

FUNCTIONALIZATION PATTERN OF TERT-BUTYLDIMETHYLSILYL CELLULOSE EVALUATED BY NMR SPECTROSCOPY

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Tert-butyldimethylsilyl cellulose with a degree of substitution (DS) of up to 2 could be obtained by homogeneous conversion of the biopolymer with tert-butyldimethylchlorosilane in *N,N*-dimethyl acetamide/LiCl in the presence of imidazole. The cellulose derivatives were characterized in detail by means of two-dimensional NMR spectroscopic techniques including subsequent derivatization of the original polymer by consecutive methylation-desilylation-acetylation. The very well resolved NMR spectra indicate that, dependent on the reaction temperature, 2,6-di-*O*-tert-butyldimethylsilyl moieties are the main repeating units. 3,6-di-*O*- and 6-mono-*O* functionalized repeating units were identified in very small amounts if the reaction is carried out at room temperature. Additionally, 2,3,6-tri-*O*-silylated functions appear if reaction is carried out at temperature of 100°C. Thus, a novel path for regioselective protection of position 2 and 6 for cellulose was established.

Keywords: Cellulose, Consecutive methylation-desilylation-acetylation, NMR, Protecting group technique, Regioselective functionalization, Tert-butyldimethylchlorosilane

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INTRODUCTION

The conversion of cellulose with reactive trialkylsilyl compounds yields organo-soluble cellulose derivatives that are interesting intermediates to form both fibres (Hermanutz et al. 2001) and ultrathin cellulose films, applying the Langmuir-Blodgett technique and subsequent desilylation (Schaub et al. 1993). Trialkylsilyl compounds with at least one bulky moiety are useful protecting groups in order to obtain products with a controlled functionalization pattern by the subsequent reaction of the remaining hydroxyl groups and deprotection. For example, the reaction of cellulose with thexyldimethylchlorosilane yields the 6-*O*-protected derivative, provided that heterogeneous reaction conditions are applied. Thus, 2,3-*O*-functionalized cellulose ethers and esters are available, on one hand (Klemm and Stein 1995). On the other, it was shown that the homogeneous silylation of the cellulose dissolved in *N,N*-dimethyl acetamide (DMA) in combination with LiCl leads to 2,6-di-*O*-thexyldimethylsilyl cellulose that is an appropriate intermediate for the preparation of 3-*O*-functionalized cellulose ethers (Koschella et al. 2006a; Petzold et al. 2004; Koschella et al. 2001). It clearly appeared that regioselectively substituted cellulose derivatives show different properties compared to the conventional products. Thus, regiochemistry is a helpful tool to design the properties.

In the context of protecting group technique with cellulose, our interest was focused on the tert-butyldimethylsilyl moiety. As early as 1987 Pawlowski et al. have found that the conversion of cellulose dissolved in DMA/LiCl with *N*-methyl-*N*-(tert-butyldimethylsilyl) trifluoroacetamide leads to the corresponding silyl cellulose with a degree of substitution (DS) of about 0.7 with a preferred functionalization at position 6 as revealed by solid state ^{13}C NMR spectroscopy (Pawlowski et al. 1987). Moreover, tert-butyldimethylsilyl cellulose with a DS of 0.96 prepared in DMA/LiCl possesses a selective modification of position 6 (Klemm et al. 1990). However, no information about the functionalization pattern of tert-butyldimethylsilyl cellulose with DS values above 1 is available. Consequently, the conversion with cellulose dissolved in DMA/LiCl with tert-butyldimethylchlorosilane was studied, and the products were characterized in detail applying two-dimensional NMR spectroscopic techniques including subsequent derivatization of the original polymer by consecutive methylation-desilylation-acetylation, which is very useful in order to get well resolved NMR spectra appropriate for the evaluation of the functionalization pattern.

EXPERIMENTAL

Materials

Cellulose (**1**) (Avicel, degree of polymerization, DP=250, Fluka) and LiCl (Merck) were dried at 100°C under vacuum prior to use. *N,N*-Dimethyl acetamide (DMA, Acros) was stored over molecular sieves. Tert-butyldimethylchlorosilane (TBS chloride, ABCR) was stored under argon atmosphere. Sodium hydride (Fluka, suspension in mineral oil) was washed with hexane and pentane, dried in vacuum at room temperature and stored under argon atmosphere. All other chemicals were used as received.

Methods

Tert-butyldimethylsilyl cellulose (9), general procedure

1.0 g (6.17 mmol) cellulose (**1**) was suspended in 30 mL DMA and stirred at 120°C for 2 h under exclusion of moisture. After cooling to 80°C, LiCl (1.8 g) was added and stirring was continued without heating until complete dissolution of the polymer occurred. Under vigorous stirring, imidazole (1.76 g, 25.91 mmol) was added. After dissolution of the imidazole, TBS chloride (3.25 g, 21.59 mmol) was added and stirring was continued for 24 h at room temperature (after about 1 h precipitation occurred). The mixture was added to 500 ml phosphate buffer (500 ml water, 3.57 g K_2HPO_4 , 1.77 g KH_2PO_4), the solid material was filtered off, washed with water (three times with 500 ml), two times with ethanol (300 ml) and dried in vacuum at 100°C.

Yield: 2.2 g; Degree of substitution (DS): 1.98 (determined by ^1H NMR spectroscopy after methylation, desilylation and peracetylation)

Tert-butyldimethylsilyl methylcellulose (9a), general procedure

To 1.6 g (4.09 mmol) 2,6-di-*O*-tert-butyldimethylsilyl cellulose (**9**) dissolved in 30 ml THF, 0.98 g (40.98 mmol) NaH (10 mol pro mol AGU) were added. The suspension obtained was stirred for 10 min and subsequently 2.56 ml (40.98 mmol)

iodomethane (10 mol pro mol AGU) was added. After stirring for 24 h at room temperature, the reaction mixture was allowed to react for additionally 48 h at 50°C. After cooling to room temperature, 5 ml 2-propanol and subsequently 5 ml water was carefully added. The mixture was put into 500 ml phosphate buffer (500 ml water, 3.57 g K_2HPO_4 , 1.77 g KH_2PO_4) and the precipitate was isolated by filtration. The precipitate was washed with 500 ml water four times and dried at 100°C under vacuum.

Yield: 1.44 g.

Desilylation of tert-butyldimethylsilyl methylcellulose (9b), general procedure

To 1.2 g (2.97 mmol) 2,6-di-*O*-tert-butyldimethylsilyl-3-mono-*O*-methylcellulose **9a** suspended in 20 ml THF, 3.75 g (11.88 mmol) TBAF \cdot 3H₂O (4 mol pro mol AGU) were added and the mixture was allowed to react for 24 h at 50°C under stirring. After cooling to room temperature, the mixture was put into 100 ml methanol and the precipitated was isolated by filtration. The product (non-dried) was dissolved in DMSO and again treated with 1.5 g (4.76 mmol) TBAF \cdot 3H₂O for 24 h at 50°C under stirring. The product was precipitated in 100 ml methanol. After filtration, washing with 50 ml methanol (four times) and drying at 100°C under vacuum product **9b** was obtained.

Yield: 0.48 g

Acetylmethyl cellulose (9c), general procedure

To 250 mg methylcellulose **9b** in 5 ml pyridine, 5 ml acetic anhydride and 25 mg DMAP were added. After a reaction time of 24 h at 80°C and cooling to room temperature, the mixture was put into 50 ml ethanol. The product was washed 5 times with 30 ml ethanol and dried at 100°C under vacuum.

Yield: 0.22 g

Measurement

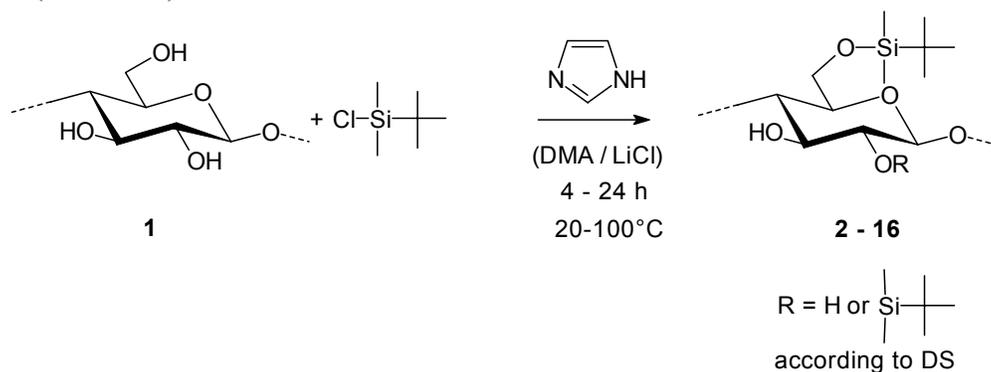
The FTIR spectra were recorded with a NICOLET AVATAR 370 DTGS spectrometer by using the KBr technique. The NMR spectra were acquired with a Bruker AVANCE 250 and AVANCE 400 in CDCl₃ (concentration of the sample: 5%) at a temperature of 30°C with the standard pulse sequences for ¹H-, ¹³C-, DEPT135-, and two-dimensional NMR spectroscopy. For the ¹H NMR spectra 16 scans and for ¹³C NMR spectra up to 55,000 scans were accumulated.

RESULTS AND DISCUSSION

Homogeneous silylation of cellulose with hexyldimethylchlorosilane is a valuable synthesis path to get cellulose derivatives that are modified at positions 2 and 6. In the context of studies on regiochemistry of polysaccharides, our interest was focused on tert-butyldimethylchlorosilane (TBS chloride) with less bulky tert-butyl moiety to study the reactivity of this silylating agent with regard to cellulose. Moreover, due to the fact that hexyldimethylchlorosilane is expensive and the removal of the protecting groups introduced after subsequent modification of the remaining OH groups is difficult,

alternative protecting groups are really needed. TBS chloride was not studied regarding a 2,6-di-*O*-protection of cellulose up to now.

Thus, conversions starting with cellulose dissolved in *N,N*-dimethyl acetamide (DMA) in combination with LiCl were studied, applying TBS chloride as reagent in the presence of imidazole at varying time, temperature, and molar ratio of cellulose to reagent (Scheme 1).



Scheme 1. Silylation of cellulose with tert-butyldimethylchlorosilane

After a usual work-up procedure, a product with a DS_{Si} of 1.85 (**2**) was obtained, applying a molar ratio of 1:3.0:3.6 (cellulose:TBS chloride:imidazole) and a reaction time of 2 h. An increase of the reaction time up to 24 h yields a slight increase of the DS_{Si} (Table 1, sample **4** and **12**).

Table 1. Conditions for and Results of the Conversion of Cellulose with Tert-butyldimethylchlorosilane in *N,N*-dimethyl acetamide/LiCl in the Presence of Imidazole.

Conditions			Product					
Molar ratio ^{a)}	Time (h)	Temp. (°C)	No.	DS	Solubility ^{c)}			
					THF	CHCl ₃	Toluene	Hexane
1:3.0:3.6	2	20/100	2	1.85	+	+	-(S)	-
1:3.5:4.2	2	20/100	3	1.92	+	+	-(S)	-
1:3.0:3.6	4	20/100	4	1.81	+	+	-(S)	-
1:3.5:4.2	4	20/100	5	1.87	+	+	+	-(S)
1:3.5:4.2	2	20	6	1.71	-S	-S	-	-
1:3.5:4.2	4	20	7	1.76	-(S)	-(S)	-(S)	-
1:3.5:4.2	6	20	8	1.85	+	+	+	-
1:3.5:4.2	24	20	9	1.98	+	+	+	-(S)+
1:3.5:4.2	24	100	10	2.04	-(S)	-(S)	+	+
1:3.5:4.2	24	100 ^{b)}	11	2.12	-(S)	-(S)	+	+
1:3.0:4.2	24	100	12	1.93	+	+	+	-(S)
1:3.0:4.2	24	100 ^{b)}	13	1.99	+	+	+	+
1:4.0:4.8	24	20	14	2.05	+	+	-(S)	-(S)
1:4.0:4.8	24	100	15	2.11	-(S)	-(S)	+	+
1:4.0:4.8	24	100 ^{b)}	16	2.09	-(S)	-(S)	+	+

^{a)} Molar ratio of cellulose:tert-butyldimethylchlorosilane:imidazole
^{b)} Reaction mixture contains additionally toluene
^{c)} + soluble, - insoluble, S swelling, THF tetrahydrofuran

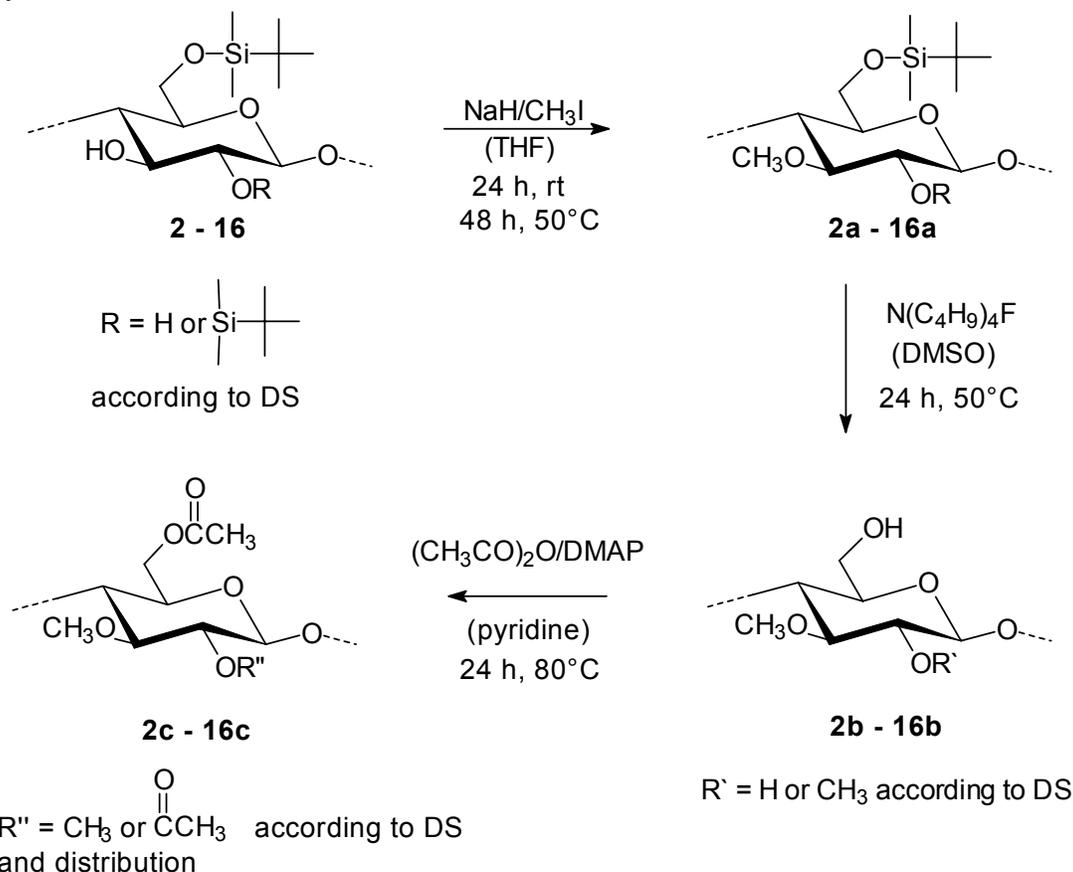
The increase of the molar ratio to 1:3.5:4.2 (cellulose:TBS chloride:imidazole) leads to samples with DS_{Si} values of about 2 after 24 h reaction time both at 20°C and 100°C (samples **9** and **10**).

Due to the fact that the TBS cellulose obtained forms a gel-like state during the reaction, toluene as co-solvent was added. However, no change in DS_{Si} appeared (compare samples **10** and **11**, **12** and **13**, **15** and **16**, Table 1). Even at higher molar ratio of 1:4.0:4.8, the total DS_{Si} does not exceed a value of about 2. Considering total DS_{Si} of the TBS cellulose, the results are comparable with those obtained by the reaction of cellulose with hexyldimethylchlorosilane in DMA/LiCl.

The TBS cellulose samples are well soluble in organic solvents (Table 1). It must be pointed out that slight difference in DS_{Si} may change the solubility significantly. Samples with a DS_{Si} of up to 2 are soluble in tetrahydrofuran and $CHCl_3$, while the solubility in these solvent does not occur at DS_{Si} of 2.1 (samples **11**, **15**, and **16**). On the contrary, samples of comparable high DS_{Si} dissolve even in hexane. From our results, no clear correlation between DS_{Si} and solubility of TBS cellulose in toluene appears. Moreover, slight changes in the functionalization pattern may vary the solubility. Thus, further detailed studies due to a completely structure characterization within AGU and along the biopolymer chain must be carried out. In any case, the samples are soluble in typical organic solvents and can be modified at the remaining hydroxyl groups; this is an important prerequisite to analyse the functionalization pattern because the resolution of NMR spectra of TBS cellulose is not sufficient. Moreover, further alternative analytical tools like GC-MS need subsequent derivatization steps. Thus, the subsequent modification of TBS cellulose is of general interest. According to our experiences in NMR spectroscopy of polysaccharides, it was decided to methylate the remaining hydroxyl groups. Subsequent desilylation and acetylation of hydroxyl groups yields samples that give very well resolved NMR spectra useful for the characterization of the functionalization pattern (Scheme 2, see e.g., Stein and Klemm 1995; Petzold et al. 2003; Heinze 2004; Koschella et al. 2006b). It is known from the consecutive methylation-desilylation-peracetylation of hexyldimethylsilyl celluloses that these reaction steps do not yield any displacement or splitting of the primary functional groups (Erler et al. 1992). Thus, it may be concluded that the chemical conversion used for analytical purpose is also suitable for tert-butyldimethylsilyl cellulose derivatives.

The 1H NMR spectra of samples **15c** and **16c** (Fig. 1) show the amazing result that the silylation of cellulose with TBS chloride under the conditions described yields a preferred functionalization of positions 2 and 6. Consequently, in the spectra the typical signals of 3-mono-*O*-methyl-2,6-di-*O*-acetyl cellulose (peak no. 1-6 in Fig. 1) are found. In addition, there are some signals of very low intensity that corresponds to repeating units with a 2,3-di-*O*-methyl-6-mono-*O*-acetyl- (peak no. 2' and 3') and 2-mono-*O*-methyl-3,6-di-*O*-acetyl- (peak. no. 2'' and 3'') substitution. After line fitting (MestRec) of the 1H NMR spectrum of sample **14**, it could be calculated that 3.9% of 2,3-di-*O*-methyl-6-mono-*O*-acetyl- and 4.2% of 2-mono-*O*-methyl-3,6-di-*O*-acetyl repeating units appear. It must be pointed out that the line fitting and calculation possess a large error; consequently another method like GC-MS should be developed to obtain reliable results regarding the quantitative determination of substructures. The 1H NMR spectra indicate that position 6 of all samples is completely silylated. An additional proof for the 6-*O*-

silylation gave the HSQC DEPT spectrum of the acetyl methyl cellulose obtained via the path shown in Scheme 2 starting from **9**, which possessed only negative signals for the acetylated position 6 as a consequence of the complete silylation of this position of polymer **9**.



Scheme 2. Synthesis path for subsequent methylation, desilylation and acetylation starting from tert-butyldimethylsilyl cellulose.

At a molar ratio of 1:3.5:4.2 (cellulose:TBS chloride:imidazole) a sample with a DS_{Si} of 1.76 (**7**) was obtained after 4 h reaction at 20°C. The ^{13}C NMR spectrum shows that 3-mono-*O*-methyl-2,6-di-*O*-acetyl cellulose is mainly formed (Fig. 2, peaks 1-11). As expected due to the $\text{DS}_{\text{Si}} < 2$, signals for a repeating unit with a functionalization pattern of 2,3-di-*O*-methyl-6-mono-*O*-acetyl moieties are found (Fig. 2; peaks numbered in red and marked with index ‘). The assignment of the peaks in ^1H - and ^{13}C NMR spectra is not only based on the two-dimensional spectroscopy (see following text) but also on the signal assignment carried out by Karakawa et al. (2002). In this work regioselectively functionalized methyl- and acetyl cellulose derivatives were prepared by ring-opening polymerization of α -D-glucopyranose 1,2,4-orthopivalate with a corresponding regioselective functionalization pattern regarding methyl moieties and subsequent acetylation.

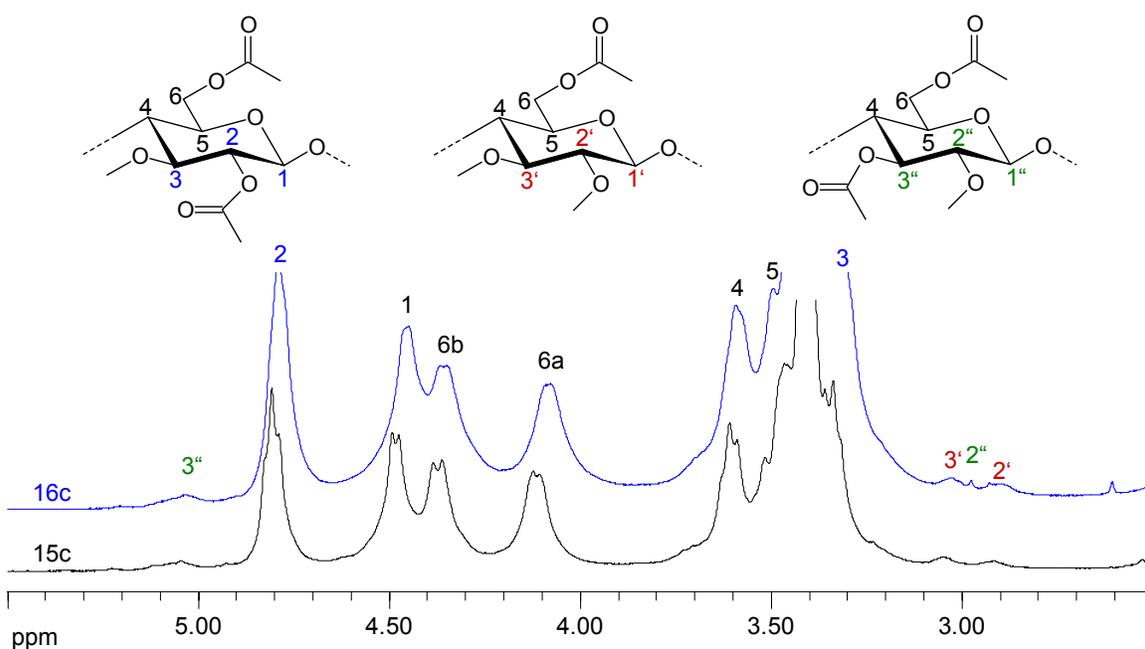


Fig. 1. ^1H NMR spectra of acetyl methyl cellulose **15c** and **16c** in CDCl_3 . Silylation conditions in DMA/LiCl : **15**: molar ratio 1:4.0:4.8 (cellulose:tert-butyldimethylchlorosilane:imidazole), 24 h, 100°C ; **16**: molar ratio 1:4.0:4.8 (cellulose:tert-butyldimethylchlorosilane:imidazole), 24 h, 100°C , addition of toluol.

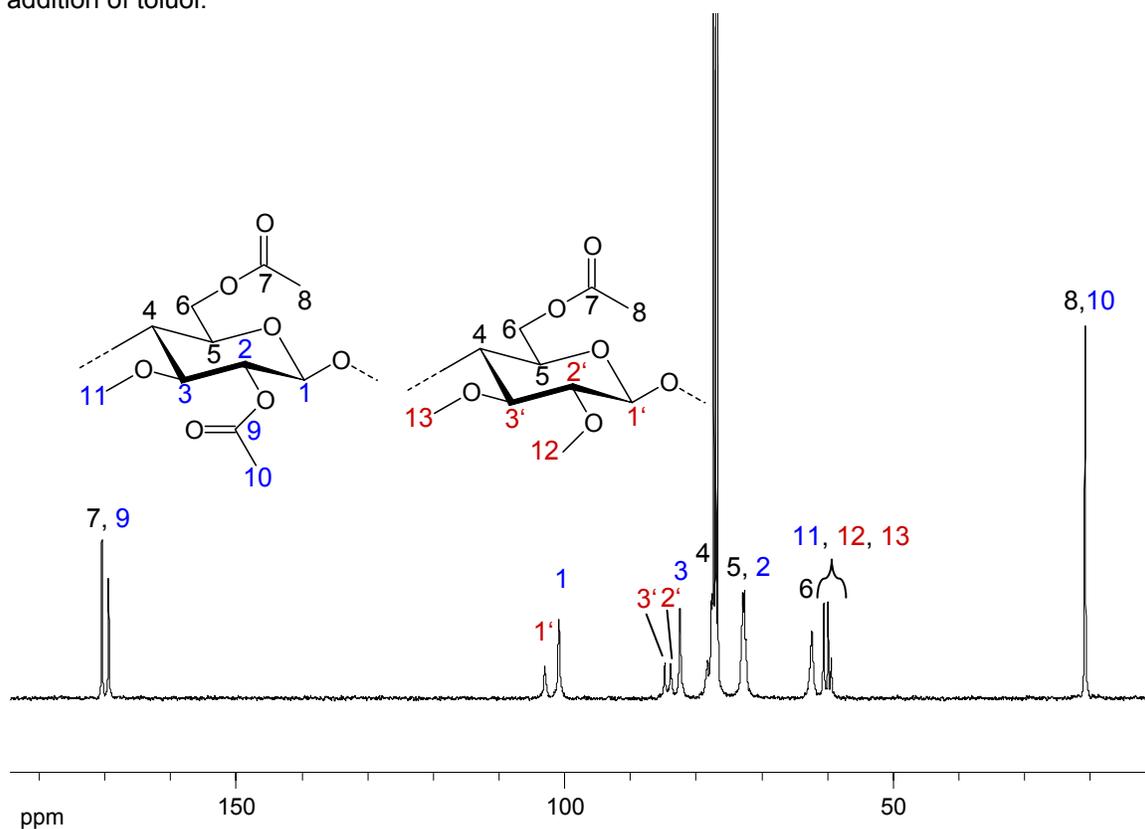


Fig. 2. ^{13}C NMR spectrum of acetyl methyl cellulose **7c** obtained from **7** (DS_{Si} 1.76) in CDCl_3 .

The $^1\text{H}, ^1\text{H}$ COSY NMR spectra of samples **9c** and **15c** additionally clearly indicate that 3-mono-*O*-methyl-2,6-di-*O*-acetyl moiety is the main repeating unit (Fig. 3, peak no. 1-3 in blue). All proton signals of this repeating unit could be identified by following the cross-peaks; beginning with the H-1 signal at 4.48-4.49 ppm, continuing by the H-2 signal at 4.78-4.80 ppm typical for an acetylation at this position and the H-3 signal at 3.32 ppm as a consequence of methylation.

The signals for the protons in position 6 were identified at 4.10 ppm for H-6a and at 4.35-4.37 ppm for H-6b as a result of the acetylation. The proton signals of position 4 (3.58-3.60 ppm) and 5 (3.46-3.47 ppm) could be detected independent of the substructure. Both, 2,3-di-*O*-methyl-6-mono-*O*-acetyl (peak no. 1', 2', and 3') and the 2-mono-*O*-methyl-3,6-di-*O*-acetyl substitution (peak no. 1'', 2'', and 3'') were identified by means of the cross-peaks although with very small amount independent of the reaction conditions. In the COSY NMR spectrum of **15c** (Fig. 3b), small amount of cellulose triacetate was found as revealed by typical peaks for H-1 (1*) at 4.33 ppm, H-2 (2*) at 4.76 ppm, and H-3 (3*) at 5.09 ppm (Heinze et al. 2006 and references herein). On the contrary, these signals could not found in the COSY spectrum of **9c**.

The triacetate structure is a result of trisilylated anhydroglucose units in the tert-butyldimethylsilyl cellulose. Trisilylation depends on the reaction conditions. Products obtained by reactions at room temperature did not contain a trisilylated moiety independent of the molar ratio although the same total DS could be realized as in the case of reactions at higher temperature.

No triacetate structures resulting from the trisilylation were found in the NMR spectra of **9c** (molar ratio 1:3.5:4.2, cellulose:TBS chloride:imidazole, Fig. 3a) as well as of **14c** (molar ratio 1:4.0:4.8, cellulose:TBS chloride:imidazole, data not shown).

However, a reaction at 100°C led to a complex structure of the silyl cellulose, i.e. the polymer contains 2,6-di-*O*-silyl units as the main component, in addition small amounts 6-mono-*O*-silyl, 3,6-di-*O*-silyl- and even 2,3,6-tri-*O*-silyl repeating units independent of the molar ratio. In the NMR spectra of the subsequent acetyl methyl celluloses, triacetate structures as a result of trisilylation were found independent of the molar ratio of the starting silylation reaction (**10**, 1:3.5:4.2, cellulose:TBS chloride:imidazole, data not shown, **15**, 1:4.0:4.8, cellulose:TBS chloride:imidazole, Fig. 3b, Fig. 4).

The assignment of the peaks in the COSY NMR spectra was additionally verified by hetero-nuclear two-dimensional methods. The HSQC DEPT spectrum of **15c** shows the main structure with 3-mono-*O*-methyl-2,6-di-*O*-acetyl moieties and all substructures, which were already identified by COSY NMR spectroscopy, as can be clearly concluded from the cross peaks (Fig. 4).

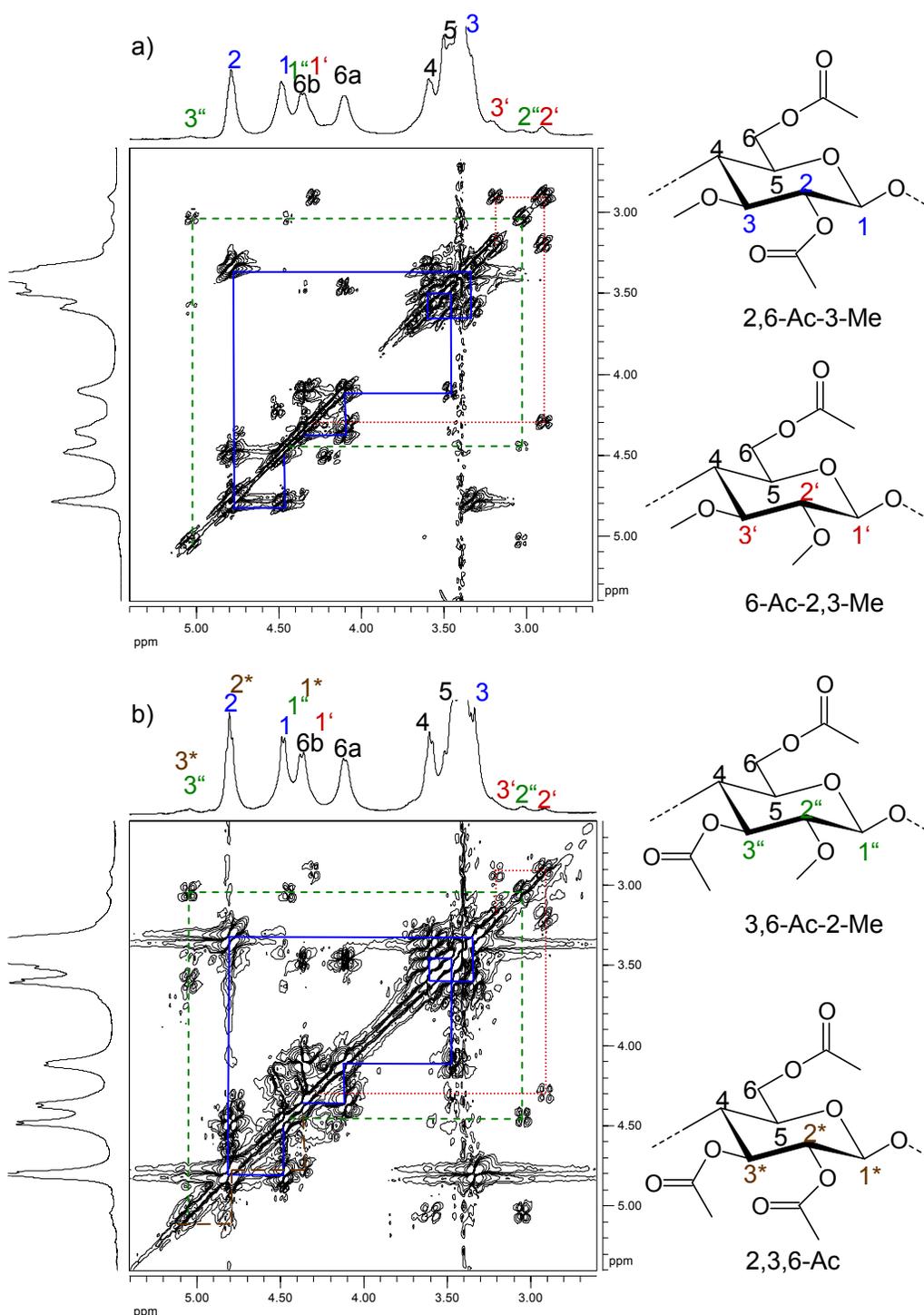


Fig. 3. $^1\text{H}, ^1\text{H}$ COSY NMR spectra of acetyl methyl cellulose **9c** (a) and **15c** (b) in CDCl_3 . Silylation conditions: **9** (DS_{Si} 1.98): molar ratio 1:3.5:4.2 (cellulose:TBS chloride:imidazole), 24 h, 20°C ; **15** (DS_{Si} 2.11): molar ratio 1:4.0:4.8 (cellulose:TBS chloride:imidazole), 24 h, 100°C ; assigned cross-peaks: — cross-peaks of the unit 2,6-di-O-acetyl-3-mono-O-methyl (2,6-Ac-3-Me); cross-peaks of the unit 6-mono-O-acetyl-2,3-di-O-methyl (6-Ac-2,3-Me), positions marked with ' , --- cross-peaks of the unit 3,6-di-O-acetyl-2-mono-O-methyl (3,6-Ac-2-Me), positions marked with " , ——— cross-peaks of the unit 2,3,6-tri-O-acetyl (2,3,6-Ac), positions marked with * .

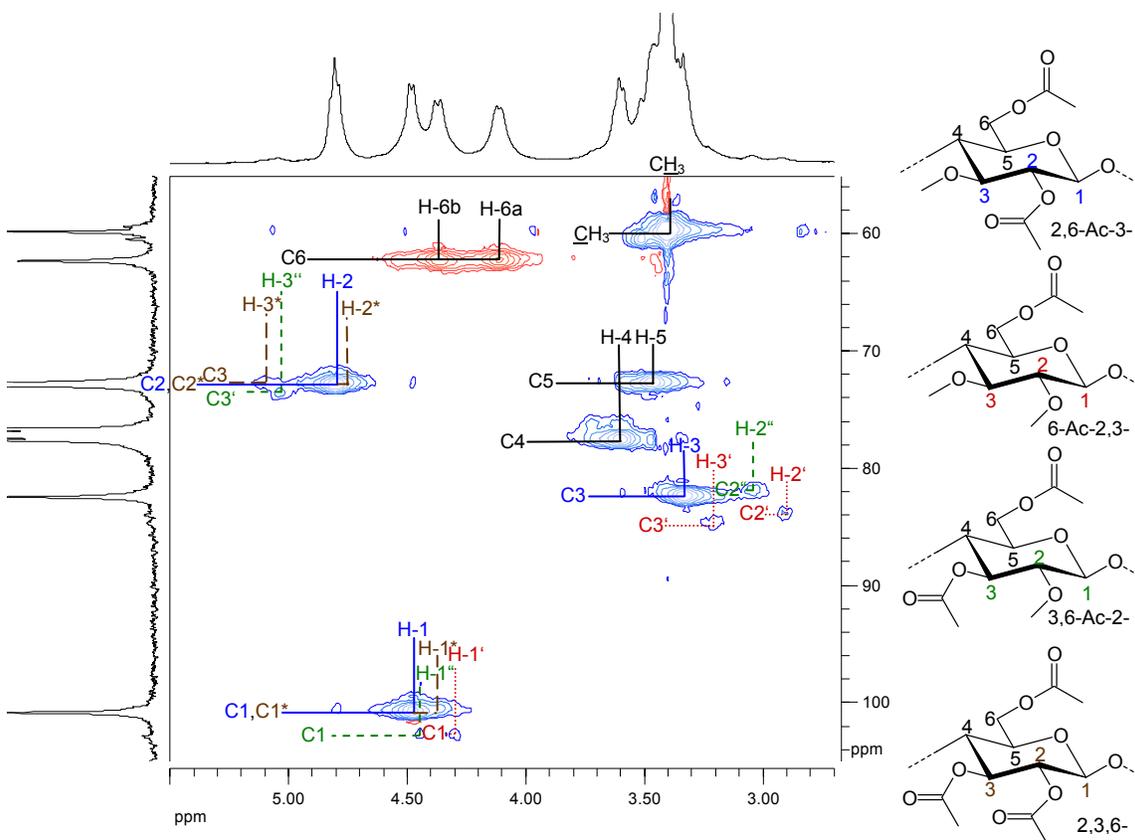


Fig.4. HSQC DEPT NMR spectrum of acetyl methyl cellulose **15c** in CDCl_3 . Silylation conditions: **15** (DS_{Si} 2.11): molar ratio 1:4.0:4.8 (cellulose:TBS chloride:imidazole), 24 h, 100°C ; assigned cross-peaks: — cross-peaks of the unit 2,6-di-*O*-acetyl-3-mono-*O*-methyl (2,6-Ac-3-Me); ... cross-peaks of the unit 6-mono-*O*-acetyl-2,3-di-*O*-methyl (6-Ac-2,3-Me), positions marked with ', --- cross-peaks of the unit 3,6-di-*O*-acetyl-2-mono-*O*-methyl (3,6-Ac-2-Me), positions marked with *, — cross-peaks of the unit 2,3,6-tri-*O*-acetyl (2,3,6-Ac), positions marked with *.

CONCLUSIONS

By silylation of cellulose with tert-butyldimethylchlorosilane in DMA/LiCl, regioselectively functionalized 2,6-di-*O*-protected biopolymer derivative is accessible for the first time. The silylation of cellulose with tert-butyldimethylchlorosilane in DMA/LiCl may show same regioselectivity as the silylation of the biopolymer with thexyldimethylchlorosilane. By means of subsequent methylation and acetylation procedures, it is possible to calculate the DS values and to identify the chemical structure of the repeating units in the polymer chain using one- and two-dimensional NMR techniques. The main structure is 2,6-di-*O*-silylated anhydroglucose. Moreover, it was even possible to analyze substructures including 3,6-di-*O*- and 6-mono-*O*-silyl repeating units, although in small amounts. 2,3,6-tri-*O*-silyl units were formed at high reaction temperatures independent of the molar ratio and the resulting DS. Thus, the results allow synthesizing products with controlled regioselectivity. Moreover, the results show again that NMR spectroscopy is a powerful tool to analyze cellulose derivatives, provided an

appropriate sample preparation is carried out, i.e., methylation, desilylation, and acetylation of the silyl cellulose.

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