Carboxymethyl Ethers of Cellulose and Starch – A Review

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Summary: This review article deals with the technically important carboxymethyl ethers of cellulose and starch. Recent developments of synthesis, characterization, and application are presented considering adequately own research work in this field. In particular, the structure characterization by means of chromatographic (HPLC) and NMR-spectroscopic techniques as well as commercially important synthesis paths and alternative methods are described.

Keywords: biopolymers; carboxymethyl cellulose; carboxymethyl starch; functionalization of polymers; structure characterization

Introduction

The chemical modification of polysaccharides is the most important route to modify the properties of the naturally occurring biopolymers and to use this renewable resource in the context of sustainable development. In general, all chemical reactions known from low molecular organic chemistry may be carried out. However, up to now only a limited number of products is produced commercially. Recent research and development is focused on the improvement of the known products and synthesis paths as well as on new derivatives and alternative synthesis concepts.[1]

Carboxymethylation of polysaccharides is a widely studied conversion since it is simple and leads to products with a variety of promising properties. In general, the polysaccharide is activated with aqueous alkali hydroxide, mostly sodium hydroxide, and converted with monochloroacetic acid or its sodium salt according to the Williamson ether synthesis yielding the carboxymethyl (CM) polysaccharide derivative. Not only cellulose and starch but also various polysaccharides from different sources are applied as starting materials. Selected polysaccharides, which were studied with regard to carboxymethylation, are summarized in Table 1.

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Carboxymethyl cellulose (CMC, as it is usually called) was first prepared in 1918 and was produced commercially in the early 1920's at the IG Farbenindustrie AG in Germany.[2] However, since then, significant improvements in process technology, in product quality, and in production efficiency have been made. A historical overview of CMC production on an industrial scale including comments about the future development of this important cellulose derivative was recently published.[3] Today CMC of different quality is applied in many areas of industry and human life (Table 2).

Carboxymethyl starch (CMS) is also known for a long time. CMS was first made in 1924 by the reaction of starch in an alkaline solution (40% aqueous NaOH) with sodium monochloroacetate.[4] Products of higher degree of substitution (DS) of up to 1.0 have been obtained in essentially non-aqueous media comparable to the CMC synthesis.[5,6] Various studies of the carboxymethylation of starch were carried out to optimize the reaction conditions, that is, to increase product yield and reaction efficiency.[7-10]

Table 1. Structure of selected polysaccharides studied for carboxymethylation.

Polysaccharide			Reference
Type	Source	Structure	
Cellulose	Plants	β-(1→4)-D-glucose	[11]
Chitin	Animals	β-(1→4)-D-(*N*-acetyl)glucosamine	[12]
Chitosan		β-(1→4)-D-glucosamine	
Curdlan	Bacteria	β-(1→3)-D-glucose	[13]
Dextran	Bacteria	α-(1→6)-D-glucose main chain	[14]
Pullulan	Fungi	α-(1→6) linked maltotriosyl units	[15]
Scleroglucan	Fungi	β-(1→3)-D-glucose main chain, β-(1→6)-D-glucose branches	[16]
Schizophyllan	Fungi	β-(1→3)-D-glucose main chain, D-glucose branches	[17,18]
Starch	Plants		[19]
Amylose		α-(1→4)-D-glucose	
Amylopectin		α-(1→4)- and α-(1→6)-D-glucose	

CMC and CMS are polymers easily to handle. Contact of finely divided dust with the eyes may cause mild irritation. Health and flammability hazards are slight. They are not metabolized by humans, but may have a laxative effect if a large amount (ca. 10 g) is orally ingested. There are no known carcinogenic effects and no known medical conditions that could be aggravated by exposure (for detail information see publications of the suppliers).

Analytical Tools for the Structure Characterization of Carboxymethylated Cellulose and Starch

The total degree of substitution (DS), that is the average number of functional groups introduced in the polymer, mainly determines the properties of polysaccharide derivatives including carboxymethylated products. Moreover, the functionalization pattern may influence the properties as well. In addition, the exact determination of DS and functionalization pattern is a prerequisite for the optimization of reaction conditions as well as for understanding of structure property relationship. With regard to the functionalization pattern both the distribution of the CM groups within the repeating unit, i.e., the partial DS at position 2, 3, and 6, and hence the eight different conceivable repeating units, which built up the polymer chain, as well as within the polymer chain, have to be considered. Moreover, a different distribution may appear between different polymer chains. Depending on the morphological structure as in particular in the case of starch granules, carboxymethylation to a low extent may lead to an uneven distribution of the CM moieties, which will be discussed later. Various methods to analyze the total DS are known and will be briefly commented.

Table 2. Carboxymethyl cellulose (CMC) grades and typical applications (adopted from [3]).

Quality of CMC	Examples of application areas	Content of CMC %	Content of salts %
Technical	Detergents, mining flotation	< 75	> 25
Semi-purified	Oil and gas drilling muds	75 – 85	15 – 25
Purified	Paper coating, textile sizing and printing, ceramic glazing, oil drilling muds	> 98	< 2
Extra purified (Cellulose gum)	Food, toothpaste, pharmaceuticals	> 99.5	< 0.5

Determination of the Degree of Substitution of Carboxymethyl Groups

The classical methods to determine the DS of CMC and CMS are very similar. They use the acidity of the carboxylic groups, i.e., the conversion of the salt form to the free acid form and *vice versa*.[20] The acid form of the CM polysaccharide, which can be obtained by a treatment of the sodium salt form of the polymer dispersed in ethanol with concentrated hydrogen chloride, can be titrated with a sodium hydroxide solution of known molarity.[21] Mostly applied is the back titration method, which was proposed as standard procedure of CMS[22] and CMC[23]. The sodium salt of the polymer is converted to the free acid form. Subsequently, aqueous NaOH is added to a known amount of the free acid form leading to the sodium carboxylate. The excess of NaOH is back titrated permitting to calculate the DS.

The sodium determination is quite simple.[24] However, there are important prerequisites to be fulfilled, i.e., the CM polysaccharide must be completely converted to the sodium salt and all by-products of synthesis (in particular NaCl and sodium glycolate) have to be completely removed. The latter one is often carried out by dialysis the polymer against water resulting in the problem that also rather low molecular parts of the samples with comparatively high DS are removed as well leading to an incorrect DS of the whole sample.

The interaction of the CM groups with salt ions leading to quantitative precipitation of the polymers with copper salt and back titration of the excess of Cu ions gives the DS as well.[25] It is assumed that exactly one mol Cu ion interacts via electrostatic bonds with carboxylic groups of the carboxymethyl moieties.[26] It may be assumed that also the hydroxyl groups are included in the interactions stabilizing the insoluble copper salts formed. For CMC, the precipitation of the polymer with an aqueous solution of uranyl nitrate and the subsequent determination of uran oxide obtained by combustion represents a useful method.[27]

In addition, many studies about the determination of DS applying various procedures as, e.g., titration of the anionic polymers with cationic polyelectrolytes forming insoluble polymeric salts (so-called symplex aggregates) have been investigated.[28,29] However, they have found only some interest for the determination of DS.

If the initial weight of the CM polymers, the amount of impurities (NaCl, sodium glycolate), and the moisture content are known, it is possible to determine DS with the methods mentioned above. It must be pointed out that these methods can be applied for

samples with DS values of up to 1.5, i.e., for the nowadays commercially important products. At higher DS various problems with regard to the necessary stoichiometric interactions appear. These sources of error are excluded in the spectroscopic and chromatographic methods provided the signals of the spectra and chromatograms can be suitably assigned and quantified. These modern methods will also give information about the functionalization pattern of the polyglucan derivatives.

However, it should be mentioned that the "classical" methods are still very useful because there is no need for expensive equipments and the DS values are obtained in a very reproducible manner provided the procedure is carried out very carefully.

Characterization of the Functionalization Pattern

At present, most important are ^{13}C CP/MAS NMR- and solution ^{13}C NMR spectroscopy, ^{1}H NMR spectroscopy and chromatographic techniques (HPLC, HPAEC-PAD) and gas-liquid chromatography[30] after complete depolymerization of the samples (For review see: Käuper et al.[31]) Capillary electrophoresis was shown to be a useful analytical tool as well.[32]

From the ^{13}C CP/MAS NMR spectrum the average DS can be calculated form the ratio of area of the carboxyl signal to that of C-1 signal provided that the scaling factors for the carboxyl and C-1 signals are very close to being equal, which can be reached by measuring with a contact time of 2 ms. A typical spectrum of a CMC with DS 2.4 is shown in Figure 1. The DS values obtained by ^{13}C CP/MAS NMR of 24 CMC samples within the range of DS from 0.2 to 2.9 agree well with those determined by gravimetric analysis of the sodium content (Figure 2). Compared with ^{13}C CP/MAS NMR, the resolution in ^{13}C NMR spectra of dissolved samples is significantly increased, which enables spectra recorded in this way to be evaluated for the purpose of determining the total DS and the partial DS at position 2 (x_2), 3 (x_3), and 6 (x_6) as shown by Reuben and Conner.[33] A problem may appear from the high viscosity of the polymer solution in D_2O because the line width increases with increasing degree of polymerization (DP) of the samples. It was found that the polymers could be partly degraded without splitting of any carboxymethyl function and no occurrence of monomeric or dimeric components applying ultrasonic treatment.[34]

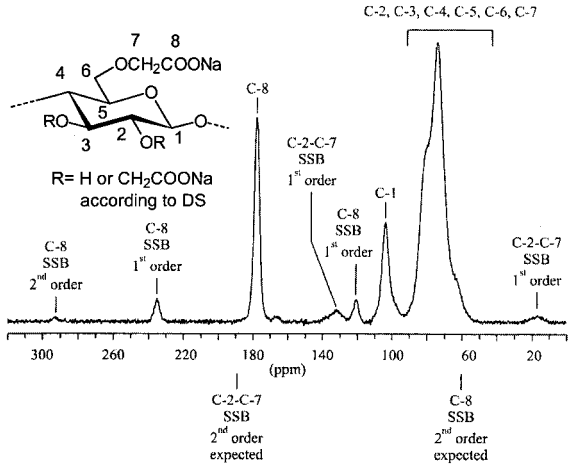

Figure 1. ^{13}C CP/MAS NMR spectrum with signal assignment of a carboxymethyl cellulose (sodium salt) with a degree of substitution of 2.4. The spectrum was recorded with a contact time of 2 ms at a spinning frequency of 5.7 kHz.

The improved spectra after ultrasonic treatment of CMC (Figure 3) show still overlapping signals, however, the accuracy of the fitting procedure for Lorentzian lines increases with improving spectral resolution and hence the DS calculation is more accurate as well.

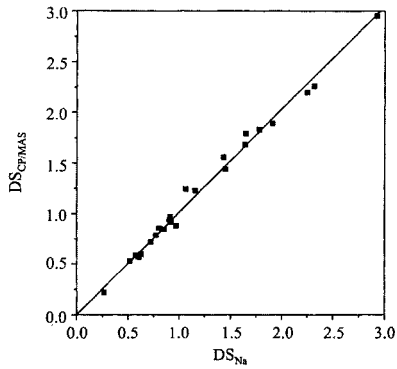

Figure 2. Degree of substitution determined by ^{13}C CP/MAS NMR spectroscopy ($DS_{CP/MAS}$) plotted against the sodium content (DS_{Na}) of 24 carboxymethyl cellulose samples.

Partial enzymatic depolymerization was also successfully applied to improve the NMR spectra of the polyelectrolytes.[35,36] The importance of selective enzymatic degradation of CMC with purified endoglucanase instead of applying a cellulase mixture will be discussed below in context with determining the distribution of CM moieties within the polymer chains.

^{1}H NMR spectroscopy of depolymerized samples is a useful tool to get information about the partial DS at position 2, 3, and 6.[37] The samples can be directly hydrolyzed in D_2O/D_2SO_4 and investigated by means of ^{1}H NMR spectroscopy. 16 Scans are sufficient to get a well-resolved spectrum, which can be used to calculate the partial DS values. Typical spectra of CMS after hydrolytic chain degradation with DS of 0.79 and 2.09 are shown Figure 4.[32] It is important to study samples free of glycolic acid or sodium glycolate because these compounds give a signal at about 4.2 ppm as well, which is the characteristic chemical shift of the CH_2 moiety bound to the 6 position of the anhydroglucose unit (AGU). To calculate the partial DS, equation 1 can be used.

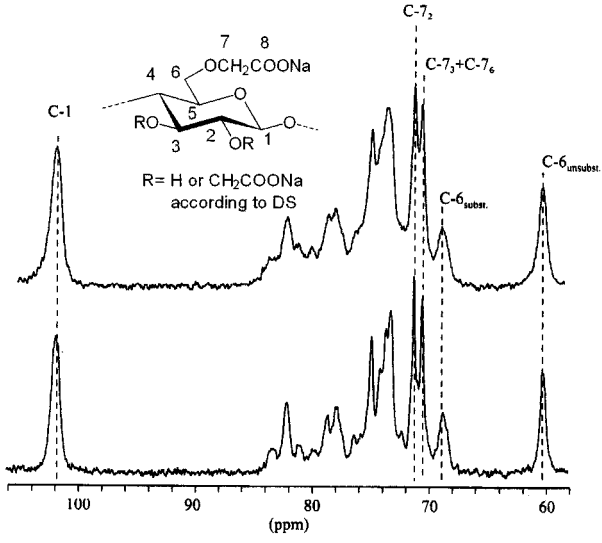

Figure 3. Part of the ^{13}C NMR spectra with suppressed nuclear Overhauser effect of carboxymethyl cellulose (degree of substitution 1.28) before (above) and after ultrasonic treatment (below).

In the following equation 1 applied for the DS and partial DS calculation, A represents the peak area, O the oxygen atom at the position i (i = 2,3,6), H-1 the hydrogen atom at the

anomeric carbon atom, α, β the configuration of glucose, s is used for substituted, u for unsubstituted positions. In case of starch of high content of amylopectin, a functionalization at position 4 should be included, which may appear at rather high total DS.

$$x_i = \frac{\frac{1}{2}A(\text{methylene protons at position O - } i)}{A(\text{H}-1\alpha,\text{O}-2\text{s}) + A(\text{H}-1\alpha,\text{O}-2\text{u}) + A(\text{H}-1\beta,\text{O}-2\text{s}) + A(\text{H}-1\beta,\text{O}-2\text{u})}$$

$$\text{DS} = \sum_i x_i$$

Equation 1

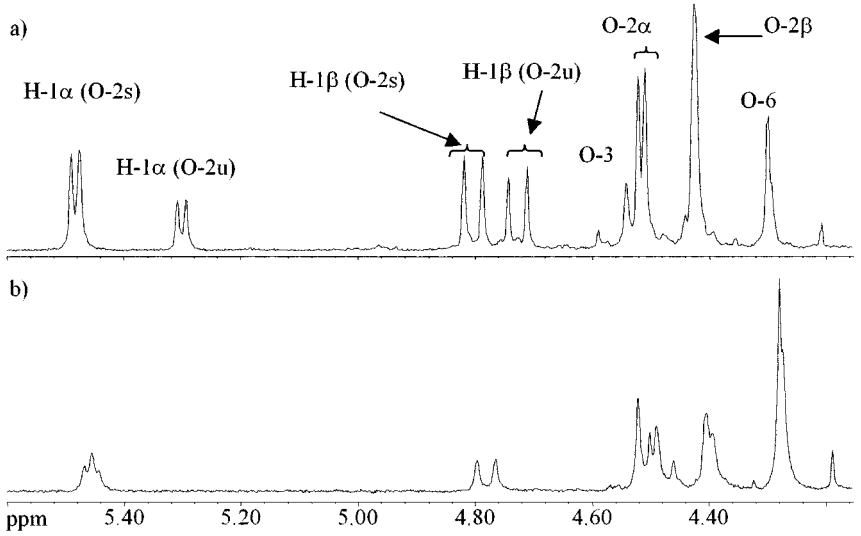

Figure 4. ^{1}H NMR spectra of carboxymethyl starch samples after hydrolytic chain degradation, a) degree of substitution, DS_{CM} 0.79) and b) DS_{CM} 2.09.

Empirical polarity parameters of CMC were studied and compared with native cellulose batches and starch. The Kamlet-Taft's α (hydrogen-bond donating ability), β (hydrogen-bond accepting ability), and π* (dipolarity/polarizability) parameters were used.[38] The α-values of CMC significantly decreases with increasing DS inasmuch the number of cellulose OH groups' decreases.

Finally it should be mentioned that the analysis of positions of functional groups in CMC was successfully carried out by a reductive-cleavage method.[39] Sequential permethylation and reductive cleavage gives eight products, which are analyzed as their acetyl derivatives

by gas-liquid chromatography.

In order to get information about the distribution of functional groups within the polymer chain single enzymes of the cellulase complex may be applied.[40] Conventional CMC up to a DS of 1.6 is markedly fragmented by mono-component endoglucanase. Obviously the highly substituted regions are not split. Thus, the analysis of the fragments obtained give a rather clear picture of the substituent distribution in the polymer chain.

An even more complex structure is the morphology of cellulose and starch particles. The discovery of channels in starch granules and the effects on the modification and digestibility was studied in recent years. Channelization is supposed to be an additional structural feature that also influences the reactivity of the starch. A new method of determining the location of anionic entities within starch granules that utilizes confocal laser scanning microscopy was established.[41]

Commercial Production of CMC and CMS

Large-scale production of CMC and CMS is exclusively carried out by slurry processes, i.e., by the conversion of the alkali cellulose and alkali starch, respectively, swollen in aqueous NaOH and an organic liquid with monochloroacetic acid or its sodium salt. "Common" CMC in the range of DS from 0.4 to 1.5 is subject of several interesting review papers.[42-45] Their synthesis, the distribution of the carboxymethyl groups within the AGU, and properties are well documented.

The kinetics of carboxymethylation of cellulose was studied and it was shown that the reaction rate increases with temperature (30-80°C) in a batch reactor. The kinetics of the reaction can be described by a nucleophilic reaction scheme. The decrease of rate during the substitution is caused by the decline of the reactivity of the hydroxyl groups, which can be expressed in the model by an exponential decrease of the kinetic constants.[46]

The typical starting materials for carboxymethylation are wood pulp (sulfate and sulfite pulp with DP from 600 to 2000) and cotton linters with DP of up to 2000. Choosing the DP of the cellulose can control the viscosity of the CMC.

The variation in pulp composition regarding the content of hemicellulose may influence the quality of the CMC formed. That means that insoluble residues may appear.[47] The amount of residuals seems to be influenced mainly by the relative fraction of cellulose in the pulp. It is believed that a high viscosity in combination with high galactomannan content reduces the amount of undissolved residuals.[47]

While cellulose (Table 1) is a very uniform polymer with regard to the molecular structure, starch consists of two polymers, namely amylose and amylopectin to a varying extent depending on the source (Table 3), which will influence the reactivity and the properties of the CMS as well.

Table 3. Amylose content of typical starch samples.

Starch type	Content of amylase
	%
Hylon VII	70
Crisp film	70
Wheat starch	25
Amioca powder	1
Pea starch	90
Potato starch	28
Waxy maize starch	1

The heterogeneous carboxymethylation of starch in various low molecular alcohols leads to CMS with significantly different DS values. The functionalization of starch heterogeneously in 2-propanol leads to CMS with the highest DS value. A reaction efficiency of up to 82% could be realized (Table 4).[48]

Multi-Step Carboxymethylation of Cellulose and Starch

The DS of CMC can be increased by a multi-step reaction, i.e., the CMC synthesized is isolated and subsequently carboxymethylated again under comparable conditions. Thus, using CMC with a DS of 1.31 (from spruce sulfite pulp) by subsequent carboxymethylation with a molar ratio of monochloroacetate to AGU of 6 and 2-propanol as slurry medium leads to a sample with a DS of 2.32. A further reaction (molar ratio of monochloroacetate to repeating unit of 9) yields a highly substituted CMC with a DS of 2.63.[49] It must be pointed out that applying one-step reaction the maximal DS is about 1.3 – 1.5. No higher DS values could be obtained by the usual heterogeneous reaction.

Recently, the multi-step carboxymethylation of starch was investigated.[32,48] Starch samples of different amylose content, namely pea starch (90%), potato starch (28%), and waxy maize starch (1%) were converted 10 times under similar conditions. The reaction was carried out in methanol/water because methanol is the usually applied slurry medium

in commercial synthesis. The DS values (Table 5) and the functionalization pattern were analyzed by HPLC and ^{1}H NMR spectroscopy.

Table 4. Conditions and results of reaction of starch (WS = wheat starch; AP = Amioca powder; CF = Crisp film) with NaOH and $ClCH_2COONa$ at 55°C for 5 h (Anhydroglucose unit : NaOH : $ClCH_2COONa$ = 1 : 1.7 : 1.7).

Starch Type[a)]	Slurry medium	DS (^{1}H NMR)				DS (HPLC)
		O-2	O-3	O-6	Σ	
WS	Isopropyl alcohol	0.87	0.12	0.67	1.66	1.40
WS	Ethanol	0.10	0.02	0.09	0.21	0.15
WS	Methanol	0.14	0.03	0.08	0.25	0.13
WS[b)]	Isopropyl alcohol	0.73	0.11	0.48	1.32	1.29
AP	Isopropyl alcohol	0.62	0.14	0.53	1.29	1.29
AP	Ethanol	0.65	0.11	0.32	1.08	0.95
AP	Methanol	0.08	0.02	0.06	0.16	0.08
CF	Isopropyl alcohol	0.83	0.15	0.69	1.67	1.40
CF	Ethanol	0.83	0.15	0.40	1.38	1.29
CF	Methanol	0.20	0.05	0.10	0.35	0.18

[a)] See Table 3, [b)] Reaction time: 2 h

It became obvious that after 10 carboxymethylation steps, the highest DS obtained is 2.35 in the case of the high amylose starch. At lower DS (< 1) the differences between the starch types are negligible. Altogether, the DS values of high amylose starch samples were higher compared with amylopectin. This may be due to the linear structure of amylose, which may allow the reactants a better accessibility to the OH groups. However, the step-wise increase in the DS values gradually decreases with increasing DS of the starting polymer. This might be an effect of electrostatic repulsion of CMS and monochloroacetate.

Detailed investigations on the distribution of the CM groups by means of ^{1}H NMR spectroscopy reveal a reactivity in the order O-2 > O-6 >> O-3. HPLC measurements of the depolymerized samples indicate mole fractions of the different substituted repeating units. Above a DS of 1.7, traces of 2,3,4,6-tetra-*O*-carboxymethylglucose units appear. A comparison of the mole fractions with the Spurlin statistics shows a remarkable good fit as found for CMC as well. There are several efforts to modify the simple Spurlin statistic by

including different rate constants for the reaction at position 2, 3, and 6 that, however, did not change the general conclusion that the heterogeneous reaction of cellulose (Williamson ether synthesis) yields CMC with a statistic content of the different possible repeating units.

Table 5. Degree of substitution (DS) of carboxymethyl starch (CMS) prepared by multi-step carboxymethylation at 55°C for 5 h (molar ratio repeating unit : NaOH : $ClCH_2COOH$ = 1.0:2.0:0.7). DS values were determined by means of HPLC and ^1H NMR spectroscopy after depolymerization.

Step	Pea starch		Potato starch		Waxy maize starch
	DS_{HPLC}	DS_{NMR}	DS_{HPLC}	DS_{NMR}	DS_{HPLC}
1	0.37	-[a)]	0.40	0.57	0.33
2	0.72	-[a)]	0.79	0.87	0.71
3	1.07	1.04	1.08	-	1.00
4	1.33	1.36	1.31	1.40	1.27
5	1.55	1.61	1.53	1.58	1.51
6	1.77	1.78	1.72	1.59	1.70
7	1.95	1.97	1.83	1.79	1.80
8	2.09	2.05	1.98	1.94	-
9	2.22	2.10	2.02	1.96	-
10	2.35	2.18	2.09	2.20	-

[a)] Not determined

Unconventional Synthesis of CMC and CMS

A number of aqueous solvents, e.g., the aqueous solution of $Ni(tren)(OH)_2$ [tren = tris(2-aminoethyl)amine], were studied as medium for homogeneous etherification reactions.[50,51] It is possible to convert cellulose dissolved in Ni(tren) in a fully homogeneous process to CMC.[52] Structure investigations by means of ^1H NMR and HPLC analysis after complete depolymerization revealed that the products show a statistic content of the different repeating units and a distribution of the carboxymethyl functions within the AGU in the order O-2 ≥ O-6 > O-3, i.e., they posses the same functionalization pattern as ethers prepared from alkali cellulose which is applied for commercial production of CMC.[53] These results clearly show that both simple activation of cellulose with aqueous NaOH (mercerization) and complete dissolution of the polysaccharide leads

to an almost even accessibility and hence there is no particular advantage for carboxymethylation of the dissolved polymer.[54]

Recently, molten inorganic salt hydrates were demonstrated to be efficient solvents for cellulose.[54,55] The dissolution of the polymer occurs without derivatization, i.e., the salt hydrates are so-called non-derivatizing solvents. Systematic investigations of carboxymethylation in the molten $LiClO_4x3H_2O$ were carried out. The dissolved cellulose (1.6%, w/w) was treated with different amounts of solid NaOH and sodium monochloroacetate.[56] A remarkable finding is that polymers with DS values as high as 2 can be prepared within a short reaction period (4 h) by applying a one-step synthesis. The values of the mole fractions of the different repeating units analyzed by HPLC (see above) in comparison with statistic calculations show that the values fit perfectly the prediction. This lead to the conclusion that CMC prepared in the molten salt hydrate contain a statistic amount of the different repeating units, i.e., the same functionalization pattern as in the case of the conventional heterogeneous procedure is obtained. In contrast, within the repeating units a distribution in the order O-6 > O-2 ≅ O-3 was analyzed by ^1H NMR spectroscopy after hydrolytic chain degradation. As revealed by SEC, a degradation of the polymer occurs during the carboxymethylation. While the DP of the starting cellulose was 1255, the resulting CMC samples had a considerable lower DP in the range from 930 to 420 depending on the reaction conditions.

Another group of molten salt hydrates acts as effective swelling agent for cellulose, e.g., $LiClx2H_2O$. The DS of CMC prepared applying $LiClx2H_2O$ as reaction medium, i.e., in the swollen state, is generally lower than DS of the samples produced from solution in molten $LiClO_4x3H_2O$.[56] However, the distribution of the CM moieties is similar compared to the homogeneously prepared samples. Consequently, CMC with a preferred functionalization of O-6 can be prepared, however, in any case a high excess of etherification reagent is necessary.

N-Methylmorpholine-N-oxide (NMNO) is a suitable medium for various etherification reactions of cellulose including carboxymethylation. DS values of up to DS 1.8 were realized in a one-step synthesis.[57]

The etherification of cellulose in N,N-dimethylacetamide (DMA)/LiCl, which is the medium of choice for acylation reactions, is generally combined with a number of difficulties, e.g., a high excess of reagents and long reaction times. Isogai compared the etherification of cellulose in DMA/LiCl, N_2O_4/dimethyl sulfoxide (DMSO), and

DMSO/SO_2/triethylamine.[58-60] It was found that benzylation is most efficient in the latter solvent and fully functionalized cellulose ethers are accessible in a one-step reaction. However, the solvent DMA/LiCl is useful for the preparation of CMC of rather high DS (up to 2.5) in lab-scale.[49,61] In addition, a defined conversion of cellulose into ethers having an unconventional distribution of functional groups was recently found.

The new cellulose solvent DMSO/tetrabutylammonium fluoride (TBAF) recently found by Heinze and co-workers[62] was applied as reaction medium for the carboxymethylation of mercerized cellulose from sisal and cotton linters. The reaction parameters studied were the molar ratio of reagent and NaOH to AGU and the addition of the NaOH either as an aqueous solution or as solid particles. The pattern of substitution within the AGU and along the polymer chains of the CMC, which was analyzed by ^{1}H NMR spectroscopy and HPLC after acidic depolymerization of the CMC, is in the order O-6 > O-2≥ O-3. With regard to the mol fractions of the different repeating units, samples prepared using aqueous NaOH possess a statistic content, while by using solid NaOH a deviation from statistically calculated values was observed. As a consequence of the non-statistics, the solubility in water of these samples starts at a DS 0.85, while conventionally prepared CMC are water-soluble at a DS as low as 0.4.[63]

Induced Phase Separation Prior to Carboxymethylation

A different concept for the synthesis of CMC and CMS with new structural features is the activation of the polymer by dissolution (cellulose, e.g., in DMA/LiCl; starch in DMSO) and a subsequent addition of solid water-free NaOH particles.[64] By means of FTIR- and polarizing light microscopy it was shown that a gel is formed due to the regeneration of cellulose II on the interface solid particle/solution. In case of starch the polymer is also fixed on the NaOH and, hence, a gel-like state is formed. This process is called induced phase separation leading to reactive microstructures.[51] The reaction of cellulose with sodium monochloroacetate yields CMC with DS values as high as 2.2 in a one-step procedure (Table 6).

The etherification at the 6 and 3 positions is more effective compared to the conventional synthesis. It is possible to completely depolymerize the polymer backbone (preferably with $HClO_4$) and to separate the repeating units of the CMC chain by HPLC.

Table 6. Carboxymethylation of cellulose dissolved in *N,N*-dimethylacetamide (DMA)/LiCl and of cellulose trifluoroacetate (CTFA), cellulose formate (CF), in dimethyl sulfoxide (DMSO) via induced phase separation with NaOH particles (size < 0.25 mm) at 70°C.

Starting material/ Degree of substitution	Molar ratio[a)]	Reaction time	Carboxymethyl cellulose	
		h	DS	Solubility in water[b)]
Cellulose/DMA/	1:2:4	48	1.13	–
LiCl/	1:4:8	48	1.88	+
-	1:5:10	48	2.07	+
CTFA/DMSO/	1:5:10	2	0.11	–
1.5	1:10:20	4	1.86	+
	1:10:20	16	1.54	+
CF/DMSO/	1:10:20	2	1.46	+
2.2	1:10:20	4	1.91	+
	1:15:30	4	1.36	–
	1:20:40	2	2.21	+

[a)] Molar ratio: Repeating unit/$ClCH_2COOH(Na)$/NaOH, [b)] – insoluble; + soluble

A comparison of the mol fractions measured with values calculated by statistics [33,49], which simulated the conversion along the polymer chain without preference of any of the OH groups and without the influence of the DS already reached, leads to very interesting results. While the statistic data meet the mol fractions of conventionally obtained CMC completely, in case of polymers synthesized via induced phase separation, significant differences between the data sets appear as can be seen in Figure 5. The comparably high amount of glucose (glc) and 2,3,6-tri-*O*-carboxymethylated glc units is a first evidence for a gradient-like distribution of ether functions along the polymer backbone. It may be concluded that after an induced phase separation the etherification is more or less limited to the area directly at the interface polymer-solid NaOH particle.

Applying organo-soluble cellulose intermediates like CTFA (DS 1.5) dissolved in DMSO for the induced phase separation technique (see Table 6), it was revealed by polarizing light microscopy and FTIR spectroscopy that by addition of solid NaOH the primary substituents (trifluoroacetate) are cleaved off and cellulose II is regenerated on the solid particles.

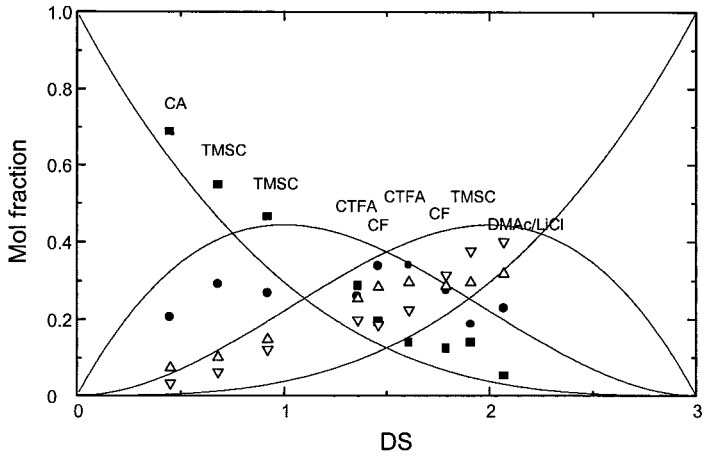

Figure 5. Representative examples of the mole fractions of (●) glucose; (■) mono-O-carboxymethyl glucoses; (△) di-*O*-carboxymethyl glucoses; (▽) 2,3,6-tri-*O*-carboxymethyl glucose in hydrolyzed carboxymethyl cellulose samples (polymers were synthesized via induced phase separation starting from cellulose acetate, CA, trimethylsilyl cellulose, TMSC, cellulose trifluoroacetate, CTFA, cellulose formiate, CF, and cellulose dissolved in *N,N*-dimethylacetamide (DMA)/LiCl) plotted as function of degree of substitution (DS) determined by means of HPLC.[65]

Additionally, the deacetylation was nicely observed by the growth of sodium trifluoroacetate on the NaOH and in the medium. It is worth to note that the decrease of the size of NaOH particles from 1 to <0.25 mm increases the DS from 0.64 to 1.12 but does not influence the distribution of the functional groups.[65]

Endoglucanase fragmentation of CMC samples followed by analytical and preparative SEC proved that samples of DS of up to 1.9 are intensively degraded, supporting the proposed block-like pattern of functionalization. The detailed analysis of the fragments obtained was carried out by preparative SEC, hydrolysis, and anion exchange chromatography with pulsed amperometric detection. From these studies a structure can be proposed with chains containing segments of very high DS alternating with areas of limited substitution. The highly carboxymethylated fragments were dominated by 2,3,6-tri-*O*-carboxymethyl glc units.[66]

Regioselective Carboxymethylation

In general, all chemical modification reactions of cellulose show at least some regioselectivity, i.e., in no case an equal reactivity of position 2, 3, and 6 appears. The reactivity of the free hydroxy groups depends on many factors including the state of activation and dissolution, the composition of the reaction mixture, the reagent in question, etc. For instance, homogeneous acylation in DMA/LiCl yields products with a preferred functionalization at position 6, while the carboxymethylation in 2-propanol/aqueous NaOH proceeds faster at position 2 compared to 6 and 3. An important area in cellulose chemistry is the close control of the substitution site within the repeating units. For the synthesis of new cellulose derivatives with a well-defined primary structure, polymeranalogous reactions are in the center of interest. However, enzymatically catalyzed regioselective functionalization, e.g., the lipase catalyzed acylation[67,68], the enzyme-catalyzed polymerization of cellulose derivatives[69] and the chemical polymerization, e.g., by ring-opening polymerization of glucose derivatives[70,71] are alternative routes. It is assumed that they will be increasingly studied in the future.

Protective Group Technique

The most widely used protective group is the triphenylmethyl (trityl) moiety. A number of homogeneous procedures were developed for its controlled introduction. Husemann et al. described first attempts exploiting *N*-ethylpyridinium chloride melts as reaction medium.[72]

Furthermore, tritylation reactions of cellulose in DMSO/N_2O_4, DMA/LiCl, and DMSO/SO_2/diethylamine (DEA) were carried out yielding polymers with DS values of 1.0.[73] The 6-mono-*O*-trityl cellulose was widely applied for the regioselective functionalization of cellulose. The synthesis of 2,3-di-*O*-substituted methyl- and benzyl cellulose as well as 6-mono-*O*-methyl- and benzyl ethers was carried out via various protection/deprotection steps.[74-76] One of the major disadvantages is the deprotection step, which is usually carried out with HCl resulting in a significant degradation of the polymer chains. Therefore, alternative protecting groups are still of interest.

Methoxysubstituted triphenylmethyl compounds are new effective protective groups in cellulose functionalization (Table 7).[77] The reaction of cellulose dissolved in DMA/LiCl with 4-monomethoxytriphenylmethyl chloride is ten times faster than the conversion with unsubstituted trityl chloride. Complete functionalization of the primary hydroxy groups is

possible within 4 h at 70°C. Even after long reaction times, excess of the reagent, and elevated temperatures alkylation of the positions 2 and 3 was less than 11%, which is in the same range as found for the unsubstituted trityl function. Moreover, the detritylation succeeds 20 times faster under mild conditions.

Table 7. Tritylation of cellulose with methoxy-substituted trityl chlorides (3 mol reagent/mol repeating unit, *N,N*-dimethylacetamide/LiCl, 70°C) and detritylation (37% $HCl_{aq.}$ in tetrahydrofuran, 1:25 v/v at 25°C) after subsequent permethylation.[77]

Protecting group	Tritylation			Detritylation
	Time (h)	DS[a)]	Relative rate	Relative rate
Trityl	4	0.41	1	1
	24	0.92		
	48	1.05		
4-Monomethoxytrityl	4	0.96	2	18
	24	0.92		
	48	0.89		
4,4'-Dimethoxytrityl	4	0.97	2×10^5	100
	24	1.05		
	48	0.90		
4,4',4''-	4	0.96	6×10^6	590
Trimethoxytrityl	24	0.92		
	48	0.93		

[a)] DS calculated from elemental analysis

A procedure for the synthesis of 2,3-*O*-CMC via 6-*O*-triphenylmethyl cellulose or more efficiently via the 4-monomethoxtritylated derivative was established. The synthesis path and the product properties were investigated in detail.[78-80] The complete determination of the molecular structure of 2,3-*O*-CMC was carried out by enzymatic and chemical methods. As a result of endoglucanase treatment, an intensive depolymerization of the samples occurred, which was more pronounced for derivatives of comparatively low DS. The degraded samples can be separated into 18 fractions by preparative SEC and the proportion of each individual repeating unit can be analyzed by AEC following complete hydrolytic chain degradation. These analytical studies indicate a homogeneous distribution of the CM functions within the polymer chain.[81]

In general, starch dissolved in DMA/LiCl can be reacted with trityl chloride as well leading the 6-*O* protected derivative. Consequently, the synthesis of monomethoxytriphenylmethyl starch and the subsequent carboxymethylation was studied. Both the reaction in DMA/LiCl or DMSO occurred homogeneously. The highest DS of trityl groups obtained after a single conversion was 0.8. A complete functionalization could be realized with the unsubstituted trityl chloride only.[82]

Derivatives of CMC and CMS

Subsequently modified water-soluble cellulosics have attracted considerable attention due to their outstanding solution properties and potential practical applications. The modification of water-soluble cellulosics in particular hydroxyethyl-, hydroxypropyl-, and methyl cellulose as well as CMC can be done by reacting the remaining OH groups of the AGU with long chain aliphatic compounds carrying reactive functions as epoxide-, chloride-, isocyanate-, acid chloride-, and acid anhydride moieties. On the other hand, the functional groups of the substituents introduced (except methyl cellulose) can be functionalized. This idea was first realized by Landoll[83] and studied by various other groups.[84,85] The solutions of the hydrophobically modified cellulosics possess enhanced viscosity efficiency, improved shear and salt stability and shear-thickening rheology compared to the starting polymers.[86-89]

Polymeric surfactants from CMC were obtained by partial hydrophobization with higher fatty acid chlorides (C_{10} – C_{18}) showing reduced surface tension of water and good emulsification efficiency.[90] By etherification of CMC with diethylaminoethyl (DEAE) chloride in aqueous NaOH solution the corresponding CM-DEAE cellulose was obtained.[91] The polyampholyte (DS_{CM} 0.64, DS_{DEAE} 0.19) with an isoelectric point at pH 3 shows a different reduced viscosity dependent on pH value compared to the parent CMC. Further amphoteric cellulose products such as CM-*O*-2-hydroxy-3-(trimethyl-amino)propyl cellulose and CM-xanthate were prepared homogeneously in aqueous NaOH.[92]

The subsequent reaction of CMC in a non-aqueous swelling system with $ClSO_3H$ or SO_3-pyridine complex yields the corresponding CMC sulfuric acid half esters of high total degree of functionalization. Even a regioselective 2,3-di-*O*-CMC-6-sulfate may be synthesized.[93]

As already mentioned CMC is soluble in either cold or hot water, insoluble in organic

solvents. However, CMC can be even dissolved in formic acid with comparatively slight chain degradation. The dissolution of the sodium salt of CMC in a wide range of DS from 0.4 to 2.0 occurs under partial formylation of the remaining OH groups, i.e., formic acid was found to be the first so-called derivatizing solvent of the polymer (Figure 6). The CMC formyl esters, which can be isolated under water-free conditions, are even soluble in dipolar aprotic solvents, and they can be regenerated to CMC (sodium salt form) by treating with aqueous sodium hydroxide solution.[94] The non-aqueous, derivatizing solvent formic acid offers opportunity of homogeneous modification of CMC including reaction of the free OH groups or of the formate functions by transesterification.

It may be assumed that also further acids like mixtures of trifluoroacetic acid and trifluoroacetic anhydride may lead to dissolution of CMC or to the formation of the organo-soluble CMC trifluoroacetate. Moreover, there are various cellulose solvents as recently discussed in detail[1] not checked with regard to the solubility of CMC up to now.

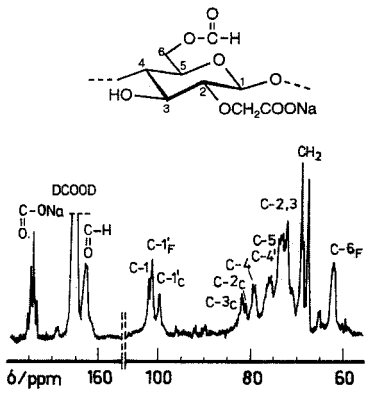

Figure 6. ^{13}C NMR spectrum of carboxymethyl cellulose (DS_{CM} 0.95) dissolved in formic acid-d_2, yielding a carboxymethyl cellulose formate (DS_F 0.50).

Properties

One of the most important goals of carboxymethylation of cellulose and starch is to obtain water-soluble derivatives, which are applied in various fields in order to control the behavior of aqueous systems and preparations. They behave as typical polyelectrolytes.

CMC is used, e.g., to stabilize clay/latex systems. The influence of the molecular weight of CMC on the rheology, dewatering, and coating performance of the system was studied. No dramatic effect of M_w was found.[95]

While the mostly applied sodium salt form of CMC is water soluble, a conversion by treating the polymer with a mineral acid leads to the water insoluble free carboxylic acid of the polymer. The pKa value was determined to be 3.2.[96] However, it should be pointed out that this pKa represents an average value because it depends on the distance of the carboxylic group from the polymer backbone, i.e., it can be controlled by the pattern of functionalization. A CMC with a preferred carboxymethylation at O-2 possesses a pKa of 3.0 while preferred O-6 modified samples give a pKa of 3.3.[57] This increase of pKa value with decreasing distance of ionic group from the polymer backbone is even more pronounced for oxidized cellulose (6-carboxyl cellulose, pKa 2.8) as expected.

The CMC (H-form) is of interest for metal ion adsorption, e.g., in wastewater treatment.[97] Experiments with Ni^{2+}, Co^{2+}, Cu^{2+}, Cd^{2+}, Pb^{2+}, Fe^{3+}, and Al^{3+} indicate a high adsorption capacity of up to 0.32 mmol Ni^{2+}/g and a very high rate of absorption. About 90% of binding is accomplished within 1 h. Applying beads of CMC optimal for separation by filtration, the spherical shape is not destroyed and hence it can be regenerated and reused.

Moreover, also still water insoluble products with a rather low DS (for CMC at DS < 0.3) are of interest due to the swelling ability and the properties of the ionic functions.

The interaction of the carboxylic groups with multivalent metal cations can be used to form so-called ionotropic gels, which are predominately stabilized by the electrostatic interactions. In addition interactions between the OH groups of the polymers and the metal ions contribute to the stability and the water insolubility of these polymeric aggregates. It should be pointed out that ionotropic gels could be simply obtained as spherical products. The formation, the structure, and some aspects of application of ionotropic gels obtained from natural, biotechnological produced and chemically modified polysaccharides containing carboxyl functions as anionic groups and multivalent metal cations is covered by many review papers (e.g., [98] and references cited therein). Special points of interest are the interactions between the carboxylic moieties and polyvalent metal cations and the selectivity of these interactions. An interesting area of application of these gels is cell immobilization and controlled release of bioactive compounds. It is even possible to dry the gel forming xerogels, which are still beads with a dense surface layer as exemplarily shown in Figure 7.

Controlled drug release was investigated with CMC. The polymer was used as carrier for, e.g., erythomycia as model drug.[99] The CMC was cross-linked with ferric salt to get biodegradable beads. Controlled release was improved by coating with gelatin/CMC and

by cross-linking. CMS is applied as a disintegration aid for tablets.

The macroscopic properties of polymer solutions are determined by microscopic (molecular) parameters. For example, the viscosity of the solution of CMC and CMS in influenced by the molar mass of the polymers, their degree of branching, and their radius of gyration, Rg, as well as their flexibility. Thickening properties of the solutions are related to the rigidity of the polymer backbone, which can be characterized by the persistence length. The intrinsic persistence length of CMC determined by SEC-MALLS as well as by potentiometric titrations with DS in the range from 0.75 to 1.25 (typical commercial samples) applying the worm-like chain theory is assessed to be 16 nm irrespective of the DS.[96]

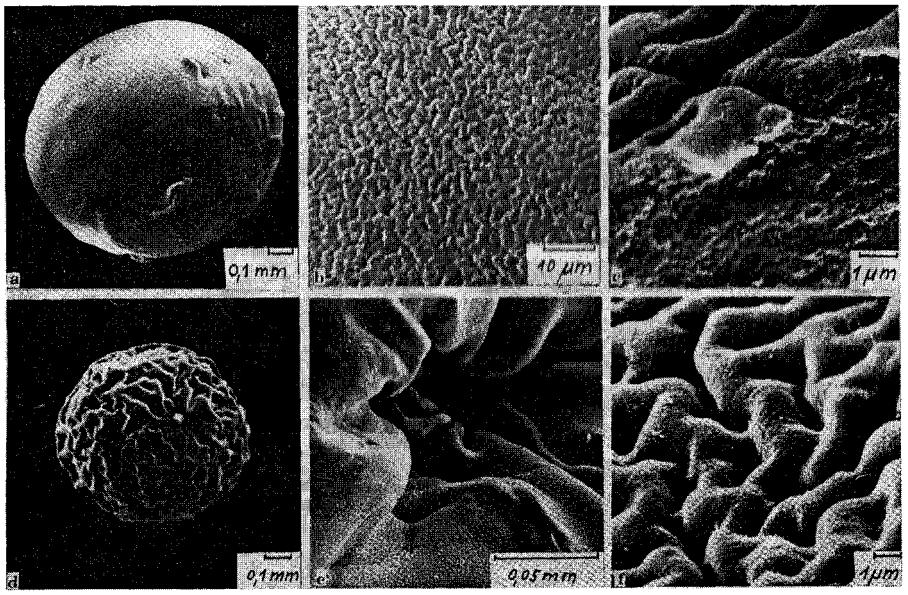

Figure 7. REM pictures of carboxymethyl cellulose gels cross-linked with Al^{3+} ions (above) and xerogels obtained by drying (bottom).[98]

Solutions of CMC and CMS are non-Newtonian, i.e., the viscosity of their solutions will be Newtonian at low shear rate but will decrease at a critical shear rate. In most case of medium to high viscosity types pseudoplasticity is predominant due to the tendency of the polymers to orient in the direction of the flow when stressed.

CMC was studied as component in blends by mixing the aqueous solution of the polymer

and further polysaccharides, e.g., konjac glucomannan.[100] The properties of such products like mechanical stability depend on the formation of hydrogen bonds, which can be controlled by the blending ratio.

Comments about Further CM-Polysaccharides

CM dextran samples with DS of up to 1.4 were synthesized by activating the polymer slurried in tert-butanol with aqueous sodium hydroxide. The molar ratio of sodium monochloroacetate to dextran was increased up to 2.5. The distribution of the functional groups within the repeating unit studied by ^{1}H NMR spectroscopy is in the order O-2 > O-3 > O-4.[101] The CM dextran was further modified to CM dextran benzylamide sulfonate/sulfate and studied with regard to the heparin-like anticoagulation activity.[14,102] On the other hand, CM dextran was used as starting material for the design of radiocontrast carriers.[103]

The heterogeneous carboxymethylation of chitin in 2-propanol or n-butanol with sodium monochloroacetate in the presence of concentrated aqueous NaOH yields N- and O-functionalized derivatives, which was confirmed by ^{13}C NMR spectroscopic studies of products synthesized with ^{13}C labeled monochloroacetic acid.[12] The structural ambiguity makes some problems in discussing structure-property relationships. Nevertheless, N- and O-CM chitin have been studied as drug carrier.[104] A selective N-carboxymethylation of chitosan was achieved by reaction with glycolic acid to form the Schiff base that was reduced with $NaCNBH_3$. It shows a high efficiency for metal ion absorption.[105] N,N-Dicarboxymethylchitosan can be formed as well depending on the degree of deacetylation.[106] N-Carboxymethylchitosan is also anticipated to be a potential biomedical material because it suppressed aflatoxin production and reduce fungal growth.[107]

CM pullulan was prepared by reaction of alkali pullulan with sodium monochloroacetate in a mixture of 2-propanol and water.[108] Values of the DS of up to about 1 could be realized. The CM pullulan was subject to further modification of the carboxylic groups with C_{16} alkylamine yielding hydrophobically modified products. The reaction of the COOH moieties with the amine was mediated with *N,N'*-dicyclohexylcarbodiimide.

The distribution of the carboxymethyl groups of CM pullulan was determined by NMR spectroscopy of oligomeric products obtained by acid hydrolysis.[109] A reactivity of the polymer in the order O-2 > O-4 > O-6 > O-3 was revealed. Regarding the maltotriosyl unit

having 9 reactive hydroxyl groups, a sample with a total DS of 3.3 (DS 1.1 regarding the AGU) possesses partial DS values of 1.96 (position 2), 0.52 (3), 0.37 (4), and 0.45 (6) and consequently a relative reactivity of 65:37:22:17 of position 2, 4, 6, and 3.

The carboxymethylation of scleroglucan, schizophyllan and further 1→3 glucans was carried out homogeneously in aqueous NaOH[110] and studied with regard to their biological properties.[111-114]

Outlook

Carboxymethylated polysaccharides, in particular CMC and CMS are based on renewable resources. They are biodegradable and non-toxic products that are finding an increasing number of applications. There are different grades of CMC and CMS. Especially the highly purified products, i.e., of low salt content have made the CM polysaccharides to a valuable additive in many areas of application including the food and pharmaceutical area. CMC is assumed to be applied in more than 200 applications today.[3]

From the author's point of view, the importance of carboxymethylation of polysaccharides will further increase in the context of increasing use of renewable resources, i.e., in the context of sustainable development, on one hand. On the other, polysaccharide possess unique structures synthesized by nature that are an excellent basis of the development of advanced and highly engineered products for present and future applications. This includes also the preparation of rather exotic (and hence highly costly) CM polysaccharide derivatives that will be useful in molecular recognition concepts as self-organizing supra-molecular systems, in nano-structures, in environmentally responsive (smart) materials, in sensors and chiral templates as well as due to their biological effects.

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