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Water-soluble 3-*O*-(2-methoxyethyl)cellulose: synthesis and characterization

Thomas Heinze*,† and Andreas Koschella

Centre of Excellence for Polysaccharide Research, Friedrich Schiller University of Jena, Humboldtstrasse 10, D-07743 Jena, Germany

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Abstract—The synthesis of novel 3-*O*-(2-methoxyethyl)cellulose via 2,6-di-*O*-thexyldimethylsilyl ethers was successfully carried out. Treatments of 3-*O*-(2-methoxyethyl)-2,6-di-*O*-thexyldimethylsilylcellulose with tetrabutylammonium fluoride trihydrate led to a complete removal of the protecting groups. Structure characterization carried out by means of 1D and 2D NMR spectroscopy proves a high regioselectivity. The novel cellulose ether is soluble in dimethyl sulfoxide, *N*,*N*-dimethylacetamide, *N*-methylpyrrolidone, and water. Size-exclusion chromatography revealed a distinct aggregation behavior in water.

Keywords: 3-*O*-(2-Methoxyethyl)cellulose; Regioselective synthesis; Thexyldimethylsilyl protecting group; NMR spectroscopy; Size-exclusion chromatography

1. Introduction

Cellulose ethers are important biopolymer derivatives used in various applications. In particular, mixed cellulose ethers including hydroxyethyl- and hydroxypropylmethylcelluloses are commercially produced in large scale and are applied in various fields.[1] The technical synthesis is carried out by conversion of alkali cellulose with the corresponding epoxide and methyl chloride to give a random distribution of the substituents within the anhydroglucose unit and along the polymer chain. Moreover, the newly formed hydroxyl groups of the hydroxyethyl- and hydroxypropyl moieties may be methylated. It is well known that the distribution of functional groups may influence the properties of cellulose ethers.[2] To gain detailed information about the influence of the structure on properties, and hence to improve the quality of the technical cellulose ethers, not only a comprehensive structure characterization but also cellulose ethers with a defined functionalization pattern are indispensable for the establishment of the structure–property relationships. Regarding commercially important cellulose ethers, 3-*O*-methylcellulose synthesized via 2,6-di-*O*-thexyldimethylsilylcellulose is insoluble in water and organic liquids,[3] while 3-*O*-ethylcellulose is well soluble in water showing a different thermal transition temperature compared to conventional ethyl cellulose.[4] These results lead to the question of whether 3-*O*-(2-methoxyethyl)cellulose (MEC) can be synthesized via 2,6-di-*O*-protected cellulose. As already mentioned, a 2-methoxyethyl moiety may be present in commercial hydroxyethylcellulose due to methylation of the hydroxyl group formed by the reaction of the ethylene oxide with the biopolymer. Moreover, the properties of regioselectively functionalized 3-*O*-MEC are of interest. In the present paper, the synthesis and detailed structure characterization of 3-*O*-MEC is discussed.

2. Results and discussion

The silylation of cellulose **1a** (spruce sulfite pulp, mercerized) and **1b** (Avicel) in *N*,*N*-dimethylacetamide (DMA)/LiCl with thexyldimethylchlorosilane

* Corresponding author. Tel.: +49 3641 948 270; fax: +49 3641 948 272; e-mail: thomas.heinze@uni-jena.de
† Member of the European Polysaccharide Network of Excellence (EPNOE).
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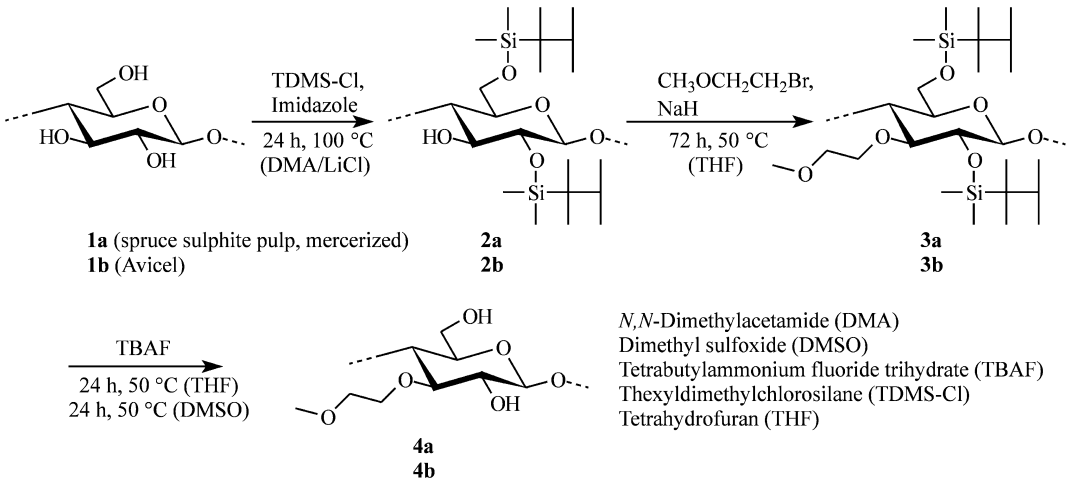


Scheme 1. Reaction scheme for the preparation of 3-*O*-(2-methoxyethyl)cellulose using the thexyldimethylsilyl protecting group.

(TDMS-Cl) in the presence of imidazole leads to 2,6-di-*O*-thexyldimethylsilylcellulose (2,6-di-*O*-TDMS-cellulose, **2a**–**b**) (Scheme 1).[3,4] The product can be simply isolated by filtration due to the fact that it becomes insoluble in the reaction mixture and precipitates. The degree of substitution of TDMS groups (DS_{Si}) was 1.98 (**2a**) and 2.10 (**2b**). The polymer is soluble in *n*-hexane, toluene, tetrahydrofuran (THF), and chloroform.

Derivatives **2a** and **2b** were allowed to react with an excess of 1-bromo-2-methoxyethane in the presence of sodium hydride as base (10 mol/mol modified anhydroglucose unit, AGU) in THF for 4 h at room temperature and 3 d at 50 °C. The products (**3a**, **3b**) isolated by a typical workup procedure were soluble in organic solvents like *n*-hexane, toluene, THF, and chloroform. All typical absorption bands of the modified repeating unit appear in the FTIR spectrum: 2959, 2874 (CH), 1466 (CH, CH_2), 1384 (CH_3), 1252 (SiC), 1125, 1091, 1044 (COC), 832, and 777 cm^{-1} (SiC). In addition, FTIR spectroscopy clearly revealed complete etherification of the hydroxyl moieties by the absence of the OH vibration.

For deprotection, polymers **3a** and **3b** were treated with tetrabutylammonium fluoride trihydrate (TBAF) in THF for 24 h at 50 °C. The partially desilylated sample obtained was treated again with TBAF in dimethyl sulfoxide (DMSO) to yield the silicon-free sample **4a** and **4b** showing no signals of silicon-containing moieties in the ^1H NMR spectrum (Fig. 1). In contrast, studies on 3-*O*-methylcellulose showed that a small silicon content remained in the sample even after several desilylation and purification steps.[3] Traces of TBAF could be removed by dialysis as confirmed by means of ^1H NMR spectroscopy.

Structure characterization of 3-*O*-(2-methoxyethyl)-cellulose (3-*O*-MEC, **4a** and **4b**) was carried out by means of NMR spectroscopy. DEPT 135 NMR spectroscopy in D_2O could be applied because no quaternary carbon atoms are present in the molecule that will not be detected with this technique (Fig. 2). The carbon atom of position 1 appears at 101.9 ppm. No signal splitting is observed due to the absence of substituents at position 2. The alkyl substituent at position 3 causes a downfield shift of the corresponding signal to 82.3 ppm. Further peaks of the modified AGU appear at 75.8 ppm (position 4), 71.7 ppm (positions 2 and 5), and 59.9 ppm (position 6). Signals at 71.8 and 71.1 ppm (methylene groups 7 and 8) as well as at 58.2 ppm (OCH_3 group 9) correspond to the 2-methoxyethyl substituent.

The DEPT 135 NMR spectrum revealed the regular structure of the 3-*O*-(2-methoxyethyl)cellulose, but 2D NMR measurements were not possible due to comparably broad peaks. This line broadening is caused by intra- and intermolecular interactions attributed to the presence of hydroxyl groups at positions 2 and 6. Therefore,

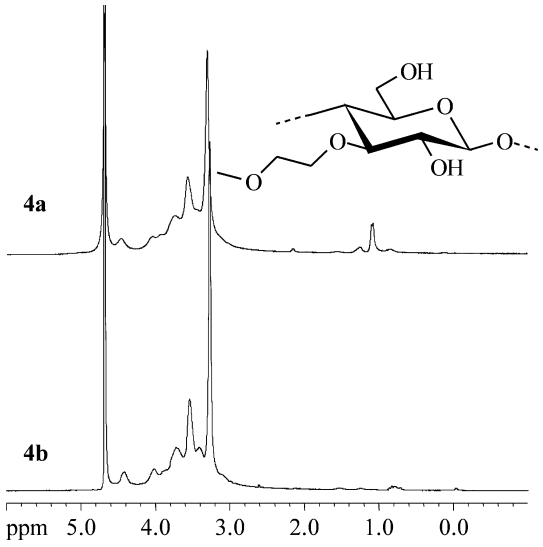


Figure 1. ^1H NMR spectra of 3-*O*-(2-methoxyethyl)cellulose (**4a** and **4b**) recorded in D_2O after two consecutive treatments with tetrabutylammonium fluoride trihydrate. Sample **4b** was additionally purified by dialysis.

conversion of **4a** and **4b** with Ac_2O in the presence of pyridine and *N*,*N*-dimethylaminopyridine afforded 2,6-di-*O*-acetyl-3-*O*-(2-methoxyethyl)cellulose (**5a**, **5b**, Scheme 2).

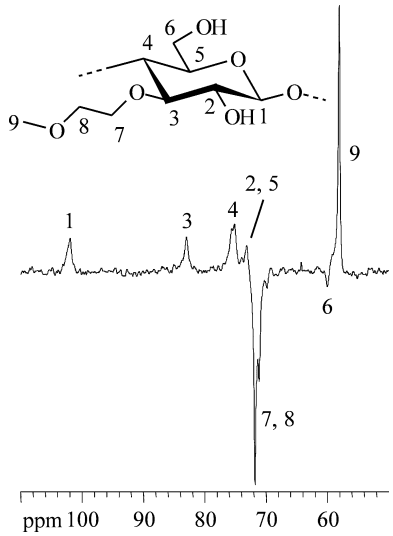
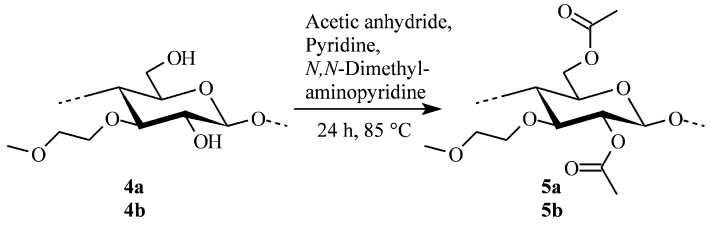


Figure 2. DEPT 135 NMR spectrum of 3-*O*-(2-methoxyethyl)cellulose **4a** prepared from spruce sulfite pulp recorded in D_2O.

These samples are freely soluble in chloroform and do not form hydrogen bonds, and, hence, well-resolved 2D NMR spectra could be acquired (COSY and HSQC/DEPT, Fig. 3). The peak assignment based on combining COSY- and HSQC/DEPT experiments is listed in Table 1. A DS of 1.02 was calculated considering the peak areas of the CH_3 signal at 2 ppm and the signal of position 2 at about 4.79 ppm.

Further peaks appear in the 2D NMR spectra if the threshold has been set low. These are caused by substructures that accompany the 2,6-di-*O*-acetyl-3-*O*-(2-methoxyethyl) repeating units. As concluded from the peak intensity, the content of the substructures, which are most probably 6-*O*-acetyl-2,3-di-*O*-(2-methoxyethyl) repeating units, is very low, below 5%.

Polymers **4a** and **4b** are soluble in aprotic dipolar solvents like DMSO, DMA, and *N*-methylpyrrolidone. Both samples swell in *N*,*N*-dimethylformamide (DMF) and are insoluble in organic solvents of lower polarity. Moreover, it is interesting to note that 3-*O*-MEC is water soluble.



Scheme 2. Preparation of 2,6-di-*O*-acetyl-3-*O*-(2-methoxyethyl)cellulose (**5a** and **5b**).

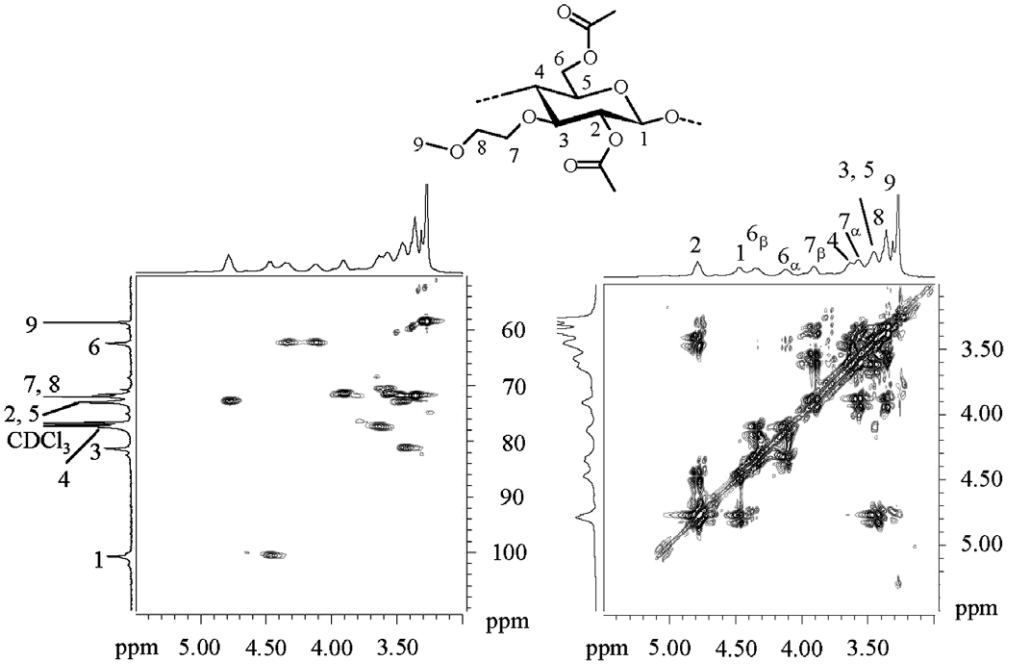


Figure 3. HSQC/DEPT NMR- (left) and COSY NMR spectrum (right) of 2,6-di-*O*-acetyl 3-*O*-(2-methoxyethyl)cellulose (**5a**) recorded in $CDCl_3$.

Table 1. Chemical shifts of the NMR signals of 2,6-di-*O*-acetyl-3-*O*-(2-methoxyethyl)cellulose (**5a**) measured in $CDCl_3$

Signal of position[a]	Chemical shift (ppm)	
	^1H	^{13}C
1	4.46	100.7
2	4.79	72.8
3	3.46	81.3
4	3.62	77.5
5	3.46	72.8
6	4.13, 4.35	62.4
7	3.90, 3.57	72.0, 71.5
8	3.36	72.0, 71.5
9	3.31	58.6
$COCH_3$	2.07	20.5
$C{=}O$	—	170.1, 169.1

[a] Numbering of position, see Figure 2.

SEC of 3-*O*-MEC dissolved in water (stabilized with 0.1% NaN_3) shows a high tendency of the polymer to aggregate. The elution profile obtained is multimodal possessing maxima at 90,000, 620,000, and 4,000,000 g/mol (Fig. 4). Although the molar mass of 90,000 g/mol corresponds to a degree of polymerization (DP) of 407 that is in the range of the starting cellulose (DP 560, **1a**), this molar mass results from aggregation (see below). The higher molar masses found (620,000 and 4,000,000 g/mol) are undoubtedly attributed to aggregates. SEC of the sample dissolved in 0.1 mol/L of aqueous $NaNO_3$ (stabilized with 0.1% NaN_3) and DMSO give different results compared to the measurements in water. The SEC profile obtained in 0.1 mol/L aqueous $NaNO_3$ leads to a molar mass of 33,000 g/mol for **4a** and 32,000 g/mol for **4b**. The molar masses determined in DMSO as eluent are slightly higher. Detailed results of the SEC studies are summarized in Table 2. It becomes obvious that both 0.1 mol/L aqueous $NaNO_3$ and DMSO are appropriate solvents for the determination of the molar mass of the novel cellulose ether. A number-average of DP (DP_n) of 77 found in aqueous $NaNO_3$ solution and of DP_n of 138 determined in DMSO as eluent is reasonable and shows that the multistep synthesis yields remarkable degradation of the biopolymer (sample **4a**). Comparable results were found for the sample prepared from cellulose **1b**. DP_n values of 46 ($NaNO_3$) and of 100 (DMSO) were calculated. Nevertheless, these biopolymer derivatives could be used for the evaluation of clear structure–property relations and for the NMR signal assignment of commercial cellulose ethers of the hydroxyethyl- and hydroxypropylmethylcellulose family.

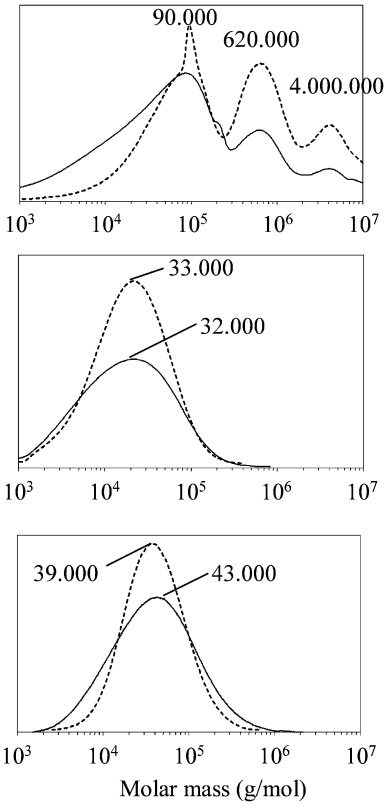


Figure 4. Size-exclusion chromatograms of 3-*O*-(2-methoxyethyl)cellulose (**4a**, dashed line; **4b**, solid line) using water (top), 0.1 mol/L sodium nitrate (middle) and dimethyl sulfoxide (bottom) as eluent.

To summarize, 3-*O*-MEC could be prepared for the first time by applying a protecting group technique. At present, this novel cellulose derivative is included in studies about structure–property relationships of cellulose ethers.

3. Experimental

3.1. General methods

Spruce sulfite pulp **1a** (Fluka, degree of polymerization, DP 560) and microcrystalline cellulose **1a** (E. Merck, microcrystalline cellulose, DP 419) were dried at 105 °C in vacuum over KOH for 24 h. LiCl (Fluka) was dried at 130 °C in vacuum over KOH for 24 h. *N*,*N*-Dimethylacetamide (DMA, Acros Organics), thexyldimethylchlorosilane (TDMS-Cl, ABCR Karlsruhe), tetrabutylammonium fluoride trihydrate (TBAF, Fluka), and all other chemicals were used as received. Anhydrous tetrahydrofuran (THF) over molecular sieves was obtained from Fluka. 1-Bromo-2-methoxyethane was purchased from Aldrich. Sodium hydride (60% in mineral oil, Fluka) was washed with *n*-hexane and pentane and dried at room temperature in vacuum. FTIR spectra were acquired with a Nicolet Avatar 370 DTGS spectrometer using the KBr technique. NMR spectra were obtained with Bruker Avance 250 (250 MHz) and Avance 400 (400 MHz) spectrometers in $CDCl_3$ or D_2O (sample concentration, 5–10%) at a temperature up to 70 °C using standard pulse sequences for ^1H-, ^{13}C-, DEPT 135-, and 2D (COSY, HSQC/DEPT) NMR spectra. The scan number was 16 for

Table 2. Size-exclusion chromatography of 3-*O*-(2-methoxyethyl)cellulose (**4a** and **4b**) in aqueous sodium nitrate (0.1 mol/L) and dimethyl sulfoxide (DMSO)

Sample	Eluent							
	0.1 mol/L $NaNO_3$				DMSO			
	M_w[a]	M_n[b]	PDI[c]	DP_n[d]	M_w[a]	M_n[b]	PDI[c]	DP_n[d]
4a	41,480	16,870	2.459	77	57,433	30,546	1.8802	138
4b	42,100	10,067	3.944	46	71,496	21,975	3.2536	100

[a] Weight-average molar mass in g/mol.
[b] Number-average molar mass in g/mol.
[c] Polydispersity index.
[d] Number-average degree of polymerization calculated for a degree of substitution of 1.

Table 3. SEC systems used for the determination of the molecular mass and molecular mass distribution of 3-*O*-(2-methoxyethyl)cellulose

	Eluent		
	Water (0.05% NaN_3)	Dimethyl sulfoxide (0.25% LiBr)	0.1 M aqueous $NaNO_3$ (0.1% NaN_3)
Flow (mL/min)	1.0	0.5	1.0
Columns	PLaquaGel OH60 PLaquaGel OH50 PLaquaGel OH40 (Polymer Standards Laboratories, Darmstadt, Germany)	Novema 3000 Novema 300 (Kromatek, Great Dunmow, Essex, UK)	Suprema 1000+ Suprema 100 (Kromatek, Great Dunmow, Essex, UK)
Length (mm)	300	300	300
Inner diameter (mm)	8	8	8
Injection volume (μL)	100	50	100
Sample concentration (mg/mL)	2.36 (sample **4a**) 1.80 (sample **4b**)	3.16 (sample **4a**) 2.38 (sample **4b**)	2.96 (sample **4a**) 2.54 (sample **4b**)
Calibration standard	Dextran[a] Pullulan	Dextran[a] Pullulan	Dextran[a] Pullulan
Solvent for calibration	Eluent	Eluent	Eluent

[a] For $M < 10^4$ g/mol.

^{1}H- and up to 65,000 for ^{13}C NMR spectra. A JASCO SEC system was applied consisting of a degasser DG 980-50, pump PU 980, UV detector 975 ($\lambda = 254$ nm), refractive index detector 930, and a column oven working at 30 °C (Table 3).

3.2. 2,6-Di-*O*-thexyldimethylsilyl cellulose (2a)

Spruce sulfite pulp **1a** (60 g, 0.37 mol) was stirred in 2 L of aq 18% (w/v) NaOH for 1 h at room temperature and filtered off. The cellulose was thoroughly washed with water until neutral. The wet cellulose was stirred in 1 L of DMA overnight at room temperature. After filtration, it was washed with DMA twice, filtered off, and immediately used.

The treated cellulose (60 g, 0.37 mol) was slurried in 2.5 L of DMA and stirred for 2 h at 120 °C under exclusion of moisture. After cooling down to room temperature, 210 g LiCl was added in three portions, and stirring was continued without further heating until dissolution of the cellulose was complete. Imidazole (120 g, 1.76 mol) was dissolved in the viscous and slightly turbid solution, followed by the addition of 272 g (1.52 mol) TDMS-Cl. The mixture was heated to 100 °C and allowed to stir for 24 h. After cooling down to room temperature, the polymer was filtered off, washed with 20 L of water and 5 L of EtOH prior to drying in vacuum with increasing temperature up to 60 °C.

Yield: 148 g (90%); DS: 1.98, based on the silicon content of 12.5%. FTIR (KBr): 3503 (OH), 2960 (CH), 1467 (CH, CH_2), 1374 (CH_3), 1254 (SiC), 1120, 1077, 1038 (COC), 833, and 777 (SiC) cm^{-1}.

The polymer is soluble in THF and chloroform.

3.3. 3-*O*-(2-Methoxyethyl)-2,6-di-*O*-thexyldimethylsilyl-cellulose (3a)

2,6-Di-*O*-TDMS-cellulose **2a** (10 g, 0.0223 mol) was dissolved in 700 mL of anhydrous THF under exclusion of moisture. After addition of 5.9 g (0.25 mol, 11 mol/mol anhydroglucose unit, AGU) NaH and 30.2 g (0.217 mol, 10 mol/mol AGU) 1-bromo-2-methoxyethane, a gelation occurred. During stirring at room temperature, the mixture liquefied and was allowed to stir for 72 h at 50 °C. After cooling down to room temperature, 200 mL of 2-PrOH was carefully added to destroy the excess NaH, followed by 100 mL of water. After pouring the mixture in 3500 mL of water and neutralization with HOAc, the polymer was collected, washed with 200 mL of water, 2500 mL of

MeOH, and dried in vacuum with increasing temperature up to 60 °C. Yield: 10.5 g (93.2%) based on $DS_{2\text{-Methoxyethyl}} = 1$ and $DS_{TDMS} = 2$. FTIR (KBr): 2959, 2874 (CH), 1466 (CH, CH_2), 1384 (CH_3), 1252 (SiC), 1125, 1091, 1044 (COC), 832, and 777 (SiC) cm^{-1}.

3.4. 3-*O*-(2-Methoxyethyl)cellulose (4a)

3-*O*-(2-Methoxyethyl)-2,6-di-*O*-thexyldimethylsilylcellulose (**3a**, 10.5 g, 0.021 mol) was dissolved in 200 mL of anhydrous THF. The mixture was allowed to stir for 24 h at 50 °C after addition of 26.5 g (0.084 mol, 2 mol per mol TDMS group) of TBAF. The polymer was precipitated with 2-PrOH, washed with 2-PrOH, and dried in vacuum. After dissolving the crude product in 100 mL of DMSO and addition of 10 g (0.03 mol) TBAF, stirring was continued for 24 h at 50 °C. The polymer was isolated by precipitation in 2-PrOH, washed with 2-PrOH, and dried in vacuum at 60 °C. Yield: 4.0 g (84%). DS: 1.02 determined by means of ^{1}H NMR spectroscopy of the peracetylated derivative. FTIR (KBr): 3437 (OH), 2958, 2933, 2874 (CH, CH_2), 1638 (H_2O), 1461 (CH, CH_2), 1372 (CH_3), 1156, 1069 (COC) cm^{-1}.

3.5. 2,6-Di-*O*-acetyl-3-*O*-(2-methoxyethyl)cellulose (5a)

In a typical procedure, 3-*O*-(2-methoxyethyl)cellulose (**4a**, 0.5 g, 0.003 mol) was stirred with 12.5 mL (0.154 mol) of pyridine, 12.5 mL (0.132 mol) of Ac_2O, and 0.1 g (0.8 mmol) *N*,*N*-dimethylaminopyridine under exclusion of moisture. The mixture was allowed to react for 24 h at 85 °C and was precipitated in 150 mL of 2-PrOH after cooling down to room temperature. The polymer was filtered off, washed with 2-PrOH, and dried in vacuum at 60 °C. ^{1}H NMR ($CDCl_3$): δ 4.79 (position 2), 4.46 (position 1), 4.35, 4.13 (position 6), 3.90, 3.57 ($OC\mathbf{H}_2CH_2OCH_3$), 3.62 (position 4), 3.46 (position 3 and 5), 3.36 ($OCH_2C\mathbf{H}_2OCH_3$) 3.31 ($OCH_2CH_2OC\mathbf{H}_3$).

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