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Effective esterification of carboxymethyl cellulose in a new non-aqueous swelling system

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Summary

Carboxymethyl cellulose (CMC) was treated in a dipolar-aprotic solvent like *N,N*-dimethylacetamide, or dimethylsulfoxide (DMSO) with *p*-toluenesulfonic acid yielding a high reactive gel-suspension of the polymer. This mixture allows a direct esterification of free hydroxyl groups of CMC as exemplified by acylation with carbonic acid chlorides, or anhydrides, and with isocyanates as well as by sulphation, phosphating and silylation. The products characterized by elemental analysis and FTIR spectroscopy possess a high degree of functionalization.

Introduction

The sodium salt of carboxymethyl cellulose (CMC) represents the most important bio-based anionic polyelectrolyte. It is manufactured by many companies throughout the world. Because of its versatile properties as a thickener, film former, protective colloid, and water retaining agent, CMC has become the largest industrial cellulose ether [1].

On the other hand, in order to optimize properties of the polymer and to create new advanced cellulosic materials, the interest was focused on chemical modifications of both the carboxy groups and the remaining free hydroxyl groups. Mixed ethers of alkyl or hydroxyalkyl CMC are already of great importance in technical applications. CM hydroxyethyl cellulose, e.g., combines the excellent salt compatibility of hydroxyethyl cellulose with the surface-protecting and suspending-stabilizing properties of CMC [2]. In case of modifications using reactive low molecular agents which are instable towards hydrolysis like acyl chlorides, the reactions have to be performed under non-aqueous conditions in, e.g., pyridine, *N,N*-dimethylformamide (DMF), *N,N*-dimethylacetamide (DMA), and dimethylsulfoxide (DMSO) as reaction medium. Because of the insolubility and low swelling capacity of CMC in common organic solvents, a preactivation of the polyelectrolyte is absolutely necessary. An effective method for activation is precipitation of an aqueous solution of CMC by DMF and the removal of the water from the swollen gel by repeated distillation under reduced pressure [3]. This method was successfully applied for the synthesis of CMC-sulphates, however, it is elaborate and time consuming.

In the course of our studies on synthesis and structure-property relations of carboxy groups-containing cellulose derivatives [4,5], our interest was focused on subsequent modifications of CMC. In the present paper we communicate effective esterification reactions of free OH-groups of CMC by using a new one-step activation and reaction system.

Experimental

Materials

The carboxymethyl cellulose (CMC) samples (sodium salt) used were purchased from FLUKA (degree of substitution, DS_{CM} = 0.76, η = 90 - 200 mPas at 4 % in water) and laboratory-synthesized by the standard solvent method in 2-propanol and water [6] (DS_{CM} = 1.28, degree of polymerization, DP = 120, DS_{CM} = 1.28, DP = 910, DS_{CM} = 1.73, DP = 210). The lithium and potassium salt of CMC was obtained by neutralization of free acid of a commercial polymer (DS_{CM} = 0.60, DP = 600, Papierfabrik Weißenborn, Germany) with aqueous LiOH and KOH, respectively.

Water-free *p*-toluenesulfonic acid was obtained by dehydration of the monohydrate at 120 °C under vacuum.

The solvents were dried and distilled prior to use according to conventional methods.

Activation method

To a stirred suspension of 1.66 g (DS_{CM} = 0.76, 7.5 mmol modified AGU) CMC in 25 ml *N,N*-dimethylacetamide (DMA) was added 0.98 g (5.7 mmol) water-free *p*-toluenesulfonic acid at 60 °C and stirring was continued for 30 min. The highly swollen gel-suspension formed was cooled to room temperature and used in chemical modifications without any additional treatment.

Esterification, typical example (CMC-esters 1-7)

To the stirred gel-suspension was added 4.17 g (22.5 mmol) *p*-nitrobenzoylchloride and then 5.93 g (75 mmol) pyridine at 60 °C. Stirring was continued for 3 h at 60 °C. The polymer was precipitated in 250 ml ethanol, collected, and washed with 100 ml dist. water. Then the polymer was suspended in 100 ml ethanol and 10 ml dilute acetic acid was added to remove basic impurities. The polymer was washed again with ethanol and dried at 50 °C under vacuum. The yellow polymer obtained had a DS_E of 0.75, see Table 1.

The synthesis of CMC-phenylurethanes (**3-4**) and CMC-maleates (**5-7**) was carried out in a similar manner, see Table 1.

Sulphation, typical example (CMC-sulphates 8-11)

To the stirred gel-suspension was added 2.38 g (15 mmol) SO_3/pyridine complex at room temperature. After stirring for 1 h, the product was precipitated in 150 ml acetone, collected, washed with acetone, suspended in dist. water and neutralized with 0.5 N aqueous NaOH against phenolphthalein. The aqueous solution formed was reprecipitated in 400 ml ethanol, collected, and washed three times with 80 % (v/v)

aqueous ethanol. After drying at 50 °C a white CMC-sulphate of DS_S =1.28 was obtained, see Table 1.

Phosphating, typical example (CMC-phosphates 12-16)

To the stirred gel-suspension was added 1.64 g (20.8 mmol) pyridine and then a solution of 2.29 g (15 mmol) $POCl_3$ in 10 ml DMA at room temperature. After stirring for 1 h the product was precipitated in 250 ml ethanol, collected, and washed with 100 ml ethanol. The polymer was suspended in 150 ml dist. water and neutralized with 0.5 N aqueous NaOH. After reprecipitation in 450 ml ethanol, the sodium salt of the CMC-phosphate formed was washed with 80 % (v/v) aqueous ethanol and dried at 50 °C. DS_P = 0.49, see Table 1.

Silylation with tert.-butyldimthylsilylchlorosilane (CMC-silylether 17)

To the stirred gel-suspension was added 5.93 g (75 mmol) pyridine and then 11.30 g (75 mmol) tert.-butyldimethylchlorosilane. After stirring for 3 h at 60 °C, the product was precipitated in 250 ml dist. water, collected and washed with 100 ml dist. water. The product was extracted with boiling ether, washed with dilute acetic acid and several times with dist. water. The product was dried at 80 °C. DS_{Si} = 0.36, see Table 1.

Measurements

Microscopy was carried out by means of a Jenapol Interphago microscope (Carl Zeiss Jena, Germany).

FTIR spectra were measured on an Impact Nicolet 400 in KBr, in case of gel-suspensions between KBr panes.

Results and Discussion

Activation of carboxymethyl cellulose (CMC)

In order to gain a considerable conversion in subsequent reactions, an activation of CMC is absolutely necessary. We have found that a treatment of the polymer suspended in a dipolar-aprotic solvent like *N,N*-dimethylformamide (DMF), *N,N*-dimethylacetamide (DMA), and dimethylsulfoxide (DMSO) with *p*-toluenesulfonic acid (Tos-OH) in a molar ratio COONa group to acid of 1 leads to a highly swollen gel-suspension of the polymer. All sodium CMC samples investigated within a range of degree of substitution (DS_{CM}) from 0.60 to 1.73 and with values of the degree of polymerization (DP) ranging form 210 to 910 showed this behaviour. Even a regioselectively substituted 2,3-*O*-CMC sample could be activated [7]. Moreover, CMC in the lithium and potassium salt form can be activated in the same manner. The degree of swelling is extremely high. Thus, the quantitative determination by the solvent retention method of Jayme and Rothamel [8] was unsuccessful. There was no separation of solvent and polymer by centrifugation up to 3000 rpm. An increase in temperature from 25 °C to 60 °C accelerates the swelling process remarkably. By optical observation, the gel-suspension is formed after some minutes.

It is worth to mention that other acids like methane sulfonic acid,

trifluoroaceticacid and monochloroacetic acid, respectively, do not swell CMC to a comparable extent. Furthermore, polysaccharides with directly at the polymer backbone bound carboxy groups like sodium alginate, sodium pectinate, and 6-carboxy cellulose do also not swell in the manner described for CMC.

To gain an insight in the swelling process, studies by means of microscopy using polarized light and positive phase contrast conditions were carried out in dependence on time. It is obvious that CMC in a dipolar-aprotic solvent and Tos-OH does not form a continuous gel within the total volume but a suspension of separate highly swollen gel particles. Figure 1 shows a typical picture. The swollen particles appear dark grey and the non-swollen ones in light grey respectively in red-violet and yellow-blue colour (colour pictures may be obtained from the authors on request). From microscopy it may be concluded that after 30 min at 60 °C the majority of CMC is swollen. Prolongation of the treatment up to 24 h does not yield a recognisable change. A dissolution of CMC was also not observed under the chosen conditions.

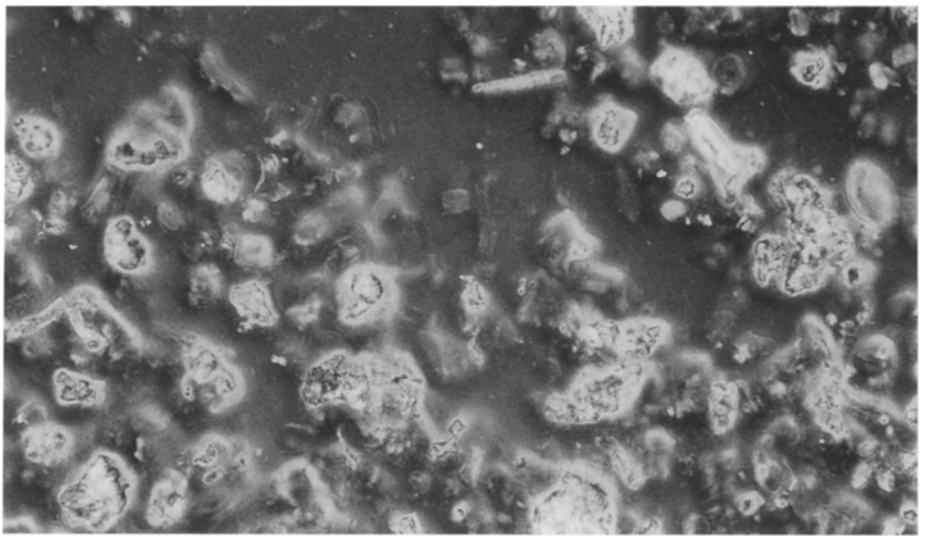


Fig 1. Polarized light microscopic picture of carboxymethyl cellulose in *N,N*-dimethyl acetamide/*p*-toluenesulfonic acid

A comparison of FTIR spectra of starting CMC (sodium salt) with that of CMC activated in DMSO/Tos-OH shows a shift of the characteristic carboxylate band at ν_{max} ca. 1610 cm^{-1} to ν_{max} 1735 cm^{-1} indicating the transformation of the sodium salt to the free-acid form of CMC.

The high state of activation respectively swelling of CMC even permits to record rather well-resolved ^{13}C NMR spectra in "solution" [9]. A spectrum recorded in DMSO-d_6/ Tos-OH 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. However, the activation converts the salt form of CMC into the carboxylic acid form. This is confirmed by a shift of the NMR signal from 179.2 to 172.5 ppm.

Summarizing these results it may be concluded that the activation is achieved via intermolecular solvent-solute interactions without covalent substitution at the OH or COONa (H) groups of the modified anhydroglucose units. From preliminary ^1H NMR studies, using the model system sodium acetate/*p*-toluenesulfonic acid/DMSO, we

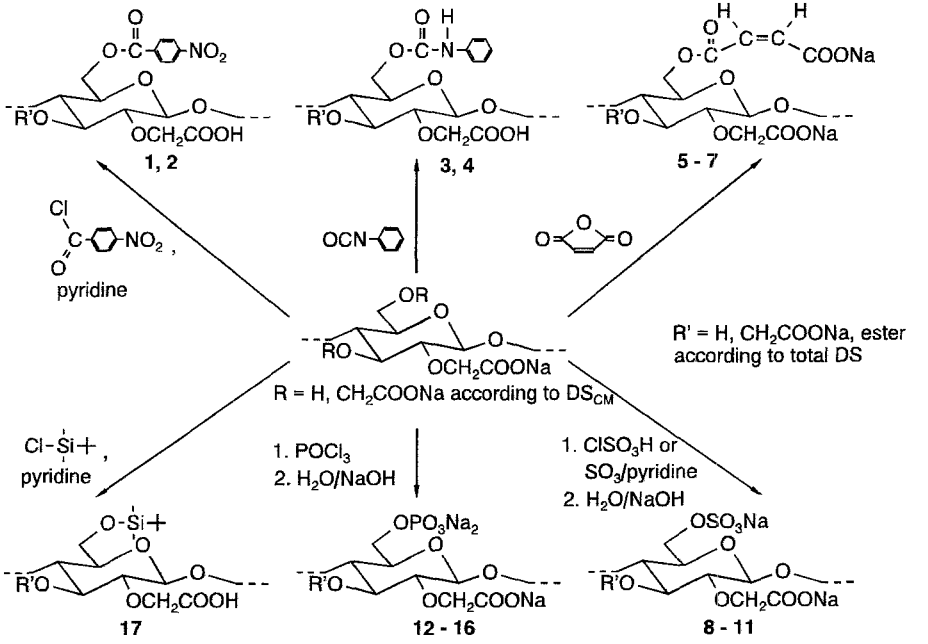
assume an interaction between the carboxylate groups of Na-CMC and the HO_3S-groups of the sulfonic acid with a rapid exchange of the acidic hydrogen as well as an interaction of the lipophilic toluene unit of the *p*-toluenesulfonic acid with the solvent.

Esterification reactions

Scheme 1 gives an overview of esterification reactions carried out directly in the activation system DMA/Tos-OH as one-pot reaction.

Esterification of CMC with acyl chlorides and isocyanates has found interest in connection with use of CMC as polymeric carrier in controlled release applications [10]. Further, by esterification of free HO groups the hydrophilic/lipophobic balance of the polymer can be controlled.

CMC-*p*-nitrobenzoates **1-2** were synthesized by a classical method using pyridine as a base and 2 or 3 mol equv. *p*-nitrobenzoylchloride (Table 1). The system CMC (CMC with DS_{CM} = 0.76 was used)/DMA/Tos-OH tolerates pyridine without deswelling. After a reaction time of 3 h at 60 °C, products of DS_E of 0.66 and 0.75 could be isolated, i.e. with rather high DS_E in a short reaction time. They show FTIR spectra with typical absorptions for CMC and, furthermore, signals at 3135, 3105, 3007 cm^{-1} (ν CH), 1736 cm^{-1} (ν C=O), 1608 cm^{-1} (ν C=C), 1529 cm^{-1} (ν_{as} NO_2) and 1352 cm^{-1} (ν_s NO_2) characteristic for the *p*-nitrobenzoate. The products are insoluble in DMA, DMF, DMSO as well as in water and aqueous NaOH.



Scheme 1

The preparation of CMC-phenylurethanes **3-4** were carried out using 5 and 10 mol equv. phenylisocyanate. The samples isolated of very high DS_E of 1.45 and 1.79, respectively, are also insoluble in the solvents mentioned above, however, they swell in

acetone to transparent gels. The characteristic FTIR absorptions were found at 3130, 3100 cm^{-1} (ν CH), 1734 cm^{-1} (ν C=O), 1602 cm^{-1} (ν C=C), and 1539 cm^{-1} (amide II).

Table 1: Conditions and results of modification reactions of carboxymethyl cellulose (DS_{CM} 0.76) in *N,N*-dimethylacetamide/*p*-toluenesulfonic acid (activation for 30 min at 60 °C and 8 h at room temperature).

Derivatizing agent		Conditions		CMC derivative		
Compound	Molar ratio[b]	Time (h)	Temperature (°C)	Sample	DS[a]	Yield (%)
p-nitrobenzoylchloride	2	3	60	**1**	0.66	78
	3	3	60	**2**	0.75	79
phenylisocyanate	5	3	60	**3**	1.45	34
	10	3	60	**4**	1.79	45
maleic anhydride	2	4	60	**5**	0.30	52
	4	4	60	**6**	0.30	41
	6	14	60	**7**	0.90	46
$ClSO_3$	1	1	rt.[c]	**8**	0.61	65
$ClSO_3$	2	1	rt.	**9**	1.23	64
SO_3/pyridine	1	1	rt.	**10**	0.57	76
SO_3/pyridine	2	1	rt.	**11**	1.28	78
$POCl_3$	2	1	rt.	**12**	0.49	69
$POCl_3/H_2O$	1/1	1	rt.	**13**	0.32	75
$POCl_3/H_2O$	2/2	1	rt.	**14**	0.49	72
$POCl_3/H_2O$	3/3	1	rt.	**15**	0.95	70
$POCl_3/H_2O$	2/4	1	rt.	**16**	0.39	75
tert.-butyldimethyl-chlorosilane	10	3	60	**17**	0.36	35

[a] Degree of substitution calculated on the basis of nitrogen-, sulphur- [3], phosphorus [13],- and silicon [14] content, respectively.
[b] Mole derivatizing agent per mole modified anhydroglucose unit.
[c] Room temperature.

The reaction of CMC in DMA/Tos-OH with 2 to 6 mole equv. maleic anhydride leads to CMC-maleates **5-7** of DS_E of 0.3 to 0.9 which are soluble in water as sodium salts, i.e. a new polyelectrolyte containing the carboxy groups in different distance from the polymer backbone is formed. These unsatured derivatives are interesting starting materials for water-born films and gels crosslinkable be UV-irradiation and radical initiation.

On the other hand, polyelectrolytes with more than one type of ionic groups are of growing importance due to their biological activity as well as their gel- and symplex-forming tendency [11,12]. For this purpose CMC-sulphates and -phosphates were synthesized.

A sulphation could be achieved with chlorosulfonic acid or SO_3/pyridine complex. In a short reaction time of 1 h and 1 or 2 mole equv. sulphating agent CMC-sulphates **8-11** of DS_S from 0.61 to 1.28 were obtained. The sodium salts of the mixed polyelectrolytes are completely water-soluble, as expected, and they show the characteristic FTIR absorptions at 815 cm^{-1} (ν SO), and 1240 cm^{-1} (ν SO_2).

Phosphating of CMC was carried out with $POCl_3$ and partially hydrolyzed $POCl_3$ because the latter system has a significantly lower tendency to cross-link the polymer. The CMC-phosphates **12-16** obtained are listed in Tab 1, too. While sample **12** is only swellable in water due to cross-linking, samples **13-16** are water-soluble as sodium salts in the freshly prepared state. As known for cellulose phosphates [13], after drying the CMC-phosphate samples lose solubility.

Silylation of cellulose has become a useful method to transfer the insoluble polymer to a organo-soluble one [14]. In the present work we studied silylation of CMC with 10 mole equv. tert.-butyldimethylchlorosilane in the presence of pyridine for 3 h at 60 °C. The product obtained by precipitation into water shows the typical FTIR absorptions at 840 cm^{-1} (ν Si-C) and 1260 cm^{-1} (δ Si-C). The DS_{Si} determined by silicon analysis was 0.36. The successful introduction of the lipophilic silyl-groups into CMC offers an interesting way to new cellulosic amphiphiles.

The described one-step activation method is a new convenient approach to reactive CMC in a highly swollen gel-state. The applicability for chemical modifications was exemplified by various esterification reactions. In comparative studies it was found that in contrast to the results of esterification reactions described, a reaction of CMC in DMA under equal conditions, however without activation by Tos-OH, leads to practically no introduction of the ester groups.

The synthesis of mixed ethers in this system is now under investigation.

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