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Synthesis and characterization of novel water-soluble 6-deoxy-6-(2-amino-2-(hydroxymethyl)propane-1,3-diol)cellulose derivatives

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ABSTRACT

Amino celluloses are semisynthetic polysaccharide derivatives that are functionalized with amino groups. This class of bio-based polymers has a number of interesting properties for advanced applications such as potential antimicrobial activity and pronounced surface affinity towards various materials. Herein, the synthesis of a novel type of 6-deoxy-6-amino cellulose derivatives with a polar and highly branched substituent (2-amino-2-(hydroxymethyl)propane-1,3-diol/TRIS) is described for the first time. Fundamental principles for the synthesis by nucleophilic displacement of tosylated intermediates are highlighted, thus, providing access to materials with well-defined molecular structures. TRIS-functionalized cellulose derivatives with degrees of substitution (DS) of up to 0.5 were obtained. The solubility and rheological properties of the products showed a strong dependence on the pH value. Due to the unique structural features of the substituent, TRIS amino cellulose derivatives possess a high application potential.

1. Introduction

In the context of current sustainability and climate change discussion, polymeric materials derived from renewable resources are of huge importance for industrial applications [1,2]. Moreover, polysaccharides are intensively studied in many areas of fundamental and applied research due to their inherent beneficial features, such as sustainability, biocompatibility, and bioactivity [2–4]. Nucleophilic displacement (S_N) reaction with activated polysaccharide derivatives is a versatile approach for the preparation of new biomaterials. Novel amino-functionalized products with regioselective substitution pattern could be prepared starting from 6-deoxy-6-bromo-polysaccharide derivatives of curdlan, pullulan, and cellulose in which the halide acts as leaving group for the S_N reaction [5–7]. Cationic cellulose ionomers were obtained by S_N reactions of 6-deoxy-6-bromocellulose with pyridine and 1-methylimidazole [8]. Moreover, the 6-deoxy-6-imidazolylcellulose was allowed to react with 1,3-propane sultone to yield zwitterionic cellulose derivatives. A broad variety of novel cellulose derivatives was accessible by S_N reactions of cellulose-*p*-toluenesulfonic acid esters; cellulose tosylates (CTOS) [9,10]. Water-soluble 6-deoxy-6-aminocelluloses could be designed by reacting CTOS (as the key intermediate) with various di- and oligoamines [11,12]. This new class of cellulose based products, the so-called amino celluloses, possesses extraordinary behavior in forming ultrathin films and even monolayers on a broad variety of substrates [13]. Commercial applications have been developed previously in which the surface functionalization with amino cellulose is used to create antimicrobial materials or to provide an active layer for the immobilization of biomolecules (e.g., enzymes and antibodies) [14,15].

2-Amino-2-(hydroxymethyl)propane-1,3-diol, commonly referred to as “tromethamine”, “tromethamol”, or simply “TRIS” is an interesting primary amine with a branched polar residue. It is water soluble, mildly basic ($pK_a \approx 8.1$), and commonly used in biochemistry in the form of buffer solutions (“TRIS buffer”) with a good buffering capacity between pH values of 7–9 [16,17]. TRIS is registered as pharmaceutical excipient, functioning as counter ion for certain anionic drugs (e.g., ketorolac), and as stabilizer for drug emulsions [18–21]. Moreover, hierarchical molecular structures are accessible by modification of the three hydroxyl groups of the branched TRIS molecule and it can function as metal chelator and anchor group for polyoxometalates [22–24].

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It can be expected that introduction of a TRIS substituent imparts new properties to the biopolymers, such as water solubility, pH responsiveness, and binding of metal ions or drug molecules. If the synthesis that is addressed herein succeeds, these compounds can be further studied in advanced applications for drug delivery, as bioactive surface coatings, as metal ion chelators (e.g., in catalysis), as well as for the synthesis of even further-branched polysaccharide derivatives. This short communication highlights the first steps in developing such materials: (i) the development of a synthesis strategy for TRIS derivatives of cellulose by S_N reaction and (ii) the establishing of analytic approaches for molecular structure characterization.

2. Experimental

2.1. Materials

Cellulose *p*-toluenesulfonic acid esters **2a** to **2d** were prepared according to procedures reported in the literature [25]. All chemicals were obtained from Sigma Aldrich and used as received (unless specified otherwise). Microcrystalline cellulose and LiCl were dried in vacuum at 105 °C over potassium hydroxide. Triethylamine was distilled from calcium hydride prior to use.

2.2. Measurements

NMR spectra of cellulose derivatives were recorded at 60 °C in DMSO-d_6 (60 mg/mL) with a Brucker Avance 250 MHz spectrometer (^{1}H NMR: 16 scans, ^{13}C NMR: > 10,000 scans) or a Brucker Avance 500 MHz NMR spectrometer (^{13}C-APT-NMR: > 50,000 scans) equipped with an Avance III HD console and a nitrogen-cooled prodigy BBFO probe head.

A VARIO EL III CHNS analyzer (Elementar Analysensysteme GmbH) was used for elemental analyses. Degrees of substitution (DS) were calculated from the sulfur (tosyl groups) and nitrogen content (amino groups). FTIR spectra (see supporting information) were recorded in transmission mode on a Nicolet iS5 spectrometer (Thermo Fischer Scientific, USA) using KBr pellets (1.5 mg sample in 200 mg KBr) that were dried under vacuum (70 °C, 72 h) prior to the measurements. Rheology experiments were performed with 2 wt% solutions at 30 °C on a HAAKE MARS rheometer (Thermo Fisher Scientific) using cone-plate geometry (1° angle, 60 mm diameter).

2.2.1. Synthesis of 6-deoxy-6-(2-amino-2-(hydroxy-methyl) propane-1,3-diol)cellulose (5c, typical example)

Cellulose tosylates (CTOS) **2c** (1.0 g, 0.0035 mol, DS_{Tos} 0.79) was dissolved in DMA (15 mL). 2-Amino-2-(hydroxymethyl)propane-1,3-diol (6.38 g, 0.053 mol, 15 mol/mol modified anhydroglucose unit) was added and the temperature was increased to 100 °C under stirring. After 5 h at 100 °C, the mixture was cooled to room temperature and poured into an excess of ethanol (200 mL), which resulted in precipitation of the polymer. The precipitate was removed by filtration and washed with ethanol (2x with 200 mL). The wet product was dispersed in water (15 mL) and diluted hydrochloric acid (10 wt%) was added until a pH value of 2 was reached upon which the product dissolved. The aqueous solution obtained was poured into an excess of ethanol (300 mL). The precipitate formed was removed by filtration, washed with ethanol (100 mL), and finally dried at 40 °C under vacuum to obtain the final product.

Yield: 0.65 g (80%), Anal. Found: C 42.37, H 6.54, N 2.86, S 1.04; ^{13}C NMR (100 MHz, DMSO-d_6, δ): 130.8–126.0 (aromatic/tosyl group), 103.2 (C-1), 81.5–70.7 (C-2, 3, 4, 5), 66.0 (C-7), 60.7 (C-6 OH), 58.5 (C-8), 43.5 (C-6 NH_2^+), 21.6 (CH_3/tosyl group).

2.2.2. Deprotonation of 6-deoxy-6-(2-amino-2-(hydroxymethyl) propane-1,3-diol)cellulose (5c, typical example)

Amino cellulose derivative **5c** (300 mg) was dissolved in water (10 mL) and aqueous NaOH (15 wt%) was added to adjust the pH value to 12. The aqueous solution obtained was poured into an excess of ethanol (60 mL). The precipitate formed was removed by filtration, washed with ethanol (20 mL), and finally dried at 40 °C under vacuum to obtain the final product.

^{13}C-APT-NMR (100 MHz, DMSO-d_6, δ): 131.7–126.0 (aromatic/tosyl group), 103.3 (C-1), 81.1–72.9 (C-2, 3, 4, 5), 62.0 (C-8), 60.9 (C-6 OH), 59.9 (C-7), 41.7 (C-6 NH), 19.0 (CH_3/tosyl group).

3. Results and discussion

Cellulose tosylates (CTOS) with degree of substitution (DS) in the range from 0.4 to 1.0 were obtained by homogeneous conversion of cellulose dissolved in *N*,*N*-dimethylacetamide (DMA)/LiCl with tosyl chloride in the presence of trimethylamine [25]. The CTOS derivatives possess an almost regioselective modification of position 6 and were used as starting materials in the subsequent S_N conversions (Fig. 1). The S_N of CTOS with the branched amine TRIS has not been studied before.

TRIS was employed in two commercially available forms; as the deprotonated primary amine and as hydrochloride (TRIS x HCl). Due to the fact that TRIS x HCl is not nucleophilic, the base *N*,*N*-diisopropylethylamine (Hünig's base) was used additionally. The conversions were carried out for 5 h at 100 °C under homogeneous conditions using DMA as solvent. These conditions are known to yield quantitative replacement of the tosyl groups by various amines. It was found that the reactions using TRIS x HCl in combination with a base do not yield a sufficient substitution under the reaction conditions applied. Although Hünig's base is reported as a week nucleophile, it showed a minor S_N of tosyl groups similar to pyridine that has previously been reported [26]. Thus, no uniform products could be obtained in these experiments.

The conversion of CTOS with TRIS yielded the desired S_N of the tosylate moieties forming 6-deoxy-6-(2-amino-2-(hydroxymethyl) propane-1,3-diol)cellulose derivatives. It was necessary to develop a stepwise work-up procedure consisting of precipitation of the product, redissolution in water, addition of HCl, and reprecipitation in order to transfer the secondary amino group formed into the ammonium form as well as to completely remove all by-products of the synthesis. Thus, it became possible to calculate the DS_{TRIS} from elemental analysis data of the pure and structurally uniform products and to acquire well-resolved NMR spectra (see below). Products with an increasing DS_{TRIS} were obtained by using CTOS with different starting DS_{Tos} (Table 1).

Starting from a CTOS with a DS_{Tos} of 0.79 (**2c**), 6-deoxy-6-2-amino-2-(hydroxymethyl)propane-1,3-diolcellulose with a DS of 0.41 (**5a**) was obtained applying a molar ratio of TRIS to CTOS of 10 to 1. This DS is reasonably high for potential applications considering the branched molecular structure and bulkiness of the substituent. Increasing the amount of TRIS to a 12.5-fold excess resulted in a slight increase of DS to 0.47 (**5b**). Surprisingly, DS $\gtrsim$ 0.5 were not accessible, neither by increasing the amount of TRIS >10 (**5b** to **5d**) equivalents nor by further increasing the starting DS_{Tos} to 1.05 (**6**). Products with a low DS_{TRIS} of 0.28 (**3**) and 0.36 (**4**) were obtained by conversion of CTOS with DS_{TOS} of 0.42 (**2a**) and 0.56 (**2b**).

In all reactions, a certain amount of tosyl groups did not react and remained in the products (indicated by DS_{Tos} after conversion) while some tosyl groups were removed by aminolysis (indicated by $DS_{Tos\,(educt)} > DS_{TRIS} + DS_{Tos\,(product)}$). It was confirmed by ^{1}H and ^{13}C NMR spectroscopic studies that the remaining tosyl groups were still covalently bound to the polymer backbone and not present as

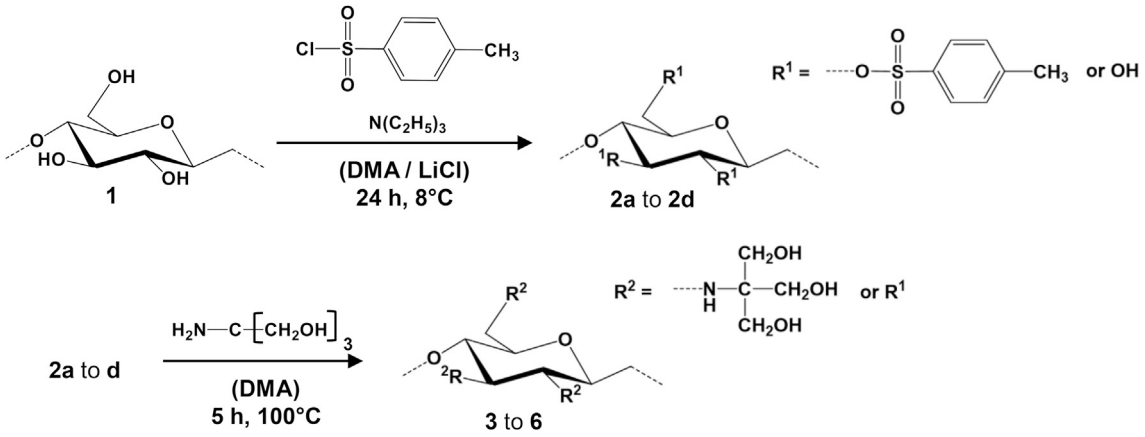

Fig. 1. Reaction scheme for the synthesis of 6-deoxy-6-(2-amino-2-(hydroxymethyl)propane-1,3-diol)cellulose.

Table 1
Conditions for and results of the conversion of cellulose tosylates (CTOS) with 2-amino-2-(hydroxymethyl)propane-1,3-diol (TRIS) at 100 °C for 5 h.

CTOS	DS_{Tos} [a]	Molar ratio (CTOS/TRIS)	Product	DS_{TRIS} [b]	DS_{Tos} [b]	Solubility (water)[c]	Solubility (DMSO)[c]
2a	0.42	1/10	3	0.28	0.03	+	+
2b	0.56	1/10	4	0.36	0.06	+	+
2c	0.79	1/10	5a	0.41	0.12	+	+
2c	0.79	1/12.5	5b	0.47	0.07	+	+
2c	0.79	1/15	5c	0.47	0.07	+	+
2c	0.79	1/20	5d	0.46	0.09	+	+
2d	1.05	1/10	6	0.53	0.23	+	+

[a] Degree of substitution (DS) with tosyl groups for the starting CTOS.
[b] DS with TRIS and tosyl groups for the product.
[c] Dimethyl sulfoxide (DMSO), +: soluble.

tosylate impurities. Both effects, residual tosyl content and extent of aminolysis, became more pronounced with increasing DS_{Tos} of the CTOS employed. This can be explained by the steric demand of the branched and bulky TRIS substituent. The S_N reaction of tosyl groups is sterically hindered if a certain amount of amines is already attached to the polymer backbone, thus, giving rise to the intrinsic threshold of $DS_{TRIS} \approx 0.5$. With increasing steric hindrance, the basic nature of TRIS becomes more pronounced than for non-branched amines with a similar pK_a value. Thus, partial cleavage of tosyl groups occurred. Similar findings have been reported previously for the conversion of activated polysaccharide carbonates with bulky amines [27].

The novel amino cellulose derivatives in their hydrochloride form were soluble both in water and dimethyl sulfoxide (DMSO). This is rare for such types of protonated polysaccharide derivatives that usually tent to be soluble in one or the other liquid only. Interestingly, even the products with a rather high residual content of hydrophobic tosyl moieties, most notably **6** with a DS_{TRIS} of 0.53 and DS_{Tos} of 0.23, were fully water soluble. This highlights the beneficial effect of the highly polar TRIS moiety. The good solubility also demonstrates that no crosslinking occurred, which would have resulted in insoluble products. In addition to the strong nucleophilic amino group, the branched TRIS substituent contains three primary hydroxyl moieties that might in principle react as week nucleophiles with adjacent tosyl groups of neighboring polymer chains. That issue might be even more pronounced taking into account that the hydroxyl groups are present in a large excess. However, this type of side reactions can be excluded in the present cases.

The 6-deoxy-6-(2-amino-2-(hydroxymethyl)propane-1,3-diol) cellulose derivatives were converted into their hydrochlorides during the workup and characterized by spectroscopic methods. A typical ^{13}C NMR spectrum of sample **5c** (ammonium chloride) is exemplarily shown in Fig. 2. The assignment of the signals was possible with the aid of ^{13}C-APT-NMR-spectra (see Fig. 3) and computer assisted prediction (ACD-Labs).

The typical signals of the modified cellulose repeating unit in the range from about 100 to 60 ppm occurred. The signal at 60.7 ppm is attributed to the non-modified primary C-6. Further signals are seen at 103.4 ppm (C-1) and in the range from 81.5 to 70.7 ppm (C-2 to C-5). A prominent peak at about 43.5 ppm was detected that is characteristic for a 6-deoxy-6-amino moiety, thus proving the proposed molecular structure [28].

The TRIS substituent introduced by the S_N reaction gave additional characteristic signals at 66.0 ppm (C-7) and 58.5 ppm (C-8) that occurred in the typical range of the quaternary and secondary C-atoms of this structural unit. For a reliable assignment of these peaks, ^{13}C-APT-NMR spectra were recorded (Fig. 3). The ^{13}C NMR spectrum additionally featured typical signals in the range from 130.8 to 126.0 ppm for the aromatic C-atoms of the residual tosyl moiety and at 21.6 ppm for the corresponding CH_3 group.

Due to the basicity of the secondary amine formed by the S_N reaction, the products **3** to **6** were partly protonated in aqueous solution. These different structures, C—NH—C or C—N^+H_2—C, influence the chemical shifts of the signals of the corresponding C-atoms. In Fig. 3, the ^{13}C-APT-NMR-spectrum of the protonated ammonium salt of sample **5c** is compared with the spectrum of the same sample after conversion into the amine with aqueous sodium hydroxide. Upon deprotonation, the signal of the substituted C-6 shifted from 43.5 to 41.7 ppm. The signal associated with the tertiary C-atom 7 shifted from 66.0 to 59.9 ppm due to the loss of the strong deshielding effect of an adjacent electron withdrawing

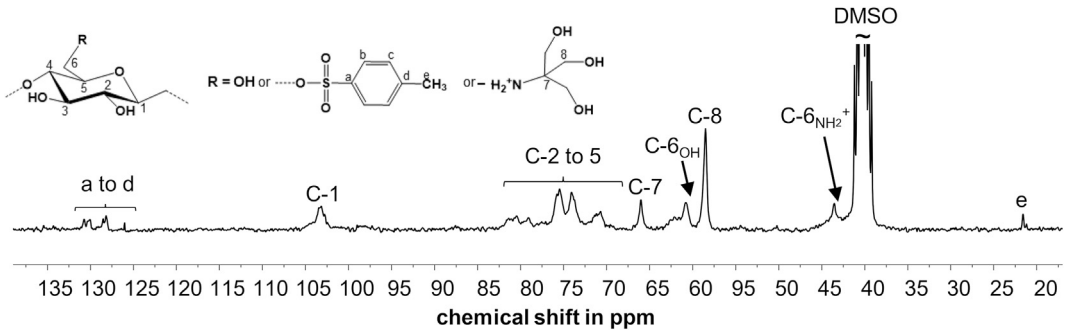

Fig. 2. ^{13}C NMR spectrum of 6-deoxy-6-(2-amino-2-(hydroxymethyl)propane-1,3-diol)cellulose **5c** with a degree of substitution (DS_{TRIS}) of 0.47 (DS of remaining tosylate moieties: 0.07) acquired in dimethyl sulfoxide (DMSO)-d_6.

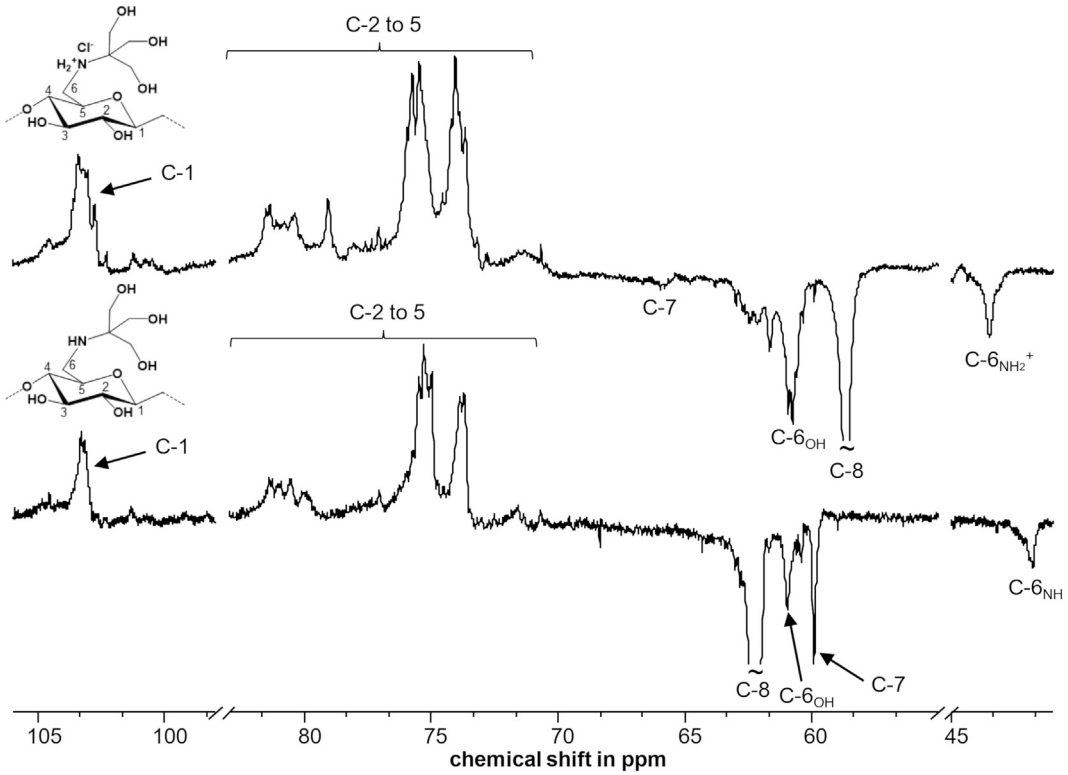

Fig. 3. ^{13}C-APT-NMR spectra of 6-deoxy-6-(2-amino-2-(hydroxymethyl)propane-1,3-diol)cellulose **5c** (top: ammonium salt, bottom: deprotonated to amino form), acquired in dimethyl sulfoxide (DMSO)-d_6.

ammonium group. The peak associated with the primary C-atom 8 shifted from 58.5 to 62.0 ppm. The ^{13}C-APT-NMR of the initial sample **5c** also showed a C-8 related peak around 62 ppm, albeit with a much lower intensity compared to the deprotonated sample. Thus, it can be concluded that a minor portion of the amino groups was deprotonated in the TRIS-functionalized 6-deoxy-6-amino cellulose derivatives obtained from the synthesis.

The novel 6-deoxy-6-(2-amino-2-(hydroxy-methyl)propane-1,3-diol)cellulose (hydrochloride form) showed good water solubility, which is the basis for many potential applications, e.g., as active surface coating material. The aqueous solutions had a pH value of about 3.5 and showed typical viscous flow behavior including shear thinning (Fig. 4). Interestingly, the DS_{TRIS} showed no significant effect on the rheological properties. The flow curves of samples **3** (DS_{TRIS} = 0.28) and **5a** (DS_{TRIS} = 0.41) were very similar. It was found that the water solubility and viscosity of the novel amino celluloses strongly depend on the state of protonation of the amine, i.e., the pH value of the solutions. Deprotonated amino celluloses were prepared by neutralization of aqueous solutions of samples **3** and **5a** followed by precipitation. Despite being soluble in DMSO, deprotonated **5a** did not dissolve in water at neutral or slightly acidic pH values. The neutralized sample **3** (DS_{TRIS} = 0.28) was insoluble in water at pH = 7 but dissolved when pH ≈ 5.3 was reached by adding hydrochloric acid. This process was reversible; increasing the pH value resulted in precipitation and decreasing it back resulted in dissolution. For drug delivery applications, this pH dependent solubility behavior can become very attractive. At higher pH value, the aqueous solution of **3** showed a significantly higher viscosity (about two orders of magnitudes). This suggests a different state of dissolution for the fully

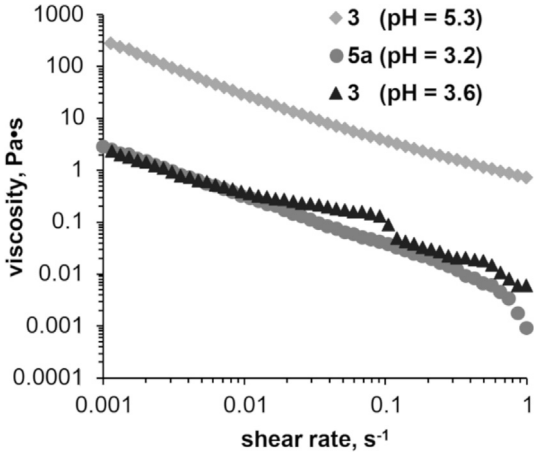

Fig. 4. Flow curves for aqueous 2 wt% solutions of 6-deoxy-6-(2-amino-2-(hydroxymethyl)propane-1,3-diol)celluloses **3** and **5a**, as hydrochlorides (pH ≤ 3.6) or in deprotonated form (pH = 5.3), recorded at 30 °C.

protonated (lower viscosity) and the partially deprotonated (higher viscosity) amino cellulose **3**.

To summarizes, the synthesis of novel TRIS-functionalized 6-deoxy-6-aminocellulose derivatives is described for the first time. These derivatives have a promising application potential due to the unique features of the highly branched TRIS substituent with its large density of polar hydroxyl groups. This communication lays the groundwork for the synthesis of derivatives with a well-defined molecular structure by S_N reaction of CTOS. The unexpected findings regarding the pH depended solubility and viscosity will be evaluated comprehensively in the context of follow-up projects. Thus, current studies in which the application of the novel amino cellulose derivatives is evaluated in detail also include extensive rheological and titration experiments.

4. Conclusion

Novel 6-deoxy-6-amino cellulose derivatives with a 2-amino-2-(hydroxymethyl)propane-1,3-diol- (TRIS) substituent were prepared with a degree of substitution (DS) of up to 0.5 by nucleophilic displacement reaction using cellulose tosylates (CTOS) as activated intermediates. A pH responsive solubility and rheological behavior was observed for the cellulose derivatives. The unique structural features of the TRIS moiety (polar, highly branched, basic character) enable different applications for the compounds obtained. The application potential of the pH responsive derivatives in three areas is currently of interest: thickening additives (e.g., in paint, concrete, food), drug delivery excipients, and surface coatings. In this context, the protonation/deprotonation behavior of the novel derivatives will be evaluated comprehensively to determine pK_a values and buffering capacities at different temperatures. The use of TRIS modified cellulose derivatives for the stabilization, immobilization, and release of anionic drug molecules will be investigated in another project. Moreover, studies on the adsorption of the novel derivatives on different kinds of surfaces will be conducted as a basis to develop functional and/or potentially antimicrobial surface coating materials.

Declaration of Competing Interest

None.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aiepr.2020.02.001.

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