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Glycosylated cellulose derivatives with regioselective distributions of pendant glucose moieties

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ABSTRACT

Inspired by the presence of diverse carbohydrates on the surface of biological systems, we present herein a method for the synthesis of sugar-bearing polymers derived from renewable cellulose. In this paper, novel glycosylated cellulose derivatives were successfully synthesized containing a series of subsequent reactions: (1) synthesis of cellulose derivatives with pendant hydroxyl groups via nucleophilic substitution; (2) further sequential reactions containing a novel TEMPO/[bis(acetoxy)iodo]benzene (BAIB)-mediated oxidation of pendant hydroxyl groups, Schiff base formation and reduction in one-pot reaction; and (3) thiol-ene click reaction as an efficient tool to generate cellulose derivatives with pendant glucosyl groups. Furthermore, the glucosyl groups were only linked with the C6 position of anhydroglucose units (AGUs) of cellulose. Moreover, the glycosylated cellulose derivatives could be reversibly cross-linked by 1,4-phenylenediboronic acid at pH 10 and dissociated into single polymer chains by using glucose, which allow such glycolated cellulose derivatives to be interesting responsive materials.

1. Introduction

In nature, carbohydrates on the cell surface perform key regulatory functions in biological and pathological processes, including innate immunity, cell adhesion, cellular communications, cancer metastasis, and so on (Paszek et al., 2014; Takano, Muchmore, & W-Dennis, 1994). Over the past decades, carbohydrate-containing polymers mimicking native glycosylated macromolecules have been successfully synthesized, which are referred to as “glycopolymers” (Wang, Dordick, & Linhardt, 2002). These glycopolymers have wide potential applications in biomedicine and materials science, such as for binding to lectins, for specific self-assembled nanostructures, for stimuli-responsive materials, and so on (Diaz-Dussan et al., 2017; Geng et al., 2007; Godula & Bertozzi, 2010; Ladmiral et al., 2006; Muller, Despras, & Lindhorst, 2016). Glycopolymers are mainly synthesized in two facile manners: via polymerization of sugar-containing monomers (Grande, Baskaran, Baskaran, Gnanou, & Chaikof, 2000; Gupta, Raja, Kaltgrad, Strable, & Finn, 2005; Pati et al., 2012) and through conjugation of pre-modified sugars to polymer backbones (Godula et al., 2009; Wu et al., 2017; You & Schlaad, 2006). In the latter method, the polymer backbones mostly refer to synthetic polymers, while only few contained native molecules as backbone, such as peptides (Sprengard, Schudok, Schmidt, Kretzschmar, & Kunz, 1996; Toyokuni et al., 1994; Wang & Kiick, 2005) and oligosaccharide (Kamitakahara et al., 1998). Only as an example, a series of cyclodextrin-based glycoconjugates have been reported, which showed promising applications in biomedicine (Zhang et al., 2014). However, only very few reports about using polysaccharides as backbone for the introduction of pendant sugar moieties are known, e.g. using chitosan as backbone (Koshiji et al., 2016).

As the most abundant renewable biopolymer on earth, cellulose has been broadly used for more than one century (Klemm, Heublein, Fink, & Bohn, 2005). In recent years, scientists around the world have devoted themselves to seeking new methods to covalently conjugate fluorescent dyes and other moieties onto cellulose and cellulose-derived nanostructures, while maintaining their favorable characteristics (Nielsen, Eyley, Thielemans, & Aylott, 2010). Cellulosic materials with sensing capabilities have charming biomedical applications such as for bioimaging, drug delivery and gene transfection (Czaja, Young, Kawecki, & Brown, 2007; Dong & Roman, 2007; Song et al., 2010).

Cellulose is a polysaccharide with β-(1 → 4)-linked AGUs and three hydroxyl groups are present in each AGU (Heinze, 1998). Chemical derivatization demonstrates an important approach for tuning the physical and chemical properties of cellulose. Traditional modification methods generally involve esterification, etherification, oxidation reaction and nucleophilic displacement reaction, taking the advantage of easy access to reagents and the straightforwardness of the reactions (Dong & Roman, 2007; Heinze, Koschella, Magdaleno-Maiza, & Ulrich, 2001; Heinze et al., 2011). However, harsh conditions, long reaction

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times and modest yields are associated with these conventional methods. In comparison, formation of Schiff base and "click chemistry" that was firstly proposed by K. B. Sharpless and his coworkers in 2001 (Kolb, Finn, & Sharpless, 2001) represent two groups of efficient reactions under mild conditions. In particular, "click chemistry" techniques including thiol-ene, thiol-Michael addition and azide-alkyne Huisgen cycloaddition, have been widely used in polysaccharide chemistry due to its high chemoselectivity in mild surroundings (Breitenbach, Schmid, & Wich, 2017; Jirawutthiwongchai, Krause, Draeger, & Chirachanchai, 2013; Maleki, Edlund, & Albertsson, 2015; Meng & Edgar, 2016).

Herein, we describe a newly designed approach to construct novel glycosylated cellulose derivatives via nucleophilic displacement (S_N) reaction, TEMPO/BAIB-mediated oxidation and subsequent UV-initiated thiol-ene click reaction. Due to the insolubility of cellulose in most solvents, homogenous esterification including carbanilation was used to enhance the solubility of cellulose derivatives. The primary hydroxyl groups were introduced in C6 position by nucleophilic substitution on the tosyl groups, which further allowed the one-pot reaction containing oxidation, Schiff base formation and reduction leading to free thiol groups. After further thiol-ene click reaction, glucosyl groups were introduced onto cellulose backbone, leading to glycosylated cellulose derivatives with reversible responsive properties.

2. Experimental

2.1. Materials

Microcrystalline cellulose (MCC) with the average size of 50 µm from Sigma-Aldrich (Steinheim, Germany) was dried at 80 °C under the vacuum of less than 133 Pa for 24 h before use. *p*-Toluenesulfonyl chloride, 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), phenyl isocyanate, cysteamine and sodium borohydride were obtained from Sigma-Aldrich (Steinheim, Germany). Ethanolamine, [bis(acetoxy) iodo]benzene (BAIB), triethylamine and lithium chloride (LiCl) were received from VWR International GmbH (Darmstadt, Germany). Anhydrous LiCl was dried at 80 °C for 2 h under vacuum. Dimethylsulfoxide (DMSO), *N*, *N*-dimethylacetamide (DMA), *N*, *N*-dimethylformamide (DMF) and tetrahydrofuran (THF) were purchased from Carl Roth International GmbH. Ethanol was obtained from TH. GEYER International GmbH. All other reagents were analytical grade and used as received. Deionized water (DI water) was used in all experiments.

2.2. Syntheses of cellulose derivatives

2.3. p-Toluenesulfonylation of cellulose leading to tosylcellulose (TosC)

According to existing synthesis method (Heinze, Genco, Petzold-Welcke, & Wondraczek, 2012), dried MCC (1 g, 6.2 mmol AGUs) was suspended in 40 mL of *N,N*-dimethylacetamide (DMA) and stirred at 130 °C for 2 h. After the slurry cooled down to 100 °C, 2 g of anhydrous LiCl were added. By further cooling to room temperature under stirring, cellulose dissolved completely. Then, a mixture of 3.1 mL triethylamine and 2.2 mL DMA (10:7, v:v) was added to this solution under stirring. After cooling to 4 °C in the ice-bath, a solution of *p*-toluenesulfonyl chloride (2.5 g, 12.4 mmol) in 4 mL DMA was added drop by drop within 10 min. The homogeneous mixture was stirred at 4 °C for another 24 h. After that, the mixture was slowly poured into 250 mL ice water. The precipitate was filtered off, washed carefully with about 750 mL of distilled water and 100 mL of ethanol, suspended in 50 mL of acetone and re-precipitated in 150 mL of distilled water. After further filtration and repeated washing with ethanol, the sample was dried at 50 °C under vacuum.

Yield: 90%, degree of substitution (DS) ascribed to tosyl groups DS_{tosyl} = 1.3 determined by means of ^{1}H NMR spectroscopy (Fig. S1).

FT-IR (cm^{-1}): 3474 ν(O—H); 2900 ν(CH); 1599, 1499 ν(C—$C_{arom.}$); 1356 $\nu_{as}(SO_2)$; 1172 $\nu_{sy}(SO_2)$; 1043 ν(C—O); 812 ν(C—$H_{arom.}$).

2.4. Carbanilation of tosylcellulose leading to tosylcellulose carbanilate (TosCC)

According to previous report (Heinze, Rahn, Jaspers, & Berghmans, 1996), tosylcellulose (1 g, 2.8 mmol repeating units) was dissolved in 10 mL DMF. The temperature of the solution was elevated to 80 °C before phenyl isocyanate (1.5 mL, 12.6 mmol) was added to the solution. The mixture was kept at 80 °C for 10 h under stirring. After the reaction, the solution was cooled down to room temperature and precipitated in 200 mL ethanol. After repeated dissolution in THF and precipitation in ethanol for several times, a brown product was separated and dried at 50 °C under vacuum.

Yield: 90%, DS_{tosyl} = 1.3 and degree of substitution ascribed to carbanilate groups $DS_{carbanilate}$ = 1.6 determined by means of ^{1}H NMR spectroscopy (Fig. S2).

FT-IR (cm^{-1}): 3310 ν(O—H); 2884 ν(CH); 1720 ν(C═O); 1599, 1499 ν(C—$C_{arom.}$); 1536 ν(C—N—H); 1448 ν(C—N); 1373 $\nu_{as}(SO_2)$; 1214 ν(C—O—C); 1043 ν(C—O); 1180 $\nu_{sy}(SO_2)$; 812, 752, 691 (ν C—$H_{arom.}$).

2.5. Synthesis of 6-deoxy-6-ethanolamino cellulose carbanilate (EaCC)

EaCC was synthesized according to a previous report with modifications (Tiller, Berlin, & Klemm, 2000). TosCC (1 g, 1.8 mmol repeating units) was dissolved in 10 mL DMSO, and ethanolamine (4 mL, 66 mmol) was added to the solution at room temperature. Then, the temperature was raised to 100 °C and the solution was kept at this temperature for 6 h. After that, the solution was precipitated in 200 mL ethanol and the product was purified by repeated dissolution in DMSO and precipitation in ethanol for several times. Thereafter, the precipitated product was dried at 50 °C under vacuum.

Yield: 60%, DS_{tosyl} = 0.2, $DS_{carbanilate}$ = 0.5 and degree of substitution ascribed to ethanolamino groups DS_{EA} = 0.8 determined by means of ^{1}H NMR spectroscopy.

FT-IR (cm^{-1}): 3307 ν(O—H); 2880 ν(CH); 1716 ν(C═O); 1599, 1499 ν(C—$C_{arom.}$); 1536 ν(C—N—H); 1445 ν(C—N); 1218 ν(C—O—C); 1043 ν(C—O); 812, 755, 691 ν(C—$H_{arom.}$).

2.6. Synthesis of 6-deoxy-6-(2-thiolethylamino)ethylamino cellulose carbanilate (ThiolCC)

ThiolCC was synthesized according to modified methods (De Mico, Margarita, Parlanti, Vescovi, & Piancatelli, 1997; Sokolsky-Papkov, Domb, & Golenser, 2006). EaCC (1 g, 3.3 mmol repeating units) was dissolved in 10 mL DMSO, before TEMPO (30 mg, 0.19 mmol) was added. Thereafter, BAIB (0.673 g, 1.98 mmol) was added to the solution. The mixture was further stirred at room temperature for 24 h. Thereafter, cysteamine (0.6 g, 7.6 mmol) was added to the solution, and the solution was kept at room temperature under an atmosphere of N_2 for up to 20 h. After that, $NaBH_4$ (0.3 g, 7.6 mmol) was slowly added to the solution at 0 °C, and the solution was stirred at ambient temperature for another 5 h. After the reaction, the solution was precipitated in 200 mL ethanol and the product was purified by repeated dissolution in DMSO and precipitation in ethanol for several times, before the product was dried at 50 °C under vacuum.

Yield: 50%, DS_{tosyl} = 0.2, $DS_{carbanilate}$ = 0.5 and degree of substitution ascribed to thiol groups DS_{SH} = 0.6 determined by means of ^{1}H NMR spectroscopy.

FT-IR (cm^{-1}): 3298 ν(O—H); 2897 ν(CH); 2600 ν(SH); 1720 ν(C═O); 1599, 1499 ν(C—$C_{arom.}$); 1532 ν(C—N—H); 1445 ν(C—N); 1215 ν(C—O—C); 1043 ν(C—O); 813, 753, 691 ν(C—$H_{arom.}$).

2.7. Synthesis of glycosylated 6-deoxy-6-(2-thiolethylamino)ethylamino cellulose carbanilate (GlcThiolCC)

Glucose-terminated eugenol (1.3 g, 3.9 mmol, Supporting Information) and DMPA (153 mg, 0.65 mmol) as photo-initiator were