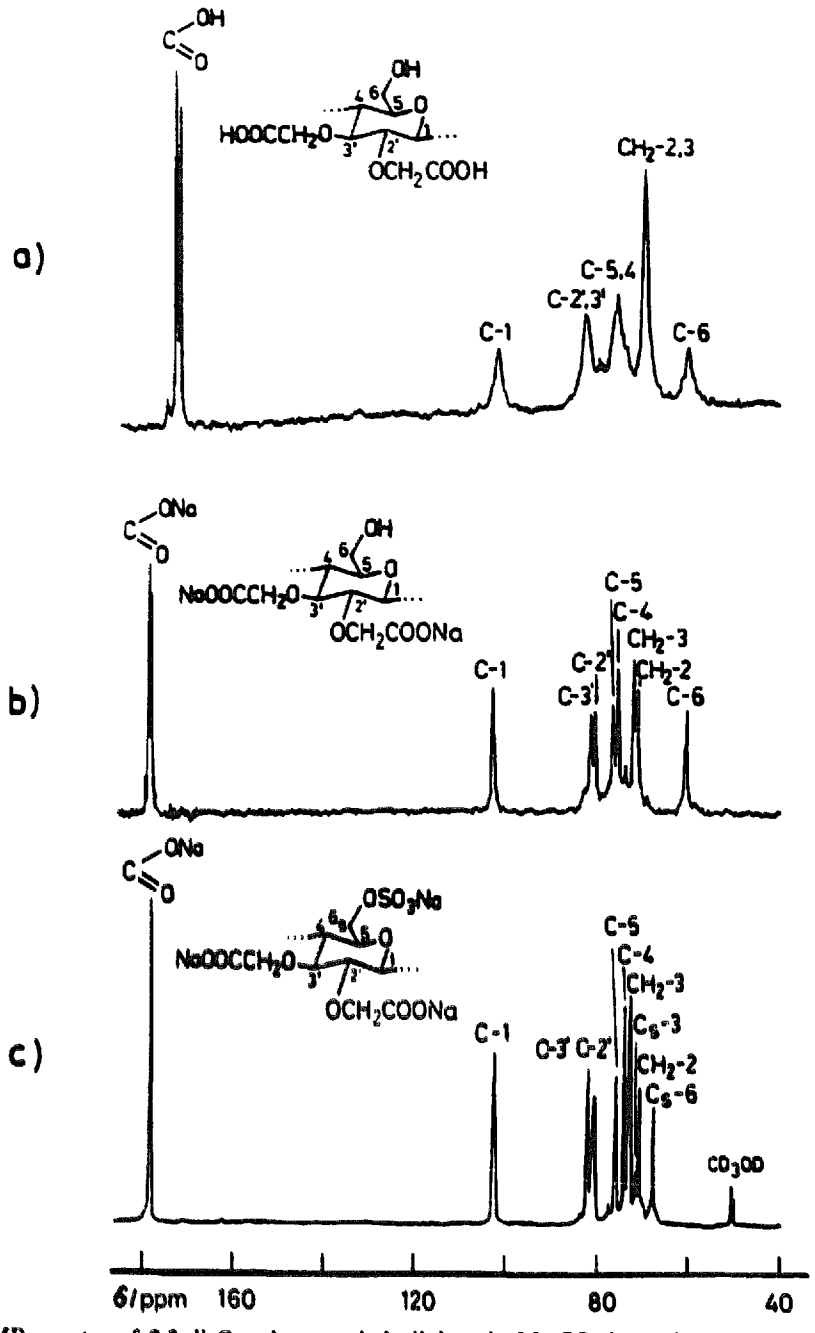


Fig. 1. ^{13}C NMR spectra of 2,3-di-*O*-carboxymethylcellulose in Me_2SO-d_6–*p*-toluenesulfonic acid (swelling system) (a) and in D_2O (b), and of 2,3-di-*O*-carboxymethylcellulose sulfate (ds_{CMC} 1.90; ds_S 1.06) in D_2O.

Apart from the characteristic carboxylate band at ν_{max} ca. 1615 cm^{-1} (COO^-) the FTIR spectra of the sulfated products (**4–14**) show absorptions at 815 (SO) and 1240 cm^{-1} (SO_2) indicating the presence of sulfate groups.

The extremely high state of swelling (up to partial dissolution) of the CMC samples even permits the recording of well-resolved NMR spectra. The ^{13}C NMR spectrum of CMC **3** with a regioselective carboxymethylation at O-2 and O-3 (Fig. 1, spectrum a) in the swelling system Me_2SO-d_6–*p*-toluenesulfonic acid (signals for *p*-toluenesulfonic acid in the expected range appear but are not shown) shows the typical signals which are also found

in spectra of CMC in solution in D_2O, the usual solvent for recording NMR spectra of CMC (Fig. 1, spectrum b). It may be concluded that the "dissolution" is achieved via intermolecular solvent–solute interactions without covalent substitution at the OH and COO^- groups of the modified AGU. The activation converts the carboxylate group (sodium salt form) into the carboxylic acid form. This is confirmed by a shift of the NMR signal from δ 179.2 to 172.5. The signals appearing at δ 71.2 and 71.9 are caused by the methylene carbons of the carboxymethyl substituents. The signal for C-6 appears at δ 60.5 (unsubstituted C-6 atom). Carbon atoms substituted by the carboxymethyl groups give two signals at δ 80.8 and 81.6, and the signal at δ 102.9 is assigned to C-1. Fig. 1, spectrum c shows the ^{13}C NMR spectrum of CMC sulfate **13** with ds_{CMC} 1.90 and ds_S 1.06, i.e., with a complete substitution of all three OH groups. The signal appearing at δ 70.0 is caused by the sulfate ester group at C-6. The sulfation of the residual free OH groups at C-3 (ds_S of C-3, 0.1) led to an additional signal at δ 71.1. The ^{13}C NMR spectra of the other CMC sulfates show comparable signals. However, because of the non-uniform distribution of substituents, the unambiguous assignment is much more complicated. In agreement with the results of Whistler et al. [14], the primary alcohol functions are more easily sulfated than secondary ones.

The described activation of CMC (**1–3**) and subsequent sulfation represents a suitable novel and efficient synthesis for CMC sulfates (**4–14**) with high total ds values. In the case of regioselectively substituted CMC, it is even possible to obtain CMC sulfates with a controlled distribution of substituents.

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