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Mixed 3-mono-*O*-alkyl cellulose: Synthesis, structure characterization and thermal properties

Thomas Heinze[a,c,*,1], Yunhui Wang[a,1], Andreas Koschella[a,1], Antonio Sullo[b,1], Tim J. Foster[b,1]

[a] *Friedrich Schiller University of Jena, Institute for Organic Chemistry and Macromolecular Chemistry, Center of Excellence for Polysaccharide Research, Humboldtstraße 10, D-07743 Jena, Germany*
[b] *University of Nottingham, Division of Food Sciences, School of Biosciences, Sutton Bonington Campus, Loughborough LE12 5RD, United Kingdom*
[c] *Åbo Akademi University, Fibre and Cellulose Technology, Porthansgatan 3, FI-20500 Åbo, Finland*

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ABSTRACT

The 3-mono-*O*-alkyl cellulose samples bearing two different ether moieties, namely methyl/ethyl, methyl/*n*-propyl, and ethyl/*n*-propyl were synthesized applying protecting group technique. The NMR spectra of the peracetylated products revealed the regioselectivity of the alkylation as well as the degree of substitution of both alkyl moieties. The number average degree of polymerization (DP_n) monitored by size exclusion chromatography decreases from DP_n 117 (Avicel PH-101, starting material) to DP_n 34 (sample **4f**) due to the multi-step synthesis. It could be demonstrated that the lower critical solution temperature (LCST) is influenced by the degree of substitution of both alkyl groups. For example, LCST values between 33 and 58 °C were measured for aqueous solutions of 3-mono-*O*-ethyl/*n*-propyl cellulose. On the contrary, the thermal behavior of a physical mixture of 3-mono-*O*-ethyl- and 3-mono-*O*-*n*-propyl cellulose, e.g., was controlled by the derivative with the lowest LCST.

1. Introduction

Cellulose ethers are widely used in daily life applications, such as adhesives, film formers, tablet binders, and thickener. The alkyl-, hydroxyalkyl-, and carboxyalkyl ethers are non-toxic compounds that are soluble in water and organic solvents depending on the type of substituents (Dönges, 1990; Majewicz & Podlas, 2004). An important property of various cellulose ethers is the presence of a LCST. Below the LCST, the cellulose ethers are soluble, while they form a gel or become insoluble at a temperature above the LCST (Heymann, 1935; Savage, 1957). This process is reversible. A typical example is MC dissolved in water. The LCST of MC is in the range from 55 to 75 °C depending on molar mass, concentration, and DS (Haque & Morris, 1993; Haque, Richardson, Morris, Gidley, & Caswell, 1993; Kern et al., 2000; Savage, 1957).

The activation of cellulose with aqueous sodium hydroxide solution and subsequent heterogeneous etherification does not yield products with a regioselective functionalization pattern, i.e., an almost complete functionalization of one or two preset positions is not possible at all. In order to establish unambiguous structure–property-relationships, it is of great importance to study cellulose ethers with a well-defined structure, i.e., regioselectively functionalized cellulose ethers. All seven possible functionalization patterns of methyl cellulose (2,3,6-tri-*O*-, 2,3-, 2,6-, 3,6-di-*O*-, 2-, 3-, and 6-mono-*O*-functionalized) were synthesized by cationic ring-opening polymerization (Karakawa, Mikawa, Kamitakahara, & Nakatsubo, 2002). In the field of polymer analogous functionalization of cellulose, several advanced synthesis methods have been developed in the recent years (Fox, Li, Xu, & Edgar, 2011; Koschella, Fenn, Illy, & Heinze, 2006). A set of 3-mono-*O*-alkyl celluloses was accessible via a 2,6-di-*O* protected cellulose derivative. The properties of these derivatives depend on the type of ether substituents. 3-Mono-*O*-methyl cellulose is insoluble in water and organic solvents (Koschella, Heinze, & Klemm, 2001), while 3EC (Koschella, Fenn, & Heinze, 2006) and 3PC (Heinze, Pfeifer, Sarbova,

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Abbreviations: 3PC, 3-mono-*O*-(*n*-propyl) cellulose; 3EC, 3-mono-*O*-ethyl; 3MC, 3-mono-*O*-methyl cellulose; AGU, anhydroglucose unit; DS, degree of substitution; DS_{Et}, DS of ethyl groups; DS_{Me}, DS of methyl groups; DS_{Pr}, DS of *n*-propyl groups; EtI, ethyl iodide; LCST, lower critical solution temperature; MC, methyl cellulose; MeI, methyl iodide; DMA, *N*,*N*-dimethyl acetamide; PrI, *n*-propyl iodide; DP_n, number average degree of polymerization; SEC, size exclusion chromatography; THF, tetrahydrofuran; TBAI, tetra-*n*-butylammonium iodide; TBAF·3H_2O, tetra-*n*-butylammoniumfluoride trihydrate; TDMS, thexyldimethylsilyl.

[*] Corresponding author. Tel.: +49 3641 948270; fax: +49 3641 948272.
E-mail address: thomas.heinze@uni-jena.de (T. Heinze).

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& Koschella, 2011) are water soluble. An aqueous solution of 3EC has a LCST of 60 °C (Koschella, Fenn, et al., 2006). The LCST of 3PC is remarkably lower and was found to depend on the DS of propyl groups (15 °C, DS_{Pr} 1 and 23.5 °C, DS_{Pr} 0.71) (Heinze et al., 2011).

In the presented work, a series of regioselectively functionalized cellulose ethers with two different ether moieties at position 3 (3-mono-*O*-R_1/R_2 cellulose) was prepared by simultaneous alkylation of 2,6-di-*O*-TDMS cellulose with two alkylating reagents and subsequent desilylation. The structure of the polymers, in particular the ratio of both alkyl moieties was characterized by NMR spectroscopy and the LCST of the aqueous solutions was determined.

2. Experimental part

2.1. Materials

Microcrystalline cellulose **1** (Avicel, Sigma–Aldrich, DP_n 117) was dried in vacuum over potassium hydroxide for 3 h at 105 °C and lithium chloride (Fluka) was dried in vacuum over potassium hydroxide for 3 h at 150 °C. Sodium hydride (Fluka) was used after washing a suspension in mineral oil (60%) with *n*-hexane and *n*-pentane and drying at room temperature. DMA (Fluka), anhydrous THF (Aldrich) and pyridine (Fluka) were stored over molecular sieves (size 3 Å). All other chemicals were used as received. 3MC (sample **4i**, DS 1.05) (Koschella et al., 2001), 3EC (sample **4j**, DS 1.07) (Koschella, Fenn, et al., 2006) and 3PC (sample **4k**, DS 1.13) (Heinze et al., 2011) were prepared according to the published procedures.

2.2. Measurements

FT-IR spectra were recorded on a Nicolet Avatar 370 DTGS spectrometer using the KBr technique. The ^1H and ^{13}C NMR spectra were acquired with Bruker Avance 250 (250 MHz) and Avance 400 (400 MHz) spectrometers in deuterochloroform ($CDCl_3$) at 60 °C. The DS of the alkyl moieties was calculated from the peak area obtained by integration of the ^1H NMR spectra. The DS_{Me}, DS_{Et}, and DS_{Pr} were calculated by Eqs. (1) and (2).

$$DS_{Me} = \frac{9 \cdot I_{AGU} - 7 \cdot I_{Ac} - 13 \cdot I_{CH_3}}{3 \cdot I_{AGU} + 3 \cdot I_{AGU} + I_{CH_3}} \quad (1)$$

$$DS_{Et(Pr)} = \frac{16 \cdot I_{CH_3}}{3 \cdot I_{AGU} + 3 \cdot I_{Ac} + I_{CH_3}} \quad (2)$$

I_{AGU} is the peak area of the AGU (anhydroglucose unit) peaks from 3.2 to 4.7 ppm. I_{Ac} is the peak area of the methyl of the acetyl moiety at 2.06 ppm. I_{CH3} is the peak area of the Me group of Et moiety (1.07 ppm) or Pr moiety (0.85 ppm). For 2,6-di-*O*-acetyl-3-mono-*O*-Et/Pr, DS_{Et} and DS_{Pr} were calculated by Eq. (3).

$$DS_{Et} + DS_{Pr} = 3 - \frac{13}{2 + 3 \cdot I_{AGI}/I_{Ac}} \quad (3)$$

I_{AGU} is the peak area of the AGU peaks from 3.2 to 4.7 ppm. I_{Ac} is the peak area of the methyl group of the acetyl moiety at 2.06 ppm. I_{CH3} (Et) and I_{CH3} (Pr) correspond to the integral value of the methyl group of the ethyl moiety (1.07 ppm) or *n*-propyl (0.85 ppm) moiety, respectively.

LCST measurements were conducted with a turbidimetric photometer TEPPER Analytik (Germany, $\lambda = 670$ nm) by heating the aqueous solutions of cellulose (1%, w/w) from 5 to 90 °C and cooling back to 5 °C with a heating/cooling rate of 1 °C/min. The transmittance at the initial temperature was set to 100%. The LCST was estimated by applying the tangents to the turbidity curves of the samples (heating curves) and determination of the temperature at the intersection point. A JASCO SEC (Size Exclusion Chromatography) system was applied consisting of a degasser DG 980-50, pump PU 980, UV detector 975 ($\lambda = 354$ nm), refractive index detector 930, column oven, and guard column. Separation was carried out using three SDV-Gel columns (10^6, 10^4, and 10^3 Å, Polymer Standards Service, Mainz, Germany) at 30 °C. The calibration standard was polystyrene.

2.3. Methods

2.3.1. Up-scaling of the synthesis of 2,6-di-O-TDMS cellulose **2**

Microcrystalline cellulose **1** (100 g, 617 mmol) was slurried in 2532 mL DMA in a 5 L reaction vessel and heated to 130 °C for 3 h. The mixture was cooled to 100 °C and LiCl (200 g, 4718 mmol, 7.6, mol/mol AGU) was added. A clear solution was obtained after stirring overnight at 30 °C. Imidazole (200 g, 2938 mmol, 4.8, mol/mol AGU) was added to the solution, followed by TDMS-Cl (500 mL, 2548 mmol, 4.1 mol/mol AGU). The mixture was allowed to react for 24 h at 100 °C under vigorous mechanical mixing. After cooling to room temperature, the reaction mixture was poured into 3 L water. The well dispersed product was filtered off, washed 2 times with 600 mL water and then 6 times with 400 mL ethanol, the product was dried in vacuum oven at 60 °C.

Yield: 273 g (99%).

Silicon content: 27.19%.

DS_{Si} 2.06.

FT-IR (KBr, cm^{-1}): 3504 νOH, 2960, 2872 νC—H, 1466 δC—H, 1252 νSi—C, 1152–1037 νC—O—C, 833, 778 νSi—C.

SEC in THF: $\bar{M}_n$ 42556 g/mol, DP_n 94.

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

2.3.2. 2,6-Di-O-TDMS-3-mono-O-Et/Pr cellulose **3c** and **3c′**

3c: To 2,6-di-*O*-TDMS cellulose **2** (13.26 g, 29.7 mmol) dissolved in dry THF (130 mL), sodium hydride (7.6 g, 292 mmol, 10 mol/mol modified AGU) was added under vigorous mechanical mixing. After 1 h, PrI (23.2 mL, 237.4 mmol, 8 mol/mol modified AGU) and EtI (4.8 mL, 59.4 mmol, 2 mol/mol modified AGU) were added drop wise. The solution solidified accompanied with an obvious exothermic effect. The mixture was stirred overnight until the paste became liquid. The mixture was allowed to react at 50 °C for 4 d under mechanical stirring. The remaining sodium hydride was destroyed by addition of 20 mL isopropanol, followed by adding 10 mL of water. The product was precipitated in buffer solution (14.68 g $Na_2HPO_4 \cdot 12H_2O$ and 3.54 g KH_2PO_4 in 1 L distilled water) and filtered off, washed 2 times with 200 mL ethanol and dispersed, then washed again 4 times with 200 mL water, and 4 times with 200 mL ethanol. The pale yellow product was dried in vacuum at 40 °C.

Yield: 12.29 g (94%).

DS_{Et} 0.54, DS_{Pr} 0.42 (determined by ^1H NMR spectroscopy after desilylation and peracetylation).

FT-IR (KBr, cm^{-1}): 3452 νOH (very weak), 2963, 2873 νC—H, 1468 δC—H, 1379 δCH_3, 1255 νSi—C, 1089, 1044 νC—O—C, 832, 777 νSi-C.

SEC in tetrahydrofuran (THF): $\bar{M}_n$ 21453 g/mol, DP_n 49.

3c′: 2,6-di-*O*-TDMS cellulose **2** was dissolved in THF and treated with sodium hydride, EtI, and PrI as described for sample **3c**. Tetra-*n*-butylammonium iodide (TBAI, 0.12 g) was added after stirring of the reaction mixture overnight. The mixture was allowed to react at room temperature for 4 days under mechanical stirring. The work up was carried out as described for sample **3c**.

Yield: 12.18 g (89%).

DS_{Et} 0.59, DS_{Pr} 0.43 (determined by ^1H NMR spectroscopy after desilylation and peracetylation).

SEC in THF: $\bar{M}_n$ 15911 g/mol, DP_n 33.

These two products are both soluble in *n*-hexane, toluene, THF and chloroform.

2.3.3. 3-Mono-*O*-Et/Pr cellulose **4c**

To 2,6-di-*O*-TDMS-3-mono-*O*-Et/Pr cellulose **3c** (12.17 g, 26.4 mmol) dissolved in THF (183 mL), TBAF·3H_2O (32.3 g, 105.6 mmol, 4 mol/mol modified AGU) was added, and the mixture was allowed to react for 24 h at 50 °C under stirring. 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 precipitate was dissolved in dimethyl sulfoxide (DMSO, 59 mL) and treated with TBAF·3H_2O (3.49 g) for 24 h at 50 °C. After cooling to room temperature, the polymer was precipitated with 800 mL diethyl ether/isopropanol 2:1 (v/v), filtered off, washed 4 times with 50 mL diethyl ether/isopropanol 2:1 (v/v) and dried in vacuum. The crude product was dissolved in 50 mL DMSO and reprecipitated in 300 mL diethyl ether/isopropanol 2:1 (v/v). The product was washed with diethyl ether/isopropanol 2:1 (v/v) and dried in vacuum at 40 °C.

Yield: 2.46 g (47%).

DS_{Et} 0.54, DS_{Pr} 0.42 (determined by ^1H NMR spectroscopy after peracetylation).

SEC in DMA/LiCl: $\bar{M}_n$ 41477 g/mol, DP_n 212.

The product is soluble in DMSO, DMA, *N*,*N*-dimethyl formamide, and water.

2.3.4. 2,6-Di-*O*-acetyl-3-mono-*O*-Et/Pr cellulose **5c**

To 3-mono-*O*-Et/Pr cellulose (**4c**, 0.2 g, 1 mmol) dissolved in dry pyridine (6 mL), 6 mL (63.5 mmol, 63 mol/mol modified AGU) acetic anhydride and 0.02 g (0.2 mmol, 0.2 mol/mol modified AGU) 4-*N*,*N*-dimethylaminopyridine were added. The mixture was allowed to react for 20 h at 80 °C and then 3 h at 100 °C under stirring and exclusion of moisture. After cooling to room temperature, the product was precipitated with 50 mL isopropanol, filtered off, washed 6 times with 50 mL isopropanol, and dried in vacuum at 40 °C.

Yield: 0.3 g, quantitative.

SEC in THF: $\bar{M}_n$ 54866 g/mol, DP_n 272;

^1H NMR (400 MHz, $CDCl_3$, ppm): 0.85 ($-O-CH_2CH_2CH_3$), 1.07 ($-O-CH_2CH_3$), 1.48 ($-O-CH_2CH_2CH_3$), 2.07 ($-COCH_3$), 3.41 (H-3), 3.43 (H-5), 3.63 (H-4), 3.53, 3.75 ($-O-CH_2CH_3$, $-O-CH_2CH_2CH_3$), 4.16 (H-6α), 4.36 (H-6β), 4.44 (H-1), 4.78 (H-2).

^{13}C NMR ($CDCl_3$, ppm): 170, 169 (C=O), 100.8 (C-1), 80.6 (C-3), 77.5 (C-4), 73.9 (C-2, 5), 67.5 ($-O-CH_2CH_3$, $-O-CH_2CH_2CH_3$), 62.6 (C-6), 23.1 ($-O-CH_2CH_2CH_3$), 20.5 ($-COCH_3$), 15.2 ($-O-CH_2CH_3$), 10.2 ($-O-CH_2CH_2CH_3$).

FT-IR (KBr, cm^{-1}): 2978, 2937, 2900 νC–H, 1748 νC=O, 1441, 1375 δCH_3, CH_2, 1231, 1047 νC–O–C.

The product is soluble in chloroform, pyridine, and ethyl acetate.

3. Results and discussion

3.1. Preparation of the cellulose derivatives

For the preparation of 3-mono-*O*-functionalized cellulose ethers, 2,6-di-*O*-TDMS cellulose **2** was prepared homogeneously in *N*,*N*-dimethyl acetamide (DMA)/LiCl with TDMS-Cl in the presence of imidazole (Scheme 1) (Koschella et al., 2001). This protected cellulose derivative was allowed to react simultaneously with two different alkyl iodides (MeI, EtI, PrI) in the presence of sodium hydride followed by desilylation.

The ratio between the two alkyl moieties bound at position 3 of the repeating unit was varied by changing the ratio of the alkylating agents while maintaining the molar ratio of hydroxyl group to alkylating agent of 1:10 as summarized in Table 1. The conversion of 2,6-di-*O*-TDMS cellulose with an equimolar mixture of EtI and PrI and subsequent desilylation afforded sample **4a** with DS_{Et} of 0.95 and DS_{Pr} 0.15. Obviously, PrI possesses a significantly lower reactivity compared with EtI. Changing the molar ratio EtI:PrI from 5:5 to 3:7 yielded sample **4b** with DS_{Et} 0.77 and DS_{Pr} 0.27. Further increase of the ratio EtI:PrI to 2:8 led to increase of DS_{Pr} while maintaining the total DS constant (sample **4c**, DS_{Et} 0.54, DS_{Pr} 0.42). Applying 1 mol EtI and 9 mol PrI per mole modified repeating unit afforded sample **4d** with DS_{Et} 0.27 and DS_{Pr} 0.56.

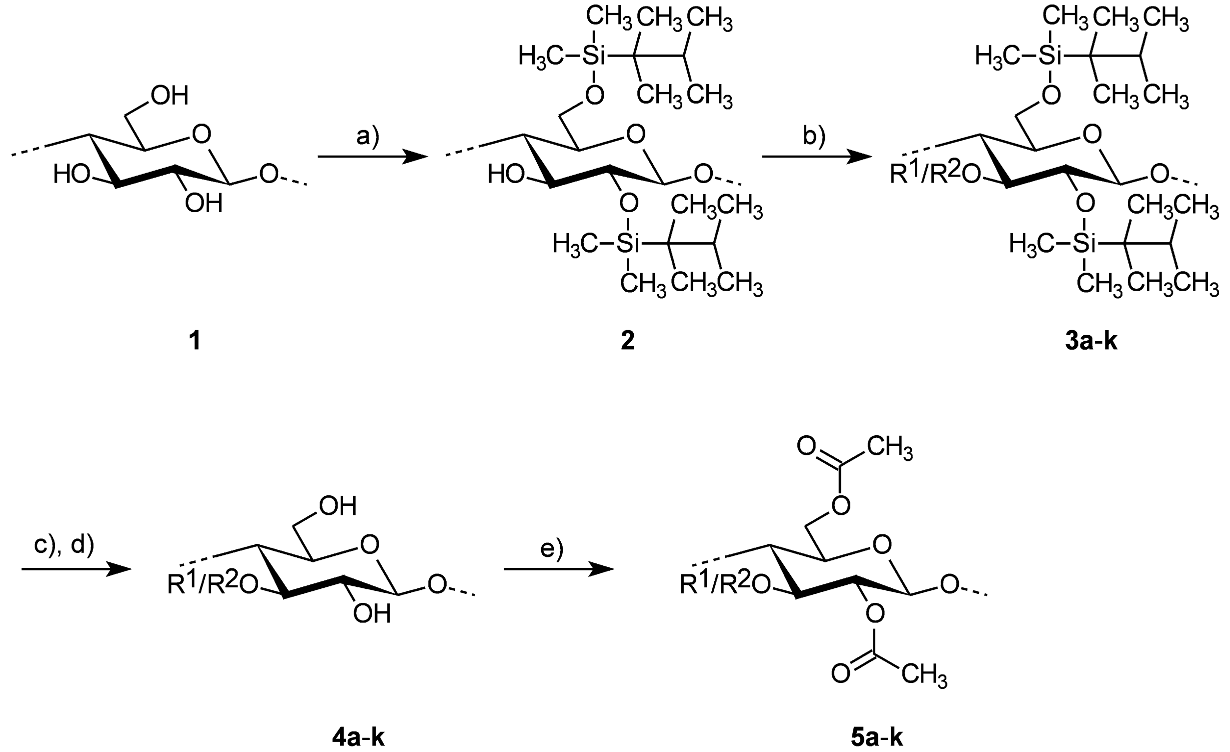
In a further set of experiments, the conversion of the 2,6-di-*O*-TDMS cellulose with MeI/EtI and MeI/PrI was studied. The reaction of 5 mol MeI and EtI per mole modified AGU (anhydroglucose unit) yielded sample **4e** with DS_{Me} 0.99, DS_{Et} 0.08. Similar to the conversion of 2,6-di-*O*-TDMS cellulose with EtI and PrI, the difference in partial DS results from the much more reactive MeI compared with EtI. A ratio of MeI:EtI = 1:9 afforded sample **4f** with DS_{Me} 0.19 and DS_{Et} 0.91. Comparable results were observed for conversion of 2,6-di-*O*-TDMS cellulose with MeI and PrI. Thus, a reaction with equimolar amounts of MeI and PrI gave sample **4g** with DS_{Me} 0.97 and DS_{Pr} 0.12. Applying a ratio MeI:PrI = 1:9 afforded sample **4h** with DS_{Me} 0.46 and DS_{Pr} 0.58. The total DS of the 3-*O*-alkyl cellulose is about 1 and in accordance with the general reaction scheme of 2,6-di-*O*-protection, 3-*O*-alkylation, and 2,6-di-*O*-deprotection. Deviations may be caused by different methods used for DS determination and their inherent errors, namely elemental analysis of 2,6-di-*O*-TDMS cellulose **2** and ^1H NMR spectroscopy after peracetylation for samples **4a**–**h**.

3.2. Structure characterization

NMR spectra were acquired after peracetylation of the samples in order to prevent the formation of hydrogen bonds, i.e., to reduce polymer-polymer interactions, which improved the resolution of the NMR spectra. The ^1H NMR spectra of 2,6-di-*O*-acetyl-3-mono-*O*-Et/Pr cellulose (**5a** and **5d**), 2,6-di-*O*-acetyl-3-mono-*O*-Me/Et cellulose (**5e** and **5f**), and 2,6-di-*O*-acetyl-3-mono-*O*-Me/Pr cellulose (**5g** and **5h**) are shown in Fig. 1. For **5a** and **5d** (numbering 1–8, 1′–9′), the signals in the high field from 0.50 to 2.25 ppm correspond clearly to the alkyl protons on 8, 8′, 9′ as well as the methyl protons of the acetyl group. The signals in the range from 2.90 to 5.20 ppm result from AGU protons and also from alkyl protons next to the oxygen of the ether bond (7 and 7′).

Sample **5e** and **5f** (numbering 1–7, 1′–8′) as well as **5g** and **5h** (numbering 1–7, 1′–9′) gave similar spectra. The difference is a sharp peak at 3.45 ppm that corresponds to the methyl protons on position 7. In addition, for samples with higher content of Et- or Pr moieties (**5g** and **5h**), the signals for AGU protons at position 5 were always overlapped by the alkyl protons on 7′. However, the peaks for position 7′ could not be clearly assigned for samples with lower content of Et- or Pr groups (**5e** and **5f**). Peaks of low intensity around 3.15 and 5.10 ppm were attributed to substructures due to deviation from the ideal structure to a small extent, which is already known from the literature (Heinze et al., 2011; Koschella, Fenn, et al., 2006).

Due to the fact that several synthesis steps are needed to get these sophisticated cellulose derivatives, polymer degradation to a certain extent must be taken into account. According to the published methods, the alkylation of 2,6-*O*-TDMS cellulose **2** was conducted at 50 °C for 4 d. It could be demonstrated that the addition of TBAI as phase transfer catalyst enables the peralkylation at room temperature within the same reaction time (Bar-Nir & Kadla, 2009; Herriott & Picker, 1975; Starks, 1971; Ugelstad, Ellingsen, & Berge, 1966). This could be proved by comparing the FT-IR spectra of sample **3i** (3-mono-*O*-MC synthesized without catalyst at 50 °C) and sample **3i**′ (3-mono-*O*-MC synthesized at room temperature in presence of TBAI, Fig. 2). Only very weak absorbances around 3500 and 1640 cm^{-1} were visible, which were attributed to trace of water, together with the typical signals of the 3-mono-*O*-alkyl-2,6-di-*O*-TDMS cellulose.



a) Thexyldimethylsilyl chloride, imidazole, *N,N*-dimethyl acetamide/LiCl, 24 h, 100°C.
b) Alkyl iodide (R^1/R^2= methyl, ethyl, *n*-propyl), sodium hydride, tetrahydrofuran (samples **3a**, **3b**, **3c**, **3d**, **3i**, **3j**, **3k**, 4 d, 50°C; samples **3c'**, **3e**, **3f**, **3g**, **3h**, **3i'**, in presence of tetra-*n*-butylammonium iodide, 4 d, room temperature).
c) Tetra-n-butylammonium fluoride trihydrate, tetrahydrofuran, 24 h, 50°C.
d) Tetra-n-butylammonium fluoride trihydrate, dimethyl sulfoxide, 24 h, 50°C.
e) Acetic anhydride, pyridine, 4-*N,N*-dimethylaminopyridine, 20 h, 80°C.

Scheme 1. Synthesis of 3-mono-*O*-alkyl cellulose bearing two different ether groups (methyl/ethyl, methyl/propyl, ethyl/propyl).

Table 1
Conditions for and results of the conversion of 2,6-di-*O*-thexyldimethylsilyl (TDMS) cellulose **2** simultaneously with two different alkylating agents in the presence of sodium hydride for 4 d in tetrahydrofuran and subsequent desilylation.

Conditions						Results										
Molar ratio[a]					Temp.[b] °C	2,6-Di-*O*-TDMS-3-*O*-alkyl cellulose			3-*O*-Alkyl cellulose							
2	MeI	EtI	PrI	NaH		Sample	$\bar{M}_n$[d] g/mol	DP_n[e]	Sample	DS[c]			Σ DS	$\bar{M}_n$[d] g/mol	DP_n[e]	LCST[f] °C
										Me	Et	Pr				
1	–	5	5	10	50	**3a**	–[b]	–	**4a**	–	0.95	0.15	1.10	45917	235	58
1	–	3	7	10	50	**3b**	18833	40	**4b**	–	0.77	0.27	1.04	49276	252	44
1	–	2	8	10	50	**3c**	21453	49	**4c**	–	0.54	0.42	0.96	41477	212	38
1	–	2	8	10	rt[g]	**3c′**	15911	33	**4c′**	–	0.59	0.43	1.02	4028	20	38
1	–	1	9	10	50	**3d**	–[h]	–	**4d**	–	0.27	0.56	0.83	33308	172	33
1	5	5	–	10	rt[g]	**3e**	–[h]	–	**4e**	0.99	0.08	–	1.07	6778	38	–[h]
1	1	9	–	10	rt[g]	**3f**	25488	53	**4f**	0.19	0.91	–	1.10	6569	34	71
1	5	–	5	10	rt[g]	**3g**	–[h]	–	**4g**	0.97	–	0.12	1.09	6419	35	–[h]
1	1	–	9	10	rt[g]	**3h**	22512	46	**4h**	0.46	–	0.58	1.04	9287	48	38
1	10	–	–	10	50	**3i**	–[h]	–	**4i**	1.05	–	–	1.05	33506	190	–[h]
1	10	–	–	10	rt[g]	**3i′**	–[h]	–	**4i′**	–[h]	–	–	–	–[h]	–	–[h]
1	–	10	–	10	50	**3j**	–[h]	–	**4j**	–	1.07	–	1.07	24698	130	60
1	–	–	10	10	50	**3k**	9342	19	**4k**	–	–	1.13	1.13	–[h]	–	18

[a] Molar ratio of 2,6-di-*O*-TDMS cellulose **2**:alkyl iodide (methyl iodide, MeI; ethyl iodide, EtI, *n*-propyl iodide, PrI):sodium hydride.
[b] Temperature, room temperature (rt).
[c] Degree of substitution of methyl (Me)-, ethyl (Et)-, and propyl (Pr) groups determined by ^{1}H NMR spectroscopy after peracetylation of the samples.
[d] Number average molar mass measured by SEC in tetrahydrofuran (samples **3b**, **3c**, **3f**, **3h**) and *N*,*N*-dimethyl acetamide/LiCl (samples **4a**–**4h**).
[e] Number average degree of polymerization calculated from SEC data.
[f] Lower critical solution temperature of 1% (w/v) solutions of the samples in water.
[g] Addition of tetra-*n*-butylammonium iodide as phase transfer catalyst.
[h] Not measured.

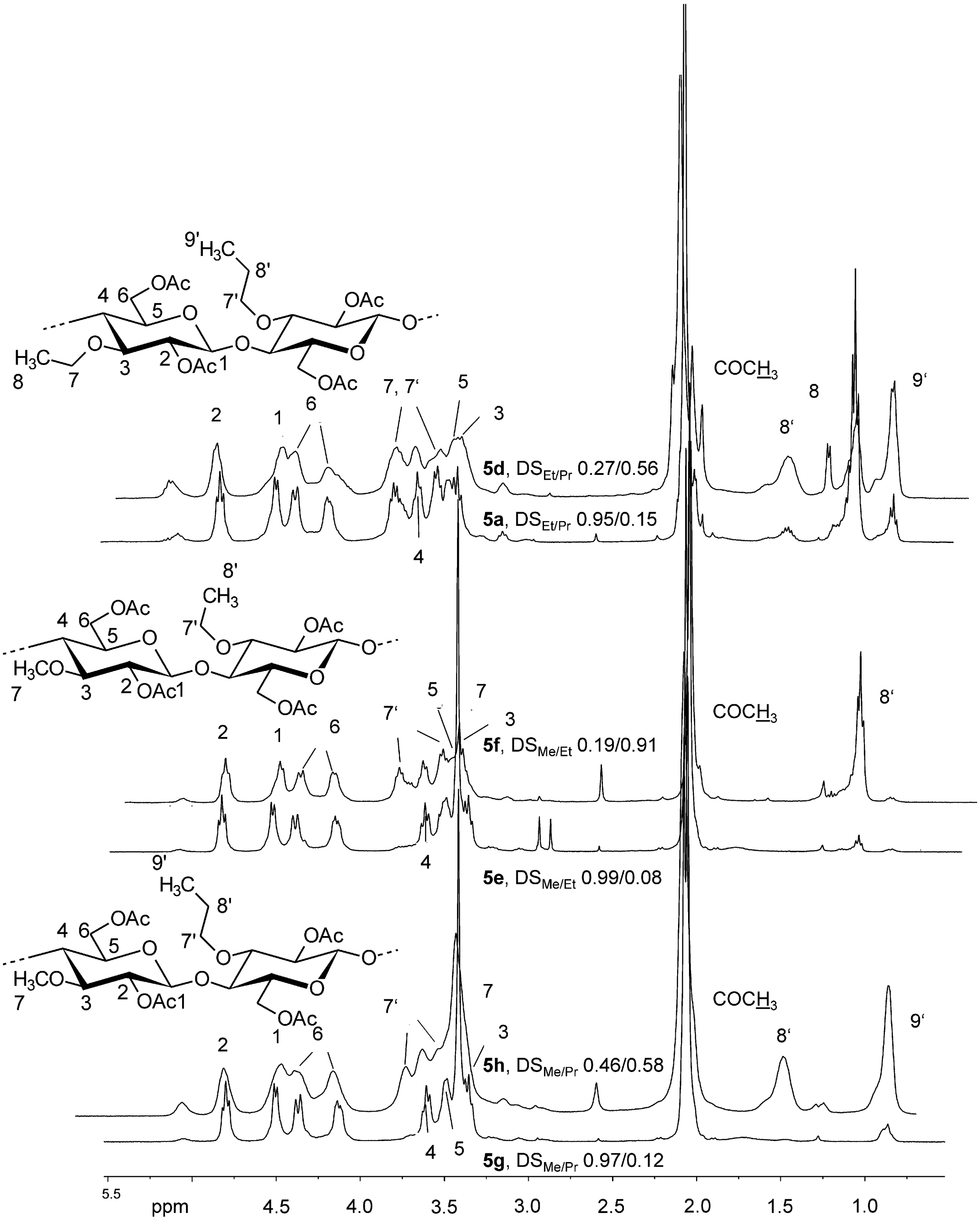


Fig. 1. ^{1}H NMR spectra of different 2,6-di-*O*-acetyl-3-mono-*O*-functionalized cellulose ethers bearing two alkyl moieties obtained by simultaneous conversion of 2,6-di-*O*-thexyldimethylsilyl cellulose with two alkylating agents in the presence of sodium hydride followed by desilylation and peracetylation (degree of substitution: DS; methyl: Me; ethyl: Et; *n*-propyl: Pr; recorded in $CDCl_3$).

3.3. Characterization of the macromolecular properties

The DP_n of the intermediates was calculated from the results of SEC. The silylation of cellulose in DMA/LiCl with TDMS-Cl in the presence of imidazole causes a slight degradation from DP_n 117 (starting material **1**) to 94 (2,6-di-*O*-TDMS cellulose **2**). The 3-*O*-alkyl-2,6-di-*O*-TDMS celluloses possess DP_n values in the range from 40 to 53 (Table 1). Obviously, the DP_n values of 3-*O*-alkyl celluloses (**4a**–**f**) depend on the reaction conditions of the alkylation step. Thus, products synthesized at room temperature in the presence of TBAI possess DP_n values in the range from 34 to 48 (samples **4e**–**h**). On the contrary, alkylation of 2,6-di-*O*-TDMS cellulose at 50 °C afforded samples with significantly higher apparent DP_n values ranging from 172 to 252 (**4a**–**d**), which are about 10 times higher compared with the DP_n of products synthesized at room temperature in the presence of TBAI. Considering the DP_n of microcrystalline cellulose **1** (DP_n 117), a different aggregation behavior of the polymers after the desilylation must be taken into account.

It was assumed that the different DP_n values result from the reaction conditions. Therefore, two 3-mono-*O*-Et/Pr celluloses were prepared by applying the same molar ratio of reagents to modified AGU but different alkylation conditions (50 °C without TBAI; room temperature with TBAI). Both DS_{Et} and DS_{Pr} of samples **4c** and **4c'** are comparable, but the DP_n values calculated from $\bar{M}_n$ measured by SEC in DMA/LiCl differ by one order of magnitude (Table 1). In order to exclude the influence of TBAI on the DP of the products, a "blind test" was conducted (see supplementary material). The 2,6-di-*O*-TDMS cellulose **2** was dissolved in THF and stirred in the presence of TBAI or without TBAI according to the

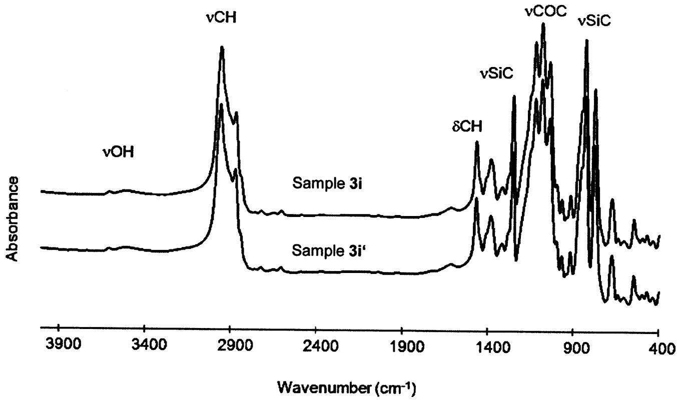


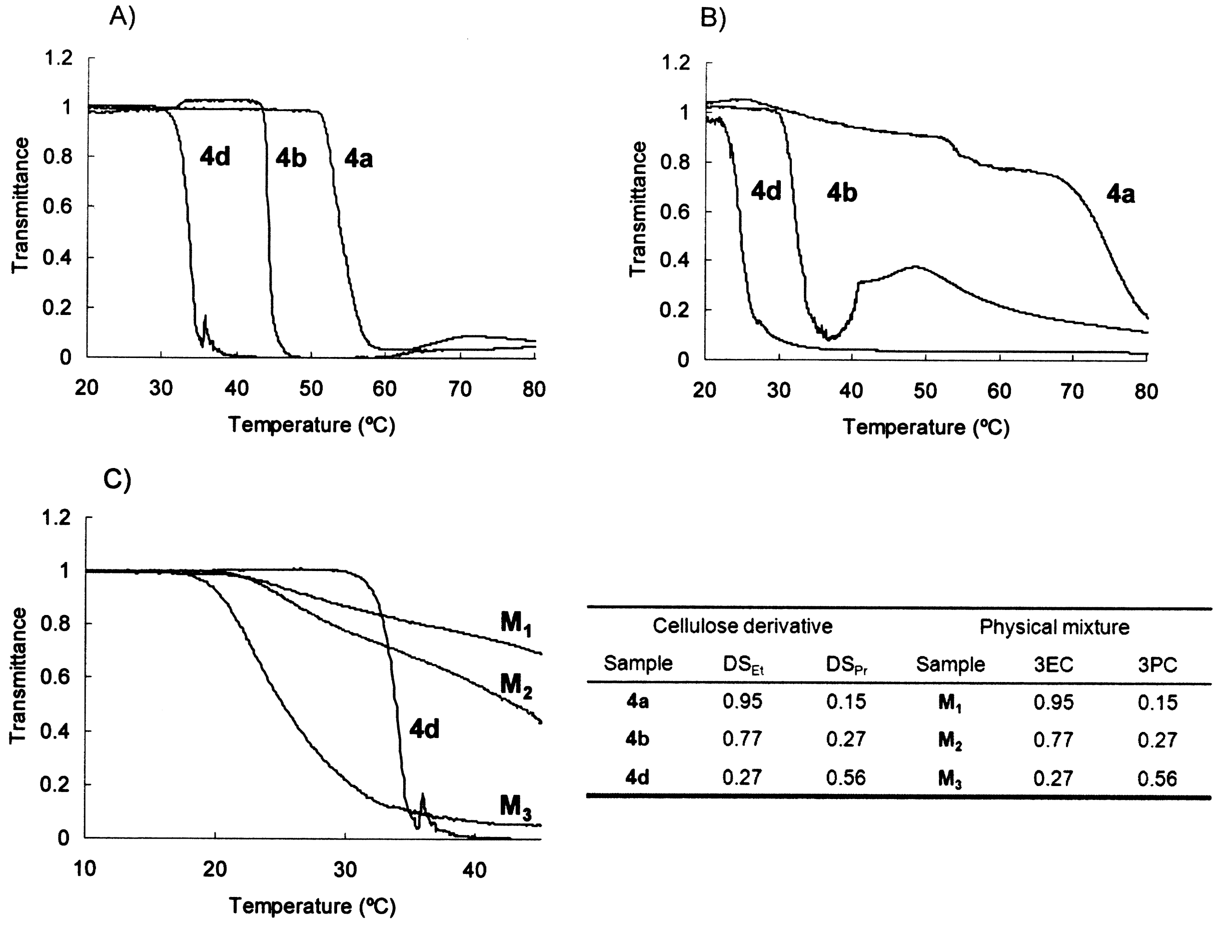
Fig. 2. FT-IR spectra of 2,6-di-*O*-thexyldimethylsilyl (TDMS)-3-mono-*O*-methyl cellulose synthesized by conversion of 2,6-di-*O*-TDMS cellulose with methyl iodide and sodium hydride at 50 °C without tetra-*n*-butylammonium iodide (TBAI, sample **3i**) and at room temperature in the presence of TBAI as catalyst (sample **3i'**).

conditions of alkylation reaction. The DP_n of the precipitated products (with TBAI, DP_n 112; without TBAI, DP_n 113) do not show significant differences from the initial 2,6-di-*O*-TDMS cellulose (sample **2**, DP_n 94). Thus, there is no influence of the catalyst on the molecular weight of the reaction products. Therefore, it is assumed that samples prepared at 50 °C tend to form aggregates (DP_n 212, sample **4c**), while samples synthesized at room temperature apparently did not form aggregates (DP_n 20, sample **4c'**). The SEC of peracetylated products **5c** and **5c'** carried out in THF (see supplementary information) revealed a DP_n of 272 (**5c**) and 138 (**5c'**). The DP_n of **5c** (peracetylated product from alkylation at 50 °C) is even higher than the DP_n of desilylated product **4c**; while DP_n of sample **5c'** obtained by alkylation at room temperature in the presence of TBAI and peracetylation is also higher as DP_n of **4c'** (before peracetylation). It is already reported in the literature that the DP value of peracetylated products depend on the DS of the ether group at position 3 (Heinze et al., 2011), i.e., DP_n values between 148 and 200 are observed for samples with DS ~ 1 compared with a lower DP_n of 40–65 for samples with DS < 1; but an explanation is not available up to now.

It was reported that benzylation of cellulose at 50 °C without any catalyst and at room temperature in the presence of TBAI could lead to products with different structures: a block-wise functionalization was detected in products synthesized at 50 °C, while a random functionalization pattern was found after reaction at room temperature (Rohleder & Heinze, 2010). A similar behavior might be possible in case of alkylation of 2,6-di-*O*-TDMS cellulose with two different alkylating agents, i.e., a block-like distribution of the different alkyl moieties may appear. It seems likely that the sequence of repeating units being differently alkylated at position 3 depends on the reaction conditions. Consequently, studies on functionalization pattern along the polymer chain are required.

3.4. Characterization of the thermal behavior of the polymer solutions

The temperature dependent solubility of the cellulose ether in water (1%, w/v) was evaluated by means of turbidimetry.



Cellulose derivative			Physical mixture		
Sample	DS_{Et}	DS_{Pr}	Sample	3EC	3PC
4a	0.95	0.15	M_1	0.95	0.15
4b	0.77	0.27	M_2	0.77	0.27
4d	0.27	0.56	M_3	0.27	0.56

Fig. 3. Temperature dependent transmittance of 1% aqueous solutions of 3-mono-*O*-ethyl (Et)/*n*-propyl (Pr) cellulose (A: heating curve, B: cooling curve) as well as mixtures of 3-mono-*O*-ethyl cellulose (3EC, sample **4j**) and 3-mono-*O*-propyl cellulose (3PC, sample **4k**, heating curve, C).

3-mono-*O*-Et/Pr cellulose derivatives (samples **4a**–**d**) are soluble in water below room temperature. Samples with pronounced methylation (**4e** DS_{Me} 0.99, DS_{Et} 0.08; **4g** DS_{Me} 0.97, DS_{Pr} 0.12) are water insoluble. This finding corresponds with the fact that the 3MC is water insoluble (Koschella et al., 2001). However, a product with higher DS_{Et} rather than DS_{Me} is water soluble (**4f**) and the aqueous solution possesses a LCST of 71 °C (Table 1). The LCST of the 3-*O*-Me/Pr cellulose **4h** (DS_{Me} 0.46, DS_{Pr} 0.58) in aqueous solution is 38 °C (Table 1).

Fig. 3 summarizes the transmittance of the aqueous solution (1%, w/v) of 3-mono-*O*-Et/Pr cellulose depending on the temperature. The LCST was found to depend on the ratio of the two alkyl groups bound at position 3. A LCST of 58 °C was detected for sample **4a** (DS_{Et} 0.95, DS_{Pr} 0.15). Increase of DS_{Pr} and decrease of DS_{Et} result in decrease of the LCST, e.g. 44 °C (sample **4b**, DS_{Et} 0.77, DS_{Pr} 0.27), 38 °C (sample **4c**, DS_{Et} 0.54, DS_{Pr} 0.42), and 33 °C (sample **4d**, DS_{Et} 0.27, DS_{Pr} 0.56). It was observed that the redissolution of the precipitate during the cooling cycle was retarded and slower compared with the heating cycle. However, the cooling curves of the cellulose derivatives with higher content of ethyl group (**4a** and **b**) show some strange changes in transmittance. This may be due to the aggregation of the precipitate during the heating cycle, which makes precipitation badly dispersed in solution and hence increased the transmittance of the liquid.

In addition, turbidimetric analyses were also conducted with 3EC (sample **4j**, DS 1.07, LCST 60 °C) and 3PC (sample **4k**, DS 1.13, LCST 18 °C), as well as their physical mixtures to achieve the same content of Et- and Pr moieties as in the samples obtained by simultaneous alkylation of 2,6-di-*O*-TDMS cellulose (Fig. 3C). The solution of a physical mixture of 3EC:3PC=0.27:0.56 provided a LCST of 18 °C, which fits the LCST of 3PC; however, the aqueous solution of **4d** with DS_{Et} 0.27 and DS_{Pr} 0.56 has the LCST of 33 °C. It could be concluded that the tuning of LCST of 3-mono-*O*-cellulose ether could not be realized by physically mixing of two kinds of 3-mono-*O*-alkyl cellulose. The three curves of the turbidimetic measurements of different polymer compositions (**M_1**–**M_3**) indicate that all physical mixtures of 3EC and 3PC solutions have LCSTs in the range of 18–22 °C, and this temperature range corresponds with the LCST of 3PC cellulose according to already published values (Heinze et al., 2011). However, it should be noted that high content of 3PC accelerated the flocculation rate.

4. Conclusions

The synthesis of 3-mono-*O*-alkyl cellulose bearing two different ether groups was accomplished by simultaneous alkylation of 2,6-di-*O*-TDMS cellulose in the presence of TBAI as catalyst. The DS of each moiety could be controlled by the molar ratio of alkylation reagents to modified AGU (anhydroglucose unit), a higher molar ratio of alkyl iodide leads to a higher DS of the corresponding alkyl ether. The alkyl moiety with shorter chain length shows a higher reactivity. The structure of 2,6-di-*O*-acetyl-3-mono-*O*-alkyl cellulose was characterized by FT-IR and NMR spectroscopy. The polymer degradation was studied by comparing the DP_n values of each intermediate within the multi-step synthesis. However, it was also observed that the DP_n of products were significantly influenced by the alkylation conditions. Samples prepared at 50 °C have a DP_n value that is higher than the DP of the microcrystalline cellulose used as starting material. On the contrary, alkylation products obtained at room temperature possessed comparably low DP_n values. Thus, aggregation of 3-mono-*O*-alkyl cellulose occurred. It is speculated that a different functionalization pattern along the polymer chain is responsible for this effect.

LCST could be tuned by introducing two alkyl moieties at position 3 that is not possible by mixing two types of 3-mono-*O*-alkyl cellulose. Detailed investigation of the thermal behavior of the samples will be published elsewhere.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carbpol.2012.05.054.

References

Bar-Nir, B. B.-A., & Kadla, J. F. (2009). Synthesis and structural characterization of 3-O-ethylene glycol functionalized cellulose derivatives. *Carbohydrate Polymers*, *76*, 60–67.

Carter Fox, S., Li, B., Xu, D., & Edgar, K. J. (2011). Regioselective esterification and etherification of cellulose: A review. *Biomacromolecules*, *12*, 1956–1972.

Dönges, R. (1990). Nonionic cellulose ethers. *British Polymer Journal*, *23*, 315–326.

Haque, A., & Morris, E. R. (1993). Thermogelation of methylcellulose. Part I: Molecular structures and processes. *Carbohydrate Polymers*, *22*, 161–173.

Haque, A., Richardson, R. K., Morris, E. R., Gidley, M. J., & Caswell, D. C. (1993). Thermogelation of methylcellulose. Part II: Effect of hydroxypropyl substituents. *Carbohydrate Polymers*, *22*, 175–186.

Heinze, T., Pfeifer, A., Sarbova, V., & Koschella, A. (2011). 3-O-Propyl cellulose: Cellulose ether with exceptionally low flocculation temperature. *Polymer Bulletin*, *66*, 1219–1229.

Herriott, A. W., & Picker, D. (1975). Phase transfer catalysis. Evaluation of catalysis. *Journal of the American Chemical Society*, *97*, 2345–2349.

Heymann, E. (1935). Sol-gel transformations. I. The inverse sol-gel transformation of methylcellulose in water. *Transactions of the Faraday Society*, *31*, 846–864.

Karakawa, M., Mikawa, Y., Kamitakahara, H., & Nakatsubo, F. (2002). Preparations of regioselectively methylated cellulose acetates and their ^{1}H and ^{13}C NMR spectroscopic analyses. *Journal of Polymer Science Part A: Polymer Chemistry*, *40*, 4167–4179.

Kern, H., Choi, S. W., Wenz, G., Heinrich, J., Ehrhardt, L., Mischnick, P., et al. (2000). Synthesis, control of substitution pattern and phase transitions of 2,3-di-O-methylcellulose. *Carbohydrate Research*, *326*, 67–79.

Koschella, A., Fenn, D., & Heinze, T. (2006). Water soluble 3-mono-O-ethyl cellulose: Synthesis and characterization. *Polymer Bulletin*, *57*, 33–41.

Koschella, A., Fenn, D., Illy, N., & Heinze, T. (2006). Regioselectively functionalized cellulose derivatives: A mini review. *Macromolecular Symposia*, *244*, 59–73.

Koschella, A., Heinze, T., & Klemm, D. (2001). First synthesis of 3-O-functionalized cellulose ethers via 2,6-di-O-protected silyl cellulose. *Macromolecular Bioscience*, *1*, 49–54.

Majewicz, T. G., & Podlas, T. J. (2004). Cellulose ethers. In A. Seidel (Ed.), *Kirk Othmer encyclopedia of chemical technology* (5th ed., pp. 445–466). Hoboken, NJ: John Wiley & Sons, Inc.

Rohleder, E., & Heinze, T. (2010). Comparison of benzyl celluloses synthesized in aqueous naoh and dimethyl sulfoxide/tetrabutylammonium fluoride. *Macromolecular Symposia*, *294*(2), 107–116.

Savage, A. B. (1957). Temperature-viscosity relationships for water-soluble cellulose ethers. *Journal of Industrial and Engineering Chemistry*, *49*, 99–103.

Starks, C. M. (1971). Phase-transfer catalysis. I. Heterogeneous reactions involving anion transfer by quaternary ammonium and phosphonium salts. *Journal of the American Chemical Society*, *93*, 195–199.

Ugelstad, J., Ellingsen, T., & Berge, A. (1966). Effect of the solvent on the reactivity of potassium and quaternary ammonium phenoxides in nucleophilic substitution reactions. III. *Acta Chemica Scandinavica*, *20*, 1593–1598.