

Water soluble 3-mono-*O*-ethyl cellulose: Synthesis and characterization

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Summary

The synthesis of 3-mono-*O*-ethyl cellulose (EC) via 2,6-di-*O*-hexyldimethylsilyl cellulose was studied. Treatments with tetrabutylammonium fluoride trihydrate lead to the complete cleavage of the protective group. The structure of the polymer was confirmed by means of one- and two dimensional NMR spectroscopy. 3-mono-*O*-EC is soluble both in aprotic-dipolar organic media and water and shows thermoreversible gelation. A gelation temperature of 58.5°C was found, which is about 30°C higher than the cloud point temperature of conventional water soluble EC.

Introduction

Ethyl cellulose (EC) is an important commercially produced cellulose ether and is applied, e.g., as ingredient of lacquers and adhesives or used as tablet binder [1]. Moreover, EC has found interest to prepare microcapsules by interfacial precipitation [2] as well as in the formation of Langmuir-Blodgett films [3]. The reaction of alkali cellulose with ethyl chloride leads to products with about equal partial degree of substitution (DS) at position 2 and 6 and a low partial DS at position 3. While EC with DS >1.5 (preferably >2) dissolves in organic liquids, derivatives with DS 0.7-1.7 are water soluble and show thermoreversible gelation [4]. Commercially available EC with DS >2 possesses thermoplasticity. It softens at 130°C and flows at 140-160°C for the preparation of films by extrusion.

It is well known that not only the degree of substitution (DS) but also the distribution of the functional groups may influence the properties of cellulose derivatives [5]. A typical property of non-ionic cellulose ethers is thermoreversible gelation. For methyl- and ethyl cellulose with a statistic distribution of alkyl moieties gelation starts at 60°C and 30°C, respectively [4]. It has been found that the functionalization pattern strongly influences the flocculation behavior [6]. In contrast, a water soluble 2,3-di-*O*-methyl cellulose with almost perfect structure does not undergo phase transitions at elevated temperature [7]. Thermoreversible gelation is also observed for EC solutions (DS 2.35) in dibutyl-, diethyl-, and dioctyl phthalate, while no effect occurs in ethyl benzoate [8].

A 3-mono-*O*-methyl cellulose, which was recently synthesized via 2,6-di-*O*-thexyldimethylsilyl cellulose is insoluble in water and organic liquids [9]. Further 3-mono-*O*-functionalized allyl-, pentyl-, isopentyl-, and dodecyl celluloses are organo-soluble [9,10]. These results imply the question if 3-mono-*O*-EC can be synthesized via 2,6-di-*O*-protected cellulose. Moreover, the properties of such regioselectively functionalized EC are of interest.

In the present paper, the synthesis and detailed structure characterization of 3-mono-*O*-EC is discussed. In addition, preliminarily results of the thermoreversible gelation are described.

Experimental

Materials

Cellulose **1** (AVICEL[®], degree of polymerization 300) was dried in vacuum over KOH at 105°C and LiCl was dried in vacuum over KOH at 150°C prior to use. *N,N*-Dimethylacetamide (DMA, Acros) and tetrahydrofuran (THF, Riedel) were stored over molecular sieves. Thexyldimethylchlorosilane (TDMS-Cl, ABCR), tetrabutylammonium fluoride trihydrate (TBAF, Fluka) and all other chemicals were used as received. Sodium hydride (Fluka, suspension in mineral oil) was washed with hexane and pentane and dried in vacuum at room temperature.

2,6-di-*O*-Thexyldimethylsilylcellulose **2**

Cellulose **1** (30.0 g, 0.185 mol) was slurried in 600 mL DMA and stirred for 2 h at 130°C under exclusion of moisture. After cooling to 100°C and addition of 33.0 g LiCl, stirring was continued without further heating until complete dissolution of the polymer. Imidazole (60.48 g, 0.899 mol) was dissolved in the mixture followed by the addition of 145.6 mL (0.740 mol) TDMS-Cl. The temperature was increased to 100°C and stirring was continued for 24 h. After cooling down to room temperature, the precipitated polymer was filtered off, washed with ethanol, water, and ethanol. The product was dried in vacuum at 60°C.

Yield: 76.1 g (93%)

Degree of substitution (DS): 1.96 (based on the silicon content of 12.32%).

The product is soluble in *n*-hexane, toluene, THF, and chloroform.

FTIR (KBr, cm⁻¹): 3499 ν (OH), 2958, 2870 ν (C-H), 1468 δ (C-H), 1256 δ (Si-C), 1156-1036 ν (C-O-C), 832, 776 ν (Si-C).

3-mono-*O*-Ethyl-2,6-di-*O*-thexyldimethylsilylcellulose **3**

To a solution of 25.0 g (0.9567 mol) **2** in 250 mL dry THF, 13.6 g (0.567 mol) sodium hydride were added under vigorous stirring followed by the drop wise addition of 45.5 mL (0.567 mol) ethyl iodide. The slurry was stirred for 4 h at room temperature and 4 d at 50°C. After cooling to room temperature about 20 mL isopropanol were carefully added in order to destroy excess NaH, which was checked by the addition of 20 mL H₂O. The mixture was poured into water and neutralized with acetic acid. The product was filtered off, washed with water and ethanol, and dried in vacuum at 60°C.

Yield: 22.7 g (85%)

The product is soluble in *n*-hexane, toluene, THF, and chloroform.

FTIR (KBr, cm^{-1}): 3483 $\nu(\text{OH})$, very weak), 2959, 2872 $\nu(\text{C-H})$, 1466 $\delta(\text{C-H})$, 1377 $\delta(\text{CH}_3)$, 1252 $\delta(\text{Si-C})$, 1089, 1046 $\nu(\text{C-O-C})$, 833, 777 $\nu(\text{Si-C})$.

3-mono-O-Ethyl cellulose 4

To a solution of 20.0 g (0.0423 mol) **3** in 300 mL dry THF, 53.41 g (0.1693 mol) TBAF were added and the mixture was stirred for 24 h at 50°C. After cooling to room temperature the polymer was precipitated with ethanol/isopropanol 2:1 (v/v), filtered off, washed with isopropanol and dried in vacuum. The polymer was dissolved in dimethylsulfoxide (DMSO) and reprecipitated in diethylether/isopropanol 2:1 (v/v), filtered off, washed with isopropanol/diethylether 2:1 (v/v), and dried. 5.9 g of the polymer were dissolved in 100 mL dry DMSO and stirred for 24 h at 50°C with 5.9 g TBAF. The product was precipitated with diethylether/isopropanol 2:1 (v/v), filtered off, washed with isopropanol, and dried in vacuum at 60°C.

Yield: 4.7 g (58%)

DS: 1.0 (determined by means of ^1H NMR spectroscopy after peracetylation)

The polymer is soluble in DMSO, DMA, *N,N*-dimethylformamide, and water.

FTIR (KBr, cm^{-1}): 3428 $\nu(\text{OH})$, 2997, 2928 $\nu(\text{CH}_2, \text{CH}_3)$, 1377 $\delta(\text{CH}_3)$, 1067 $\nu(\text{C-O-C})$.

^{13}C NMR (DMSO- d_6 , ppm): 103.2 (C-1), 83.8 (C-3), 77.1 (C-4), 75.8 (C-5), 74.8 (C-2), 67.3 (CH_2CH_3), 61.0 (C-6), 15.9 (CH_2CH_3).

2,6-di-O-Acetyl-3-mono-O-ethyl cellulose 5

A mixture of 0.5 g **4** with 10 mL dry pyridine, 10 mL acetic anhydride, and 0.02 g 4-*N,N*-dimethylaminopyridine was stirred for 16 h at 80°C and subsequently for 3 h at 100°C under exclusion of moisture. After cooling down to room temperature the product was precipitated with isopropanol, separated by centrifugation, washed with isopropanol, and dried in vacuum at 60°C.

Yield: 0.51 g

FTIR (KBr, cm^{-1}): 2977, 2927 $\nu(\text{CH}_2, \text{CH}_3)$, 1748 $\nu(\text{C=O})$, 1442 $\delta(\text{CH}_2, \text{CH}_3)$, 1375 $\delta(\text{CH}_3)$, 1230 $\nu(\text{C-O-C}_{\text{Ester}})$, 1047 $\nu(\text{C-O-C}_{\text{Anhydroglucose unit}})$.

^1H NMR (CDCl_3 , ppm): 1.05 (CH_2CH_3), 2.06 (COCH_3), 3.37 (H-3), 3.43 (H-5), 3.61 (H-4), 3.49, 3.75 (CH_2CH_3) 4.14 (H-6 $_{\alpha}$), 4.33 (H-6 $_{\beta}$), 4.44 (H-1), 4.78 (H-2).

^{13}C NMR (CDCl_3 , ppm): 170, 160 (C=O), 100.8 (C-1), 82.6 (C-3), 77.5 (C-4), 72.8 (C-2, 5), 68.0 (OCH_2CH_3), 62.4 (C-6), 15.3 (OCH_2CH_3).

Measurements

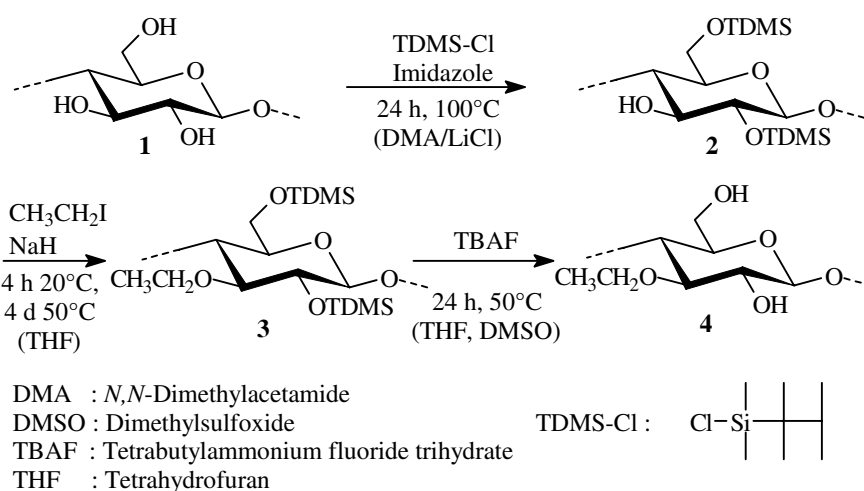
FTIR spectra were acquired with a NICOLET AVATAR 370 DTGS spectrometer using the KBr technique. NMR spectra were obtained with a Bruker DRX 400 in CDCl_3 or DMSO- d_6 (sample concentration 5-10%) at a temperature up to 70°C using standard pulse sequences for ^1H -, ^{13}C -, DEPT 135-, and two-dimensional (COSY, HSQC/DEPT) NMR spectra. The scan number was 16 for ^1H - and up to 65,000 for ^{13}C NMR spectra.

The temperature dependent turbidity of the polymer solutions was determined by means of UV/VIS spectroscopy (Lambda 16, PerkinElmer). The sample was placed in a cuvette, thermostated at the desired temperature and the absorbance was determined at a constant wavelength of 700 nm.

Results and discussion

Preparation and structural characterization of 3-mono-*O*-ethyl cellulose

The silylation of cellulose **1** in *N,N*-dimethylacetamide (DMA)/LiCl with hexyldimethylchlorosilane (TDMS-Cl) in the presence of imidazole leads to 2,6-di-*O*-TDMS cellulose **2** (Scheme 1, [9]). The product can be simply isolated by filtration because it becomes insoluble in the reaction mixture and precipitated. Washing with water and ethanol yields pure 2,6-di-*O*-TDMS cellulose **2**. The degree of substitution of TDMS groups (DS_{Si}) was 1.96. The polymer is soluble in *n*-hexane, toluene, tetrahydrofuran (THF), and chloroform.



Scheme 1. Reaction scheme for the preparation of 3-mono-*O*-ethyl cellulose using the hexyldimethylsilyl protective group.

2 was allowed to react with excess of ethyl iodide in the presence of sodium hydride as base (10 mol/mol anhydroglucose unit, AGU) in THF for 4 h at room temperature and 4 d at 50°C. The product **3** isolated by a typical work-up procedure is soluble in organic solvents like *n*-hexane, toluene, THF, and chloroform. FTIR spectroscopy revealed complete etherification of the hydroxyl functions. All typical absorption bands of the modified repeating unit appear in the FTIR spectrum: 2959, 2872 $\nu(\text{C-H})$, 1466 $\delta(\text{C-H})$, 1377 $\delta(\text{CH}_3)$, 1252 $\delta(\text{Si-C})$, 1089, 1046 $\nu(\text{C-O-C})$, 833, 777 $\nu(\text{Si-C})$. For deprotection, polymer **3** was treated with tetrabutylammonium fluoride trihydrate (TBAF) in THF for 24 h at 50°C. ^1H NMR spectroscopic investigations of the precipitated 3-mono-*O*-ethyl cellulose (EC) reveal an incomplete cleavage of the TDMS moieties (Figure 1). The partially desilylated sample was treated again with TBAF in dimethylsulfoxide (DMSO) to yield the silicon-free sample **4** showing no signals of silicon containing moieties. In contrast, studies on 3-mono-*O*-methyl cellulose showed that a small silicon content remained in the sample even after several desilylation and purification steps [9]. Structure characterization was carried out by means of NMR spectroscopy. DEPT 135 NMR spectroscopy in $\text{DMSO-}d_6$ could be applied because no quaternary carbon atoms are present in the molecule that will not be detected with this technique (Figure 2).

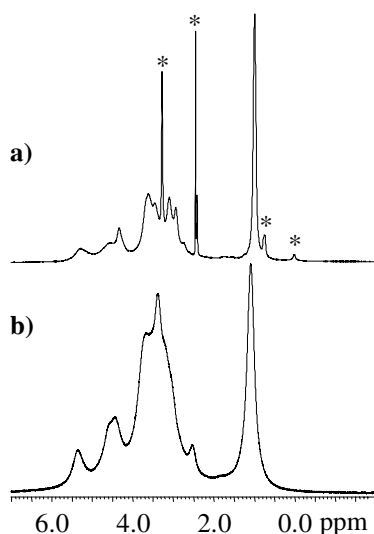


Figure 1. ^1H NMR spectra of 3-mono-*O*-ethyl cellulose **4** after one (a) and two (b) desilylation steps recorded in dimethylsulfoxide- d_6 . Silicon containing moieties are marked with an asterisk.

C-1 appears at 103.2 ppm. No signal splitting is observed due to the absence of substituents at position 2. The peak for C-3 bearing the ethyl ether is shifted downfield to 83.3 ppm. Further peaks of the modified AGU appear at 77.1 (C-4), 75.8 (C-5), 74.2 (C-2), and 61.0 ppm (C-6). In addition, the signal at 67.3 ppm is assigned to CH_2 - and at 15.9 ppm to the CH_3 group of the ethyl moiety. Only one resonance appears for every carbon atom of the AGU that indicates the regular structure of the 3-mono-*O*-EC.

The structure was confirmed by means of two-dimensional NMR measurements. For this purpose sample **4** was converted to 2,6-di-*O*-acetyl-3-mono-*O*-ethyl cellulose **5** according to scheme 2.

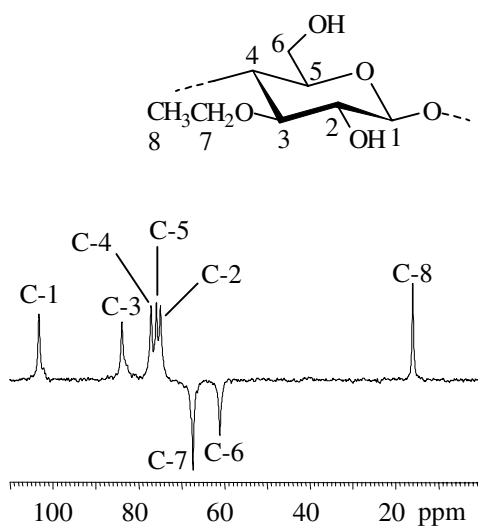
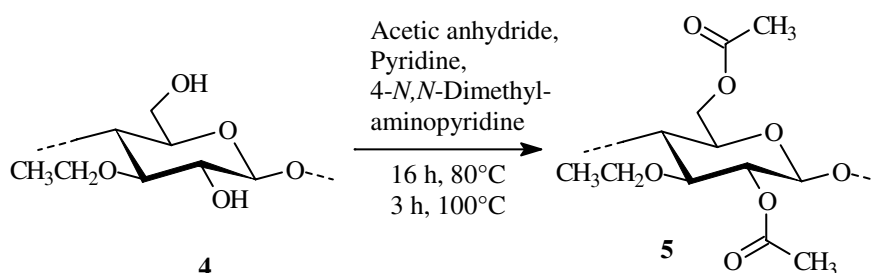


Figure 2. DEPT 135 NMR spectrum of 3-mono-*O*-ethyl cellulose **4** recorded in dimethylsulfoxide- d_6 (60°C, 3250 scans).

Thus, the spectral resolution is increased by decrease of intermolecular interactions caused by hydrogen bonds. Sample **5** was subjected to NMR analysis in CDCl₃ solution (Figure 3). The signal of H-3 is shifted downfield to 3.37 ppm, while acetyl groups at position 2 lead to a highfield shift to 4.78 ppm. Further signals of the modified AGU appear at 3.43 (H-5), 3.61 (H-4), and 4.44 ppm (H-1). Two signals are observed for H-6 at 4.14 and 4.33 ppm due to the neighboring chiral carbon atom at position 5. In addition, two signals are found for the methylene group of the ethyl moiety (C-7) at 3.75 and 3.49 ppm due to the chiral carbon atom at position 3. A peak at 2.06 ppm is clearly assigned to CH₃-group (acetate), while the peak at 1.05 ppm belongs to the proton of the methyl moiety of the ethyl ether (C-8).



Scheme 2. Preparation of 2,6-di-*O*-acetyl-3-mono-*O*-ethyl cellulose **5**.

The peak assignment was possible for the ¹³C NMR spectrum as well. The signal for C-1 is found at 100.8 ppm. A signal at 82.6 ppm is assigned as position 3 bearing the ethyl function. The peak of the carbon atom at position 4 overlaps with the intensive CDCl₃ signal and is detected at about 77.5 ppm. C-2 and C-5 are found at 73.07 ppm. C-6 bearing an acetyl function leads to a signal at 62.5 ppm. Moreover, the peaks of the ethyl ether are found at 15.3 ppm (CH₃) and 66.7 ppm (CH₂). In addition, two signals are detected at 170.2 and 169.1 ppm as well as one at 20.6 ppm belonging to the acetic acid ester moiety. Although the DEPT 135 NMR spectrum revealed an uniform structure corresponding to the 3-mono-*O*-EC, further signals of low intensity appear in the COSY- and HSQC/DEPT NMR spectra if the threshold has been set low. They are caused by substructures due to the small deviation of polymer **2** from an absolute 2,6-di-*O*-protected cellulose derivative. Therefore, position 2 may be ethylated as well to a very low extent, which leads to signals in the range from 2.9 to 3.2 ppm. FTIR spectroscopy revealed the incomplete ethylation of polymer **2**. Thus, acetyl functions are introduced at position 3 after desilylation and peracetylation leading to a weak peak at 5.0 ppm. A cross-peak with the signal of H-2 at 3.1 ppm bearing an ethyl moiety indicates this. Weak cross-peaks are observed in the range from 4.1 to 4.4 ppm, which correspond obviously to H-1 of the substructures. These findings could be proved by means of the HSQC/DEPT spectrum. For instance, two different H-1 signals are detected beside the main-peak of H-1 indicating the presence of two different substructures. However, an exact assignment of the existing substructures may be achieved applying NMR equipment working at higher field strength and higher frequency.

Product **4** is soluble in aprotic-dipolar solvents like DMA, *N,N*-dimethylformamide, and DMSO. An amazing result is that 3-mono-*O*-EC is in contrast to other 3-*O*-functionalized cellulose ethers described up to now also soluble in water.

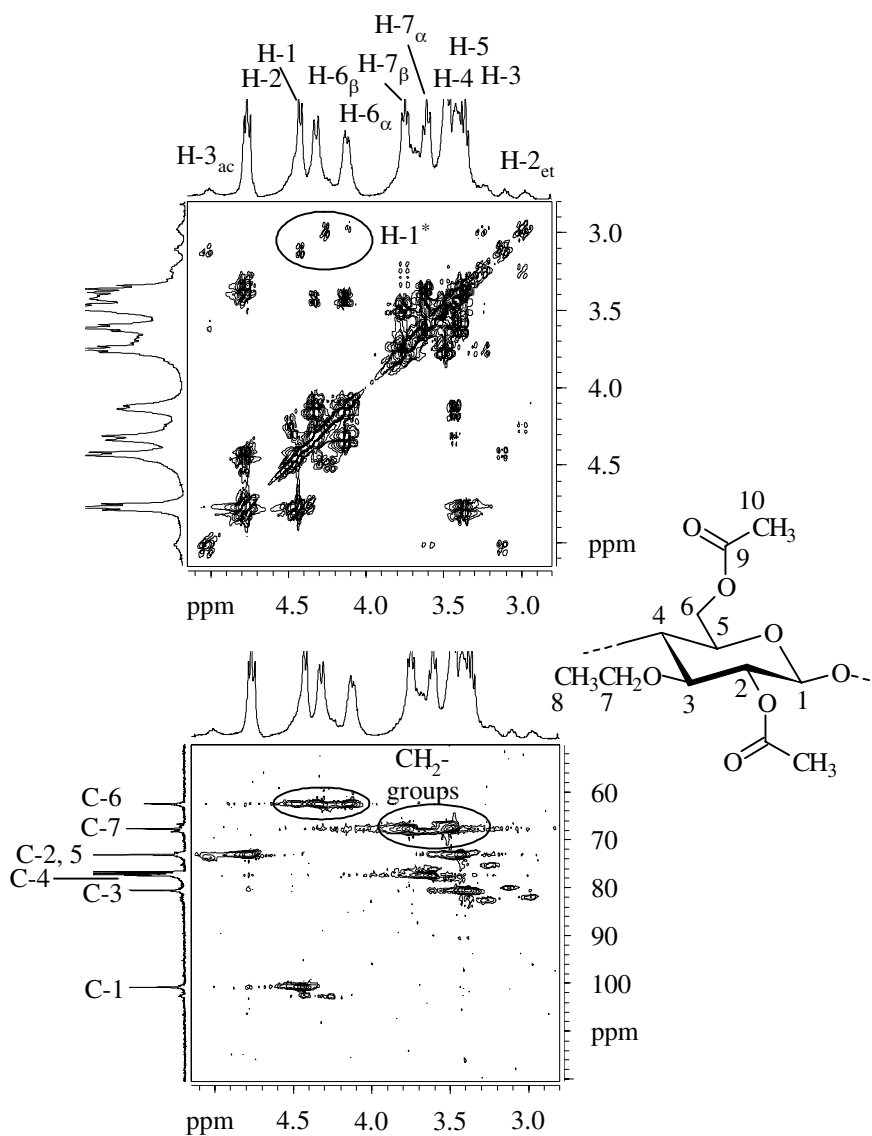


Figure 3. $^1\text{H}/^1\text{H}$ COSY NMR spectrum (top) and HSQC/DEPT NMR spectrum (bottom) of 2,6-di-*O*-acetyl-3-mono-*O*-ethyl cellulose **5** (CDCl_3 , 55°C). Signals < 2.8 ppm (^1H) and < 50 ppm (^{13}C) not shown. Peaks of substructures are marked by the indices et and ac for the ethylated respectively acetylated position as well as by an asterisk.

The thermoreversible gelation (cloud point) is an important property of cellulose ethers. Figure 4 shows the temperature dependent absorbance of aqueous solutions of 3-mono-*O*-EC (sample **4**). At a polymer concentration of 10% (w/v) the thermoreversible gelation can be clearly detected at a temperature of 58.5°C . Applying a concentration of 1% the slope is low and, hence, the onset temperature is hard to determine.

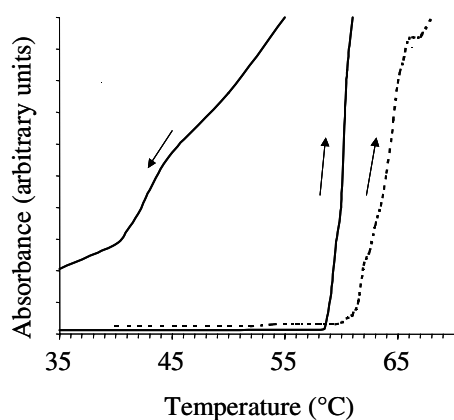


Figure 4. Temperature dependent absorbance of aqueous 3-mono-*O*-ethyl cellulose solutions at a concentration of 10% (solid line) and 1% (dotted line) measured at $\lambda = 700$ nm. The arrows indicate heating and cooling of the sample.

Obviously, the functionalization pattern influences the cloud point of ethyl cellulose. While the thermoreversible gelation of EC with statistic functionalization pattern occurs already at 30°C [4], 3-mono-*O*-EC becomes insoluble at a distinct higher temperature of 58.5°C. The gelation is reversible that has been shown for the 10% solution. However, in contrast to the gelation the dissolution is retarded and slower.

Conclusions

3-mono-*O*-Ethyl cellulose (EC) of highly uniform structure revealed by DEPT 135 NMR spectroscopy was synthesized from 2,6-di-*O*-hexyldimethylsilyl cellulose. By two-dimensional NMR spectroscopic techniques of the peracetylated sample, the presence of substructures to a very low extent was found.

The water-soluble 3-mono-*O*-EC possesses a different thermoreversible gelation compared to conventional EC. This knowledge leads to a better control of the properties of cellulose ethers.

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References

1. Klemm D, Philipp B, Heinze T, Heinze U, Wagenknecht W (1998) Comprehensive Cellulose Chemistry. Vol. 2, Wiley-VCH, Weinheim, pp 220
2. Ohta Y, Arakawa M, Kondo T (1978) Maku 3:283
3. Basque P, de Gunzbourg A, Rondeau P, Ritcey AM (1996) Langmuir 12:5614
4. Dönges R (1990) Br Polym J 23:315
5. Heinze T (2004) Chemical Functionalization of Cellulose. In: Dumitriu S (ed) Polysaccharides: Structural Diversity and Functional Versatility. Marcel Dekker, New York, Basel, Hong-Kong, pp 551-590
6. Hirrien M, Chevillard C, Desbrieres J, Axelos MAV, Rinaudo M (1998) Polymer 39:6251

7. Kern H, Choi SW, Wenz G, Heinrich J, Erhardt L, Mischnick P, Garidel P, Blume A (2000) *Carbohydr Res* 326:67
8. Lizaso E, Muñoz ME, Santamaría A (1999) *Macromolecules* 32:1883
9. Koschella A, Heinze T, Klemm D (2001) *Macromol Biosci* 1:49
10. Petzold K, Klemm D, Heublein B, Burchard W, Savin G (2004) *Cellulose* 11:177