Cellulose (2018) 25:4919–4928
https://doi.org/10.1007/s10570-018-1908-y

ORIGINAL PAPER

Efficient and catalyst-free synthesis of cellulose acetoacetates

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Received: 2 January 2018 / Accepted: 13 June 2018 / Published online: 19 June 2018

Abstract An efficient path to prepare cellulose acetoacetates is reviewed in detail. The biopolymer dissolved in *N*,*N*-dimethylacetamide-LiCl is allowed to react with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one at elevated temperatures without any catalyst. The procedure, which is briefly described in the literature (Marson and El Seoud in J Appl Polym Sci 74:1355–1360, 1999), utilizes simple to handle, commercially available compounds and requires only a short reaction time to obtain pure products that are promising starting materials for the design of advanced cellulose-based materials. Cellulose acetoacetates with degree of substitution of up to 1.84 can be obtained. A side reaction forming comb-like polymer structures was realized applying high molar ratio of cellulose to reagent (above 2 mol per mol) that was not known up to now. The hydrophobic cellulose acetoacetates can be transferred easily into nanoparticles with particle sizes ranging from 120 to 300 nm.

Keywords Cellulose ester · Esterification · Acetoacetate · Side reaction · NMR spectroscopy · Nanoparticles · Catalyst-free

Introduction

Cellulose is the most abundant biopolymer and its derivatives have found a broad variety of applications (Hon 1994; Klemm et al. 2005). The esterification of cellulose is discussed in a large number of papers (for review see e.g., Heinze et al. 2006; Heinze 2016). Applications of various cellulose esters range from membrane materials for micro and ultrafiltration, sponges for pharmaceutical applications (Cabasso 1989) to nanoparticles for drug delivery systems (Obermayer 1980; Bissery et al. 1983; Hornig and Heinze 2008).

The class of soluble cellulose acetoacetates (CAA) has been introduced in the literature in 1953 (Staudinger and Eicher 1953). Regenerated cellulose was allowed to react with diketene in acetic acid in the presence of sodium acetate under heterogeneous conditions to obtain CAA with a high degree of substitution (DS) of 3.0 according to elemental analysis. Later it was shown that tert-butylacetoacetate is a useful reagent for the partial acetoacetylation of

Member of European Polysaccharide Network of Excellence (EPNOE, http://www.epnoe.eu).

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10570-018-1908-y) contains supplementary material, which is available to authorized users.

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cellulose (Edgar et al. 1995). It was found that homogeneous conversion applying cellulose dissolved in *N*,*N*-dimethylacetamide (DMAc)-LiCl or *N*-methylpyrrolidone (NMP)-LiCl with diketene and acid anhydrides yields mixed cellulose esters with varying DS values. The solubility of the products can be tuned by the amount of acylation reagent introduced. The mixed cellulose esters are water soluble with DS values in the range from 0.39 to 0.72. The synthesis developed was expanded to the reaction of cellulose dissolved in an ionic liquid applying a large excesses of tert-butylacetoacetate (up to 15 equivalents reagent per anhydroglucose unit, AGU). CAAs with DS of up to 1.35 could be prepared, which are water soluble at DS ranging from 0.58 to 0.87 (Liu et al. 2016). Even an enzymatic catalyzed acetoacetylation of starch and hydroxyethyl cellulose with diketene was described (Wang et al. 2003).

Although CAA is of special interest because of the versatility of the acetoacetate function, they are not comprehensively studied. The most familiar property of the 1,3-dicarbonyl moiety is their tendency to form chelates with transition metal ions (Rudolph et al. 1967; Charles and Bryant 1963). Regarding chemical modification, the methylene group containing acidic hydrogens is capable of reacting in aldol condensations according to the well-known Knoevenagel reaction (Knoevenagel 1896). Moreover, the keto group can be transformed to imine- and enamine functions as well as may form hydrazones with hydrazine derivatives (Nef 1891; Ballini and Petrini 2004; Liu et al. 2010; Samantaray et al. 2011). The ability to form enaminones has been utilized to generate cross-linked CAA with melamine (Edgar et al. 1995). Furthermore, hydrogels were obtained by reacting CAA with chitosan (Liu et al. 2016).

CAA is commonly prepared employing diketene as reagent or generating an acylketene in situ from tert.-butyl acetoacetate (Witzeman and Nottingham 1991). The thermal treatment of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (THD) is a further approach to generate acylketene in situ. The acetoacylation through thermal acylketene formation from THD was studied using a broad range of different alcohols and amines (Clemens and Hyatt 1985). Later, it was shown that hydroxypropyl cellulose could be converted to the acetoacetate form with this reagent up to DS = 3.0 (Pawlowski et al. 1986). The products formed are able to form lyotropic and thermotropic liquid-crystalline phases (Pawlowski et al. 1987). THD could later be applied to acetoacetylate a group of chiral, temperature-sensitive alcohols in boiling tetrahydrofuran in the presence of sodium acetate as catalyst (Sridharan et al. 2010). The compound was also mentioned to be useful for the homogeneous conversion of cellulose (Edgar and Blount 1993; Edgar and Lawniczak 1995; Kuo and Edgar 1997). Using this reagent, it was found that THD can react with cellulose dissolved in DMAc-LiCl homogenously forming products with a DS of up to 2.0 (Marson and El Seoud 1999). A further increase of DS is prohibited, according to the authors, due to side reactions following the thermal decomposition of THD. Although the homogenous reaction of cellulose with THD has been described in this literature, no analytical background has been given of the products obtained or about side products. In order to use CAA as soluble platform compound for the design of novel cellulose-based products, it is required to gain a better understanding about synthesis, structure, and properties of this useful class of cellulose derivatives. Therefore, the homogeneous acetoacetylation of cellulose was studied using DMAc-LiCl with THD at elevated temperatures with different ratios of THD to cellulose to gain a better understanding of the DS limit described in the literature. The nature of the side reactions limiting the acetoacylation of cellulose was studied using NMR- and IR-spectroscopic techniques.

Materials and methods

N,*N*-Dimethylacetamide (DMAc), 99.5% extra dry over molecular sieves (Alfa Aesar) was used as received, cellulose Avicel PH-101(DP = 152) was dried over KOH at 0.02 mbar at 100 °C for 2 h prior to use. 2,2,6-Trimethyl-4*H*-1,3-dioxin-4-one (THD, Alfa Aesar) was used as received.

Elemental analysis was performed by EA 3000 (EuroVector)

The NMR spectra were recorded on a Bruker Avance 250 MHz and a Bruker Avance 400 MHz at 60 °C with 16 scans for ^{1}H-NMR spectroscopy and up to 20,000 scans for ^{13}C-NMR spectroscopy using 80 mg per mL of solvent. A mixture of deuterated dimethyl

sulfoxide (d_6-DMSO) and trifluoroacetic acid (TFA, 6/1, v/v) was used for the measurements.

FTIR spectra were recorded on a Nicolet Avatar 370 DTGS spectrometer using the KBr pellet technique with a spectral resolution of 4 cm^{-1}.

Characterization methods for nanoparticles

The hydrodynamic diameter of the nanoparticles was determined by dynamic light scattering using a Malvern Zetasizer NanoZS instrument (He–Ne laser 633 nm, scattering angle: 173°). The mean particle size was approximated as the effective (Z-average) diameter and the width of the distribution as the polydispersity index (PDI). Both parameters were achieved using the cumulants method for data analysis, assuming spherical particle shape and log-normal size distribution. The effective zeta-potential of the nanoparticles was determined by electrophoretic light scattering (ELS) using a Malvern Zetasizer Nano ZS instrument. It was calculated using the Smoluchowski equation. The measurements were repeated three times for each sample. The intrinsic error of the measured zeta-potential was ± 5 mV.

The scanning electron microscope (SEM) imaging was performed with a Sigma VP Field Emission Scanning Electron Microscope (Carl-Zeiss AG, Germany). The samples were coated with a thin layer of platinum via sputter coating before the measurement.

General procedure for the synthesis of CAA

In a dried two-neck round bottom flask, 2 g dried cellulose and 60 mL DMAc were heated for 2 h at 130 °C under a nitrogen atmosphere. After cooling to 100 °C, 6 g of anhydrous LiCl were added to the mixture, which was allowed to cool to room temperature, leading to complete dissolution of cellulose.

The cellulose dissolved was heated to 120 °C and 7 mL (1.33 eq. based on the OH of the anhydroglucose unit, AGU) of THD were added in one portion with a syringe. After 1 h at 120 °C, the reaction mixture was poured into 1 L methyl alcohol. The precipitate was collected by filtration over a G3 glass filter frit. The off-white material was treated twice with 200 mL boiling methyl alcohol for a minute and filtered again. The solid product was washed successively with 200 mL methyl alcohol, twice with 200 mL diethyl ether, and dried at 60 °C in vacuum for 12 h.

Yield: 3.77 g (74%)

^{1}H-NMR (250 MHz, d6-DMSO/TFA, 6/1, δ in ppm): 6.30–6.00 (vinyl-H, enolester); 5.50–3.05 (AGU); 3.58 (–CH_2–, acetoacetate); 2.35–2.00 (–CH_3, acetoacetate).

^{13}C-NMR (100 MHz, d_6-DMSO/TFA, 6/1, δ in ppm): 202–200 (–C(O)– acetoacetate); 175–174 (=C(OR)–, enolester); 167–166 (–OC(O)–, acetoacetate ester); 120.8 (= C(OR)CH_3, vinyl moiety); 113.8 (–CH=, vinyl unit); 102.8 (AGU, C1 unsubstituted C2); 99.8 (AGU, C1 substituted C2); 80.0 (AGU, C-4); 75.9 (AGU, C-3); 72.5 (AGU, C-2,C-5); 62.6 (AGU, C-6); 49.8–49.4 (–CH_2–, acetoacetate); 30.3 (–CH_3, acetoacetate); 20.9–19.2 (–CH_3, enolester).

IR (KBr, cm^{-1}): 1746 (v C(O)); 1711 (v C(O)); 1666 (v (C=C, enolester)).

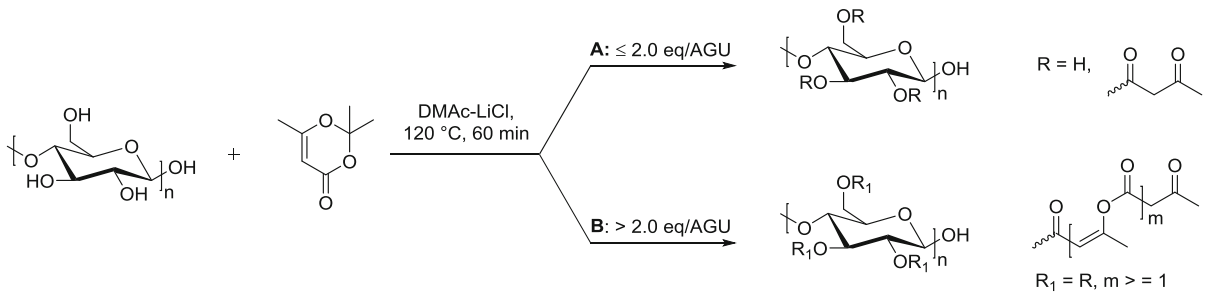
Preparation of nanoparticles (typical procedure)

CAA samples (sample **9**, 3, 6, 12, 21.6, and 43,2 mg) were dissolved in 6 mL DMAc and dialyzed against deionized water (500 mL) using a regenerated cellulose dialysis membrane (Spectra/Por, molecular weight cut off of 12,000 g/mol). The water was renewed every hour for 4 h, then again after 12 h three times every hour.

Results and discussion

Cellulose dissolved in *N*,*N*-dimethylacetamide (DMAc)-LiCl can readily react with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (THD) at elevated temperatures without any catalyst to obtain cellulose acetoacetates efficiently (Marson and El Seoud 1999) (Scheme 1). In our investigations, the reaction conditions were set to 120 °C at 60 min. An increase in reaction temperature leads to insoluble products. An increase of the reaction time does not increase the DS value significantly (Table 1). The molar amount of acetoacylating reagent is comparable to the amount of diketene used in the procedure introduced in the literature (Edgar et al. 1995).

It was found that the CAA samples strongly bind traces of the solvent, which cannot be removed by



Scheme 1 Reaction of cellulose homogeneously in *N*,*N*-dimethylacetamide (DMAc)-LiCl with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one. A: Up to 2 eq./AGU of reagent lead to cellulose acetoacetates with a degree of substitution (DS) of up to 1.84. B: Above 2 eq./AGU of reagent leads to enol ester formation and hence to a molar degree of substitution (MS)

Table 1 Time- and temperature dependence of the degree of substitution (DS) of acetoacylation of cellulose dissolved in *N*,*N*-dimethylacetamide (DMAc)-LiCl with one equivalent of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one

Sample no.	Reaction time (min)	Reaction temperature (°C)	DS
3a	120	120	0.89
3b	60	120	0.86
3c	30	120	0.84
3d	10	120	0.77
3e	60	80	0.19
3f	60	100	0.68
3g	60	110	0.77

simple washing. Thus, a purification step including treatment of the CAA with boiling methanol was introduced, allowing the removal of DMAc completely, i.e., no traces of DMAc could be found in the samples.

It was realized that the data of elemental analysis (C–, H content) are not appropriate for the calculation of DS. The mass of carbon to calculate the DS values is not appropriate because the error may increases drastically in particular at high DS values as can be concluded from the relationship of C-content of the samples and MS as indicated in Fig. 1a. In contrast to this observation, the integrated signals of the ^{1}H-NMR spectra of the samples investigated show a linear correlation between the MS and the amount of THD used in the synthesis as displayed in Fig. 1b.

The ^{1}H-NMR spectra of cellulose ester samples and methyl acetoacetate, as a model compound, are shown in Fig. 2. On the contrary to the method discussed by Liu et al. (2016), the samples investigated have been dissolved in d_6-DMSO with addition of trifluoroacetic acid (TFA) to shift the signals for protons of remaining hydroxyl groups and HDO/H_2O out of the spectral range of interest. It was possible to calculate the amount of ester moieties in the cellulose chain accurately. The reaction products, the molar degree of substitution (MS) and the solubility are summarized in Table 2.

The ^{1}H-NMR spectrum of a CAA with low DS of 0.33 (sample **1**) shows two distinct sets of signals (Fig. 2, middle). At 2.18 ppm, the methyl group of the acetoacetate moiety can be found. Using this signal, it was possible to subtract the integral of the methylene signal at 3.56 ppm of the acetoacetate moiety and integrate the range of the AGU signals from 3.05 to 5.50 ppm of the spectrum separately. With the integrals obtained, the amount (DS/MS) of ester moieties of the derivatives synthesized could be calculated.

Interestingly, using an excess of acetoacylation reagent above 2 eq. per AGU, the ^{1}H-NMR spectra of the products show the appearance of an additional signal at 6.15 ppm (Fig. 2, bottom, signal 4). It may be concluded that not only the hydroxyl groups of the polymer backbone are acetoacylated but also the

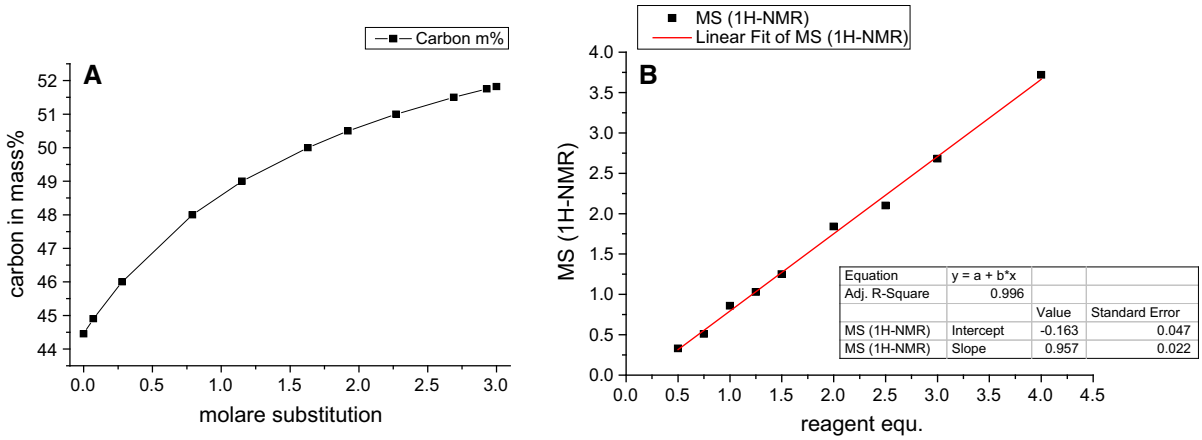


Fig. 1 **a** Percentage of carbon of cellulose acetoacetates depending on content of acetoacetyl moieties. **b** The molar substitution (MS) of cellulose acetoacetate (CAA) depending on the equivalents of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (THD) used in the synthesis versus signal integral of the ^{1}H-NMR spectra

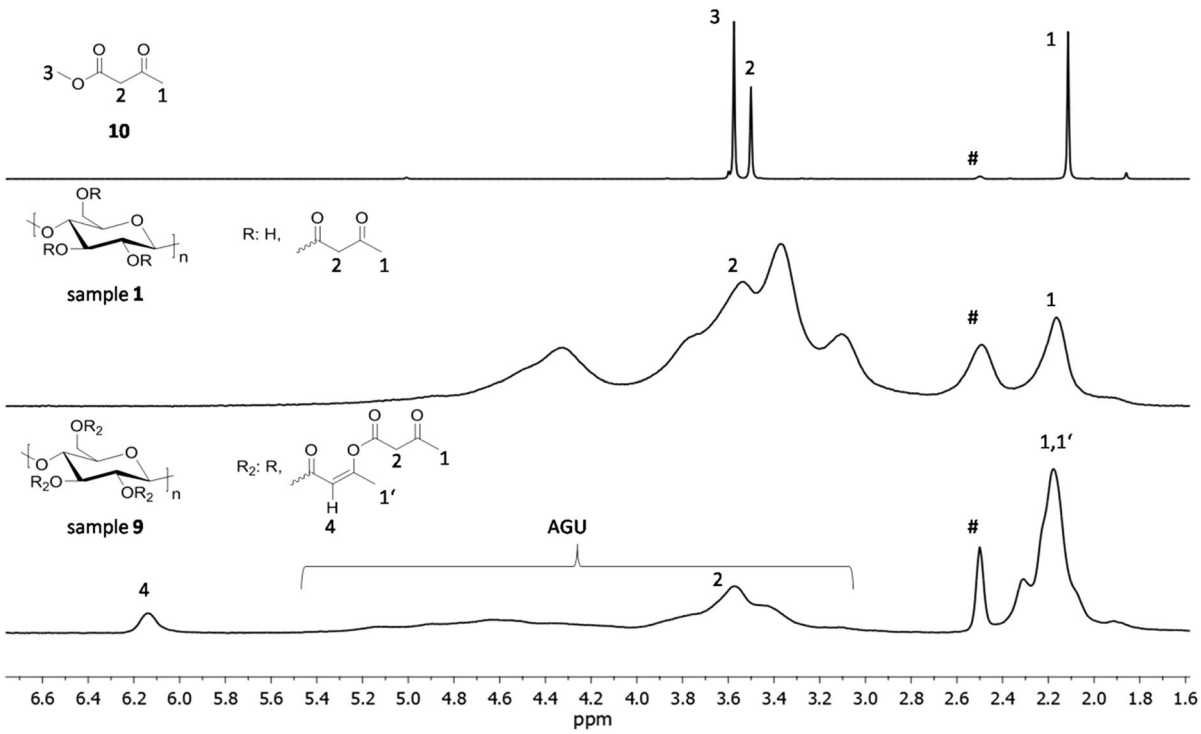


Fig. 2 ^{1}H-NMR spectra of methyl acetoacetate (top), cellulose acetoacetate with degree of substitution of 0.33 (middle, sample **1**) and cellulose acetoacetate with molar degree of substitution of 3.72 (bottom, sample **9**) measured in d_6-DMSO-TFA at 60 °C,# d_6-DMSO signal

hydroxyl groups of the enolic form of the already attached acetoacetate moieties are included in the conversion. Obviously, they are formed in larger number due to enol structures with increasing conversion. The reaction at the OH groups of enol ester yields side chains. Thus, the DS is not sufficient anymore to describe the product. As commonly used in polysaccharide chemistry, the molar degree of substitution (MS) must be applied to describe the products adequately. In previous studies (Edgar et al. 1995;

Table 2 Dependence of the molar degree of substitution (MS) on the molar ratio of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (THD) by the reaction with cellulose dissolved in *N*,*N*-dimethylacetamide (DMAc)-LiCl (120 °C, 60 min) and solubility of the products

No.	THD eq. per AGU*	MS**	Yield in g (%)	Solubility***					
				H_2O	DMF	DMAc	DMSO	$CHCl_3$	Acetone
1	0.50	0.33	2.15 (86)	−	−	−	+	−	−
2	0.75	0.51	2.00 (72)	+	+	+	+	−	−
3b	1.00	0.86	2.95 (97)	+	+	+	+	−	−
4	1.25	1.03	1.69 (51)	−	+	+	+	−	−
5	1.50	1.25	2.95 (83)	−	+	+	+	−	−
6	2.00	1.84	2.82 (69)	−	+	+	+	−	−
7	2.50	2.10	4.04 (88)	−	+	+	+	−	−
8	3.00	2.68	4.06 (79)	−	+	+	+	−	+
9	4.00	3.72	3.77 (61)	−	+	+	+	+	+

*Anhydroglucose unit (AGU); **Calculated from the ^{1}H-NMR spectra;***N,N-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMAc), dimethylsulfoxide (DMSO)

Marson and El Seoud 1999; Liu et al. 2016), no comparable conversion of the side chain has been described. It seems plausible that the conversion with diketene proceeds much faster than with THD, so that there is not sufficient time for the formation of the enolic form of the acetoacetate, on one hand. On the other hand, the conversion with tert-butyl acetoacetate is much slower compared to THD, which explains the low DS value gained (maximum DS of 1.8 using tert-butyl acetoacetate). The DS of 1.8 is also the limit value to obtain a pure CAA without any side chains, i.e., DS = MS for the conversion with THD. The conversion with THD takes longer than the reaction with diketene. Thus, a certain percentage of the enol form of acetoacetate may be formed in the reaction mixture that subsequently becomes acetoacylated (Scheme 1, b). This process leads to the formation of the side chain and consequently to the signal of vinyl proton found in the ^{1}H NMR spectrum (Fig. 2, sample **9**).

For methyl acetoacetate, as investigated by ^{1}H-NMR spectroscopy in d_6-DMSO-TFA, the enolic form was found to be 4% (Bunting and Kanter 1993). Thus, in accordance with the literature, the equilibrium is strongly shifted to the side of the ketoform. The same behavior applies for CAA with low DS values (samples **1**–**6**). That means no or only a very small amount (less than 5%) of enol species of the acetoacetate can be detected.

The ^{13}C-NMR spectrum of sample **9** is shown in Fig. 3. The spectrum contains two signals at 19 ppm and at 30 ppm corresponding to the methyl group at the vinyl moiety (Fig. 3, signal 10) and the acetoacetate moiety (Fig. 3, signal 14). At 50 ppm, the signal for the methylene of the acetoacetate moiety (Fig. 3, signal 12) is found. The signals of the AGU are located between 60 and 105 ppm. The methylene unit at C-6 of the modified AGU at 63.6 ppm gives a uniform signal, which leads to the conclusion that the functional group is completely modified. The signals at 72.7 and 75.8 ppm correspond to C-2, C-5, and C-3 of the modified AGU, which cannot be separated. Thus, they allow no further insight into the substitution pattern of the cellulose at C-2 and C-3. At 80.3 ppm the signal for the C-4 carbon can be found. The carbon C-1 gives two distinct signals at 99.9 ppm and at 103.1 ppm. The first one corresponds to a substituted C-2 position of the AGU, the latter can be correlated to a hydroxyl group at this position. Although not all hydroxyl groups of the polymer backbone have been consumed during the reaction, the substitution of the CAA already forms enolester moieties, which give signals at 113.9 and 120.8 ppm corresponding to carbon atoms of the vinyl moiety (Fig. 3, signal 8 and 9). In the far low field, the signals of the carbons for the acetoacetate ester, the vinyl ester, and the keto carbonyl moiety can be found between 165–167, 175.6, and 201.6 ppm (Fig. 3, signal 11, 7, and 13).

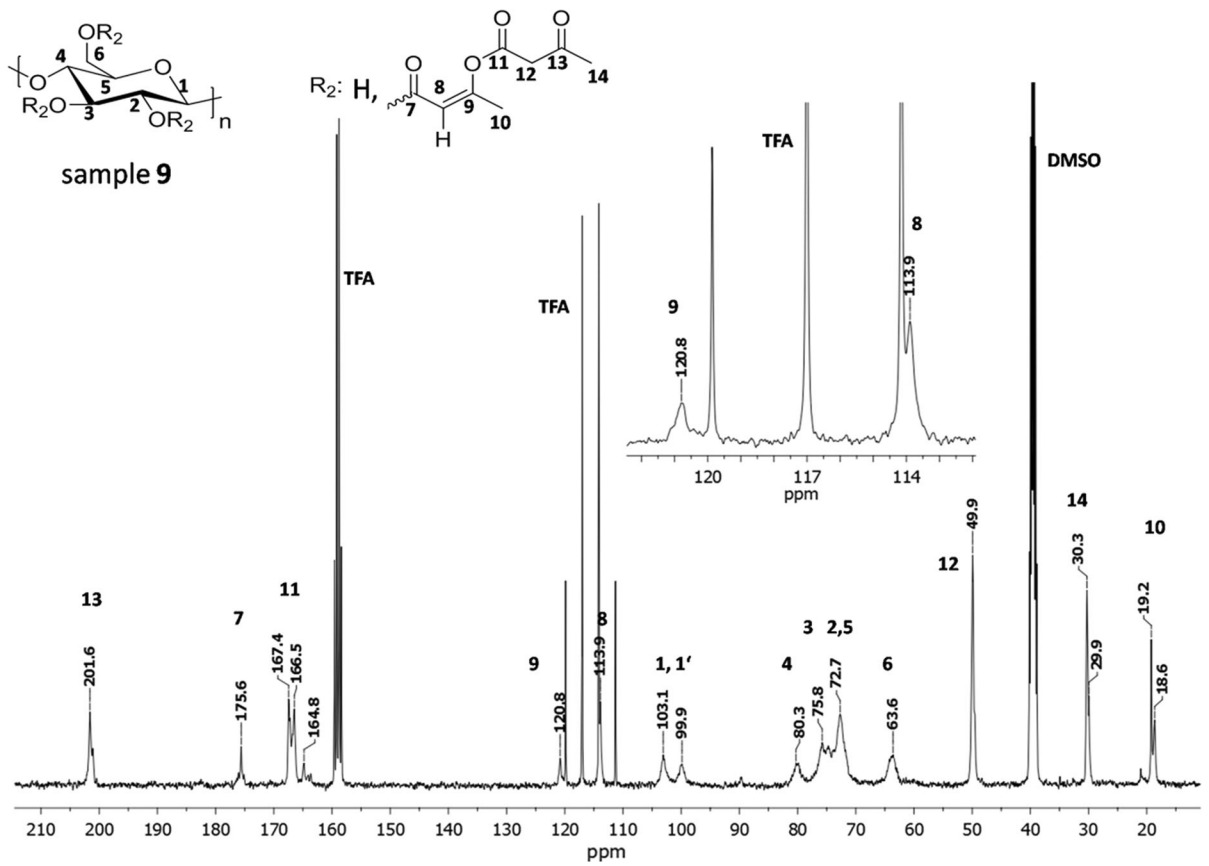


Fig. 3 ^{13}C-NMR spectrum of cellulose acetoacetate (sample **9**) acquired in d_6-dimethyl sulfoxide with trifluoroacetic acid

Additional 2D NMR experiments did not lead to a more detailed structure elucidation. The reason for that fact is the fast transversal relaxation of the proton signals of the AGU. From the FID of the proton NMR spectrum, it could be approximated that the magnetization for the AGU protons is already lost after about 30 ms. Thus, only signals of the substituent are detected in the 2D correlation NMR-experiments (HMBC). A selective NOESY NMR spectrum (Figure 6, supporting information) for the vinyl signal at 6.1 ppm shows signals for the methyl group of the enolic moiety and even a signal for the methylen group of the attached acetoacetate substituent. A broad unspecific signal between 4 and 5 ppm indicates the proximity of the AGU protons.

The findings discussed are supported by the FT-IR spectroscopic studies of the derivatives as well. In Fig. 4, the FTIR spectra of CAAs with different DS show a strong double signal appearing at 1711 and 1746 cm^{-1} compared to pure cellulose. These signals can be attributed to the C=O stretching vibrations of the acetoacetate moiety (Hesse et al. 2012). With increasing MS, a new signal appears at 1666 cm^{-1}. This signal can be assigned to the enolester moiety that is formed during the acetoacylation of the substituent introduced and confirms the structure proposed for the products.

It is possible to obtain CAA with a DS of up to 1.8 with the method presented. Exceeding this value, the formation of enolester becomes a competing reaction, which leads to a comb-like polymer structure. The solubility of the products changes as well with increasing DS/MS values. Low substituted derivatives (samples **1**) are soluble in DMSO only. The derivatives with DS values of 0.51 and 0.86 (samples **2** and **3**) show water solubility, which is in agreement with the DS values for water-solubility given by Liu et al. (2016). Derivatives **8** and **9** with a MS of 2.68 and 3.72 are soluble in acetone, the latter compound even in chloroform (see Table 2).

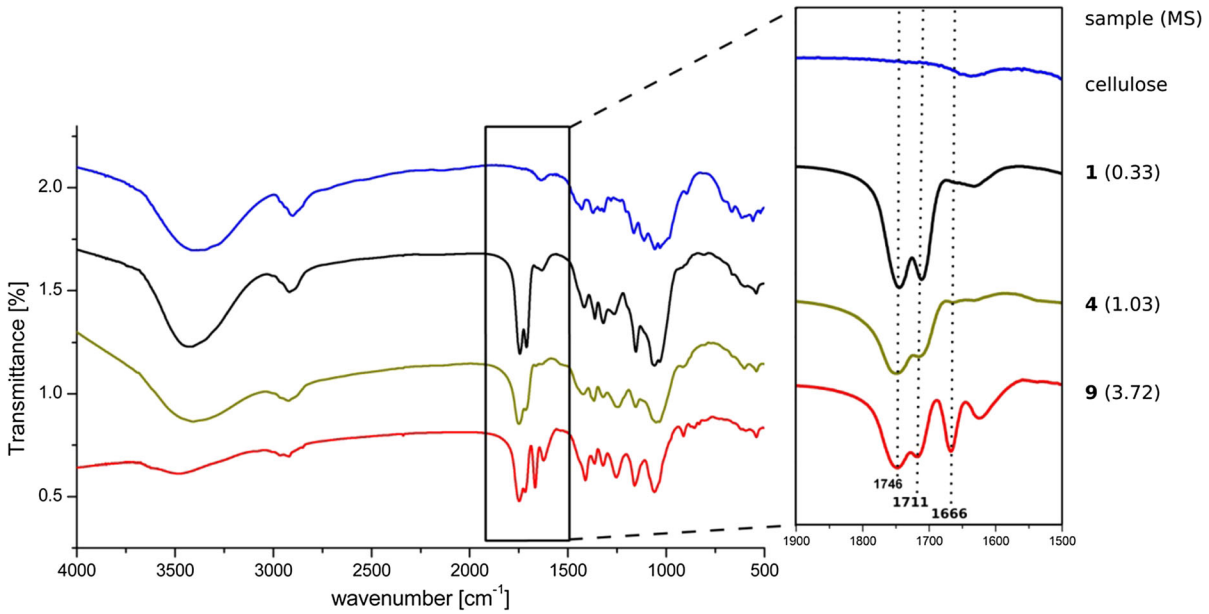


Fig. 4 FTIR spectra of cellulose and cellulose acetoacetates with increasing molar degree of substitution (MS)

Nanoparticle formation

A CAA insoluble in water, but well soluble in DMAc with high MS (Table 2, sample **9**, MS 3.77), which is a prerequisite for the dialysis process to prepare nanoparticles, was studied regarding the formation of nanoparticles. Thus, the solvent DMAc of the sample **9** dissolved was exchanged against the non-solvent water as described in the literature (Hornig and Heinze 2008). Solutions of CAA with different concentrations ranging from 0.5 to 7.3 mg/mL were investigated. The size, the polydispersity index, and the ζ-potential of the nanoparticle obtained are summarized in Table 3. The particle size, as found by dynamic light scattering (DLS), ranges from 122 to 304 nm and gradually increases with increasing polymer concentration in DMAc. The surface charge (ζ-potential) is almost constant with a value of about − 33 mV and can be attributed to the free electron pairs of the carbonyl group and the enolic hydroxyl groups of the acetoacetate substituent. The spherical shape of the nanoparticles can be seen in the SEM image (Fig. 5). The particle size of the DLS

Table 3 Size, polydispersity index (PDI), and zeta-(ζ)-potential of nanoparticles prepared from cellulose acetoacetate (molar degree of substitution = 3.72) depending on the concentration of the polymer solution used

Concentration (mg/mL)	Size (nm)	PDI	ζ-potential (mV)
0.5	122	0.174	− 29
1.0	147	0.110	− 33
2.0	174	0.186	− 33
3.6	195	0.068	− 34
7.3	304	0.178	− 35

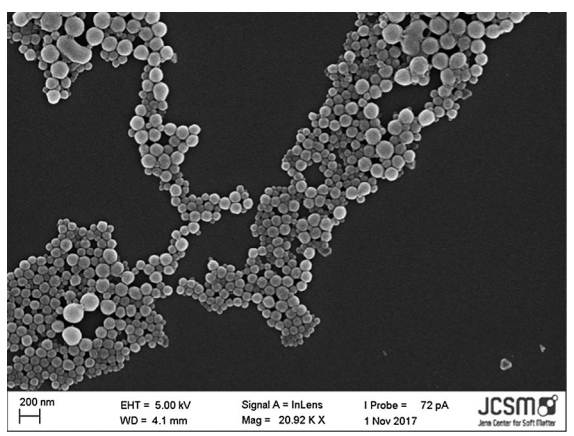


Fig. 5 Scanning electron microscope (SEM) image of nanoparticles showing their spherical shape with diameter below 200 nm (molar degree of substitution = 3.72, sample **9**, magnification: 20,920×)

measurements is consistent with the diameters found by SEM of the dried polymer particles.

Conclusion

The reaction of cellulose with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one leads to reactive cellulose esters, which can be further tuned by reacting with nucleophiles or electrophiles, due to the reactivity of the acetoacetate substituent. An excess of acetoacylation reagent leads to the formation of comb-like polymer structures. Further investigations will focus in particular on the reaction of CAA nanoparticles formed with nucleophiles, while keeping the size and the shape of the particles unchanged. A two-step loading of the nanoparticles (core and shell loading) with substrates is also of interest for further research. In addition to these issues, we are strongly interested in the general applicability of THD for acetoacylation of polysaccharides including starch and pectin.

Acknowledgments The authors would like to thank Steffi Stumpf from the group of Prof. U.S. Schubert (Center for Soft Matter, Jena Germany) for the SEM images. The SEM/TEM facilities of the Jena Center for Soft Matter (JCSM) were established with a Grant from the German Research Council (DFG) and the European Funds for Regional Development (EFRE). The studies were financially supported by the DFG-funded Collaborative Research Centre PolyTarget (SFB 1278, Project A02).

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