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Nucleophilic displacement reactions on tosyl cellulose by chiral amines

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Summary

New 6-deoxy-6-amino cellulose derivatives with a degree of substitution (DS) in the range from 0.4 to 0.6 were synthesized by nucleophilic displacement (S_N) reactions of cellulose tosylates (DS_{Tos} 0.74 and 1.29) with R(+)-, S(-)- and racemic 1-phenylethylamine under homogeneous conditions in *N*,*N*-dimethylformamide and water. The structure of the polymers was characterized by elemental analysis, FTIR and ^{13}C NMR spectroscopy. The DS values obtained as well as the optical rotation and circular dichroism measurements in dimethyl sulfoxide reveal that the initial chirality of the cellulose backbone does not have any significant influence on its reactivity with either of the two enantiomeric amines.

Introduction

Carbohydrates are amongst the classic groups of compounds for which an optical activity has been demonstrated. Cellulose is the most abundant polysaccharide with a unique structure of repeating anhydroglucose units (AGU). Each AGU possesses 5 chiral carbon atoms at positions 1 to 5, while only the primary C6 is achiral. Due to its intrinsic local chirality, cellulose also appears to be able to assume a globally chiral conformation. These properties render cellulose suitable as a chromatographic material for separating low molecular weight chiral compounds [1]. By chemical functionalization of cellulose a broad variety of new polymers have been obtained, and some of them form liquid crystals under appropriate conditions [2-4]. Especially cellulose phenylurethanes with various substituents in the aromatic moieties have attracted much attention [5,6].

From these properties the question arises whether the overall chirality of cellulose could influence its reactivity towards chiral low-molecular weight compounds, i.e., whether the polymer could act as a template-like material. However, there are no references available in the literature with regard to this issue. It may be expected that a regioselective distribution of enantiomeric substituents within the polymer could be used to develop advanced materials with unconventional properties on the basis of polysaccharides.

While studying the regioselective functionalization of polysaccharides, our interest converged on organo-soluble *p*-toluenesulfonyl (tosyl) esters of these biopolymers, since they can serve as intermediates for a broad variety of subsequent reactions including nucleophilic displacement (S_N) [7-12]. Using S_N reactions it is possible to carry out a selective conversion at the C6 tosylate function only. In this paper we communicate our first results on introducing chiral functional groups into cellulose. We describe the regioselective functionalization at the achiral C6 position

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using S_N reactions of tosyl cellulose with R- and S-1-phenylethylamine and with the corresponding racemate. The new cellulose derivatives were characterized by elemental analysis, FTIR and ^{13}C NMR spectroscopy. Moreover, the optical properties of the new cellulose derivatives are described by polarimetry and CD (circular dichroism) measurements.

Experimental

Cellulose **1** (AVICEL PH101) was dried under vacuum at 105°C. Triethylamine and *N,N*-dimethylformamide (DMF) were distilled over calcium hydride before use. All other chemicals were used without further purification.

p-Toluenesulfonyl (tosyl) esters of cellulose ***2a-b***

The tosylation of **1** was carried out according to the method described by Rahn et al. [13]. A solution of cellulose in *N,N*-dimethylacetamide (DMA) was treated with tosylchloride in the presence of triethylamine for 24 h at 8°C to obtain polymer **2a** and **b** with a degree of substitution (DS_{Tos}) of 0.74 and 1.29 respectively.

6-Deoxy-6-(1-phenylethyl)aminocellulose ***3a-f***

In a typical procedure, 2.0 g of **2** were dissolved in 100 ml *N,N*-dimethylformamide (DMF). 30 ml water were added slowly, followed by 5 equivalents of 1-phenylethylamine. The temperature was raised to 100°C and the reaction mixture stirred for 16 h. After cooling down to ambient temperature the mixture was poured into 500 ml acetone. The polymer was filtrated off and washed several times with acetone. It was dried under vacuum at 60°C.

Yield: 1.1 g, DS_{DA} 0.44, DS_{Tos} 0.10 (determined by elemental analysis, 2.75% N, 1.49% S), see Table 1.

FTIR (KBr): 1359 cm^{-1} ν_{as} (SO_2), 1178 cm^{-1} ν_s (SO_2)

^{13}C NMR (DMSO-d_6): 21.9 ppm CH_3, 47.4 ppm $C6_{deoxyamino}$, 57.2 ppm C-N, 68.39-102.4 ppm cellulose backbone, 125.2-145.2 ppm $C_{aromatics}$, see Fig. 1.

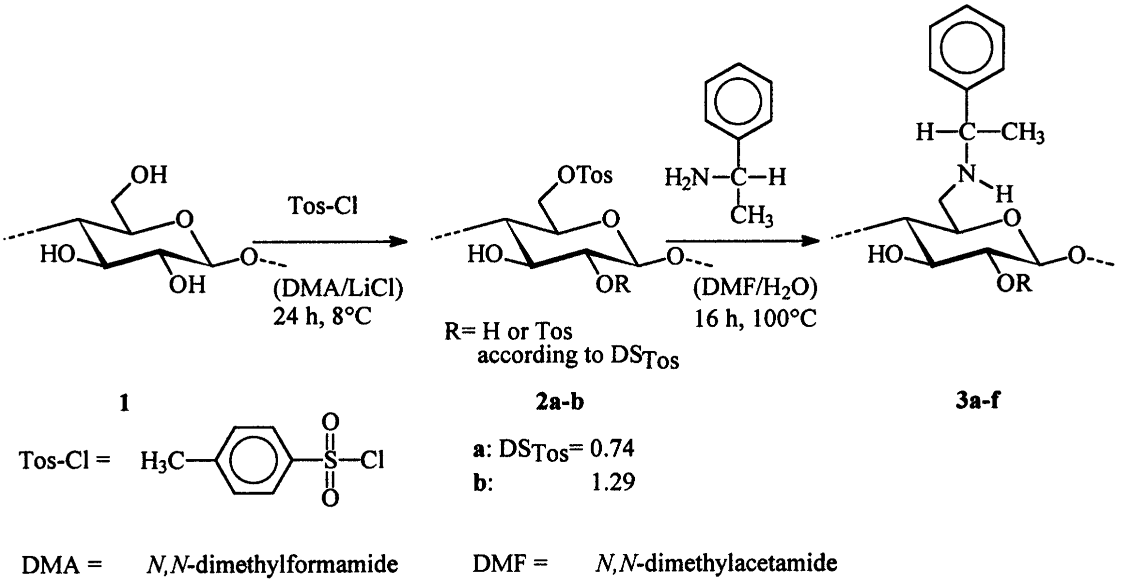
Measurements

NMR spectra were recorded on a Bruker AMX 400 spectrometer at 60°C using DMSO-d_6 as solvent. FTIR spectra were obtained from a BioRad FTS 25 spectrometer using the KBr technique. A Leco CHNS 932 analyser was used for elemental analysis. Specific rotations at 589 nm (Na D-line) were measured on a Schmidt+Häensch Polartronic E semi-automatically polarimeter. CD spectra were recorded at room temperature on a Jasco 710 spectropolarimeter in the range of 250 and 600 nm. The phenylethylamines and the cellulosic products (**2d, 3d-3f**) were measured in a 1 mm cuvette in DMSO at concentrations of around 4 mg/dl. The solvent baseline was subtracted from all spectra, and the relative signal intensities were corrected for the respective sample concentrations. All polarimetric measurements were carried out at ambient temperature in a 1-5 g/dl (w/v) DMSO solution.

Results and discussion

The *p*-toluenesulfonic acid esters (tosyl) of cellulose are valuable intermediates for various subsequent reactions in the design of advanced cellulosic materials [8-12,14,15]. The tosyl celluloses (**2a-b**) used in this work were synthesized under homogenous reaction conditions in *N,N*-dimethylacetamide (DMA)/LiCl as a cellulose solvent, at 8°C using triethylamine as a base [13]. As a starting material cellulose powder AVICEL was used with a degree of polymerization of 280. The tosyl cellulose (**2a-b**) with a degree of substitution (DS_{Tos}) of 0.74 and 1.29 are soluble in DMA, dimethyl sulfoxide (DMSO) and *N,N*-dimethylformamide (DMF). Our ^{13}C NMR spectra show that tosyl celluloses **2a** and **2b** are preferably substituted at the primary hydroxyl groups.

It is known that under appropriate reaction conditions the nucleophilic displacement (S_N) reaction occurs regioselectively at the C6 position only. Polymers **2a** and **b** were allowed to react with 1-phenylethylamine (R- and S-enantiomer, and the racemic mixture, respectively) in a DMF/water mixture for 16 h at 100°C. After the usual isolation procedure, the products are still soluble in DMSO and DMF, but insoluble in water (**3a-f**). They were characterized by elemental analysis, FTIR, and NMR spectroscopy.



Products **3a-f** contain a significant amount of nitrogen and significantly less sulfur compared to the starting tosyl cellulose **2** (Tab. 1). Correlation of the sulfur and nitrogen content gives the DS values of tosyl- and deoxyamino groups. Using the tosyl cellulose **2a** of comparatively low DS_{Tos}, a DS for the deoxyamino groups (DS_{DA}) in the range from 0.37 to 0.44 was achieved using the chiral amine. The tosyl cellulose sample **2b** (DS_{Tos} = 1.29) yields products with a slightly higher DS_{DA}. Values in the range of 0.48 to 0.56 were obtained. Furthermore, residual tosylate groups were detected in all samples. The remaining DS_{Tos} is higher in case of samples **3d-f**, since the starting tosyl cellulose **2b** possesses more tosyl groups at the secondary OH groups which cannot undergo the S_N reaction under the conditions applied.

The sum of the values of DS_{DA} and DS_{Tos} of samples **3a-f** does not reach the overall DS_{Tos} of the starting tosyl cellulose. Consequently, some of the tosylate functions were removed from the cellulose backbone via a different synthesis path. This must be due to the presence of water in the reaction mixture, which can hydrolyze tosylate ester functions.

Table 1. **Preparation of 6-deoxy-6-(1-phenylethylamino) cellulose by reacting tosyl cellulose with 5 equivalents of R(+)-, S(-)- and racemic 1-phenylethylamine, in *N,N*-dimethylformamide/water mixture for 16 h at 100°C**

Starting tosyl cellulose	Amine [stereo-isomer]	Sample No.	Elemental analysis (%)				$[\alpha]_D^{20}$ [a]	DS_{DA} [b]	DS_{Tos} [b]
			C	H	N	S			
2a	-	-	47.61	5.11	-	8.60	14.34	-	0.74
2b	-	-	49.39	4.90	-	11.41	-[c]	-	1.29
2a	Rac.	**3a**	55.65	6.68	2.75	1.49	-[c]	0.44	0.10
2a	R(+)	**3b**	53.15	6.48	2.40	1.61	-[c]	0.37	0.11
2a	S(–)	**3c**	49.63	6.53	2.58	1.20	-[c]	0.40	0.08
2b	Rac.	**3d**	55.01	6.18	2.59	3.68	34.63	0.48	0.29
2b	R(+)	**3e**	55.93	6.35	3.15	2.45	31.71	0.56	0.19
2b	S(–)	**3f**	55.54	6.29	3.02	2.61	60.92	0.54	0.20

[a] Measured in DMSO.

[b] Degree of substitution, DS_{DA} of 6-deoxy-6-amino groups and DS_{Tos} of tosyl groups.

[c] Not determined.

Moreover, the protolysis equilibrium between the amine and water gives rise to strongly nucleophilic hydroxyl anions.

These nucleophilic agents can cause a partial detosylation without forming any aminodeoxy functions. This effect was demonstrated in the ^{13}C NMR spectra, which show a very strong peak at 60.2 ppm indicative of a C6 carbon with a hydroxyl group. One of our main motivations in carrying out this series of reactions was to find out whether the local and global chirality of cellulose may have an influence on its reactivity towards chiral low-molecular weight compounds. Inspection of the DS_{DA} values obtained with the R(+)- and S(-)-amine shows that - contrary to what may have been expected - there is no significant correlation with the chirality of this reagent. Therefore we conclude that the chirality of the cellulose backbone does not influence the S_N reaction at the C6 tosylate under the reaction conditions applied here.

The regioselective reaction at C6 was evaluated by ^{13}C NMR spectroscopy. Fig. 1 shows a typical ^{13}C NMR spectrum of the resulting 6-deoxy-6-(1-phenylethylamine) cellulose sample **3c**. The peaks for the methyl groups of the 1-phenylethylamine moiety as well as of the residual tosylate functions appear in the range of 20.0 to 23.1 ppm. The carbon atom of the 6-deoxy moiety is shifted to higher field and appears at 47.4 ppm. Furthermore, the carbon atom directly bound to the amino function of the 1-phenylethylamine group appears at 57.3 ppm. A peak of high intensity is observed at 60.2 ppm, indicating that the C-6 carbon of the anhydroglucose unit (AGU) bears a hydroxyl group. The signals of the C-2, 3, 4 and 5 were detected in the range from 73.1 to 79.1 ppm and the peak for C-1 appears at 102.5 ppm. Peaks of aromatic carbon atoms were found in the range from 125.3 to 145.3 ppm.

The new cellulosic polymers were also examined by FTIR spectroscopy, and the results are in agreement with the structures described above (data not shown).

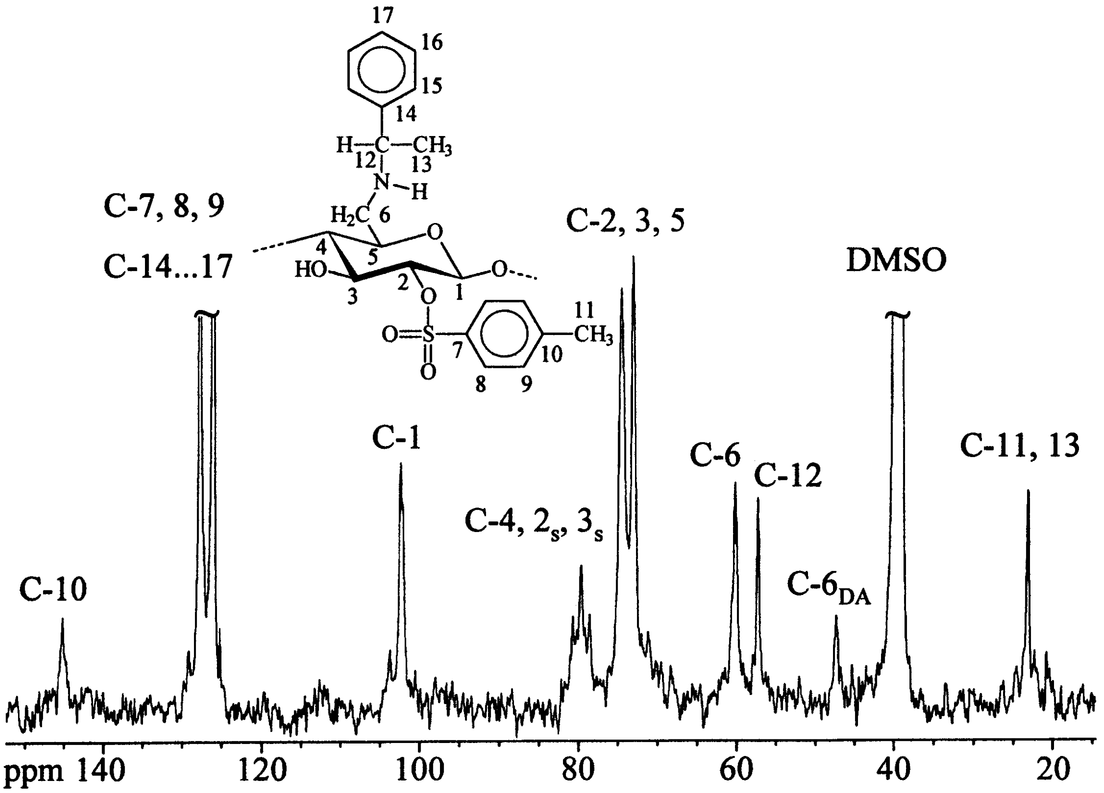


Fig. 1. ^{13}C NMR spectrum of the sample **3c** in DMSO-d_6 at 60°C

Furthermore, the 6-deoxy-6-amino cellulose products were characterized by routine polarimetric measurements, because it had been speculated that the chirality of the reagents might influence the stereoselectivity of the nucleophilic substitution reaction.The specific rotation $[\alpha]_D$ was determined at 589 nm for the reaction products **3d-3f**, as listed in Table 1. At this wavelength neither the AGU nor the substituents possess any significant absorbance, and the optical activity represents the sum of the contributions from all stereocenters in the polymer, namely from all chiral atoms C1 to C5. The numerical $[\alpha]_D$ values may thus be regarded as a characteristic signature of the different products, which are sensitive to the exact reaction conditions and DS values. However, the specific rotation at 589 nm does not reveal any direct information about the sites on cellulose that have been substituted by the optically active amine, i.e. about the stereospecific outcome of the S_N reaction.

Circular dichroism is a suitable method to characterize specifically those optically active groups which possess an intrinsic absorbance [4], as it is the case for the aromatic amines used here. CD spectra were recorded for the unreacted phenylethylamines and for the reaction products **3d-3f** between wavelengths of 250 to 600 nm. The pure R(+)- and S(-)-amines exhibit strong and complementary Cotton effects in the region between 250 and 275 nm, while their racemic mixture produces virtually no CD signal above the baseline, as seen in Fig. 2. Likewise, the arithmetic average of the two enantiomeric spectra is close to zero, within an error of approximately 5%.

Fig. 3 shows that the cellulose derivatives from the R(+)- and the S(-)-amines give rise to CD spectra with pronounced positive and negative Cotton effects. Since these lineshapes resemble those of the pure amines, they must be dominated by the chiral C-atom of 1-phenylethylamine.

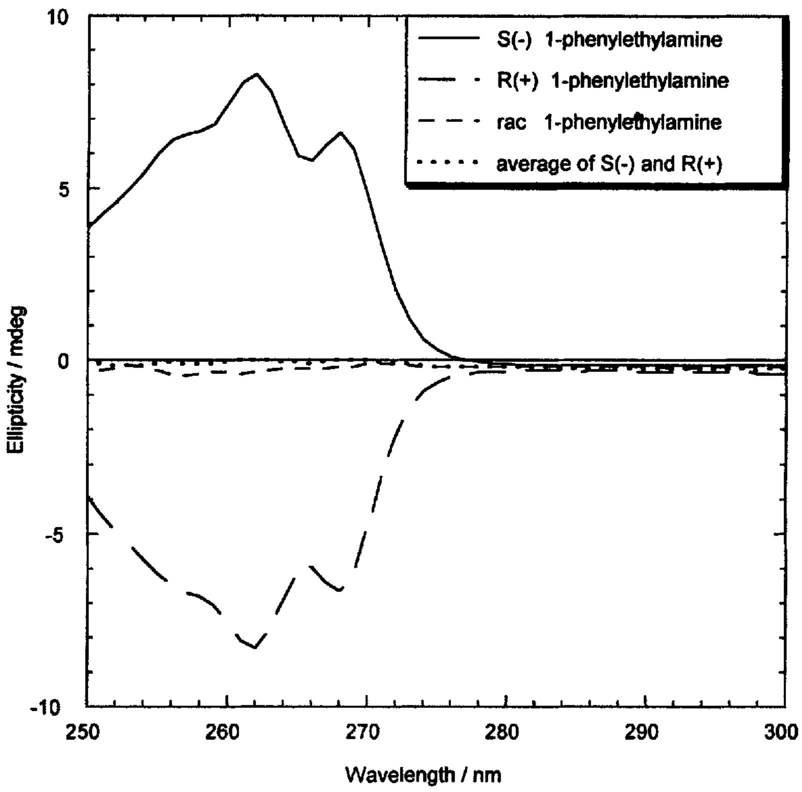


Fig. 2. CD spectra of the stereoisomersof 1-phenylethylamine in DMSO

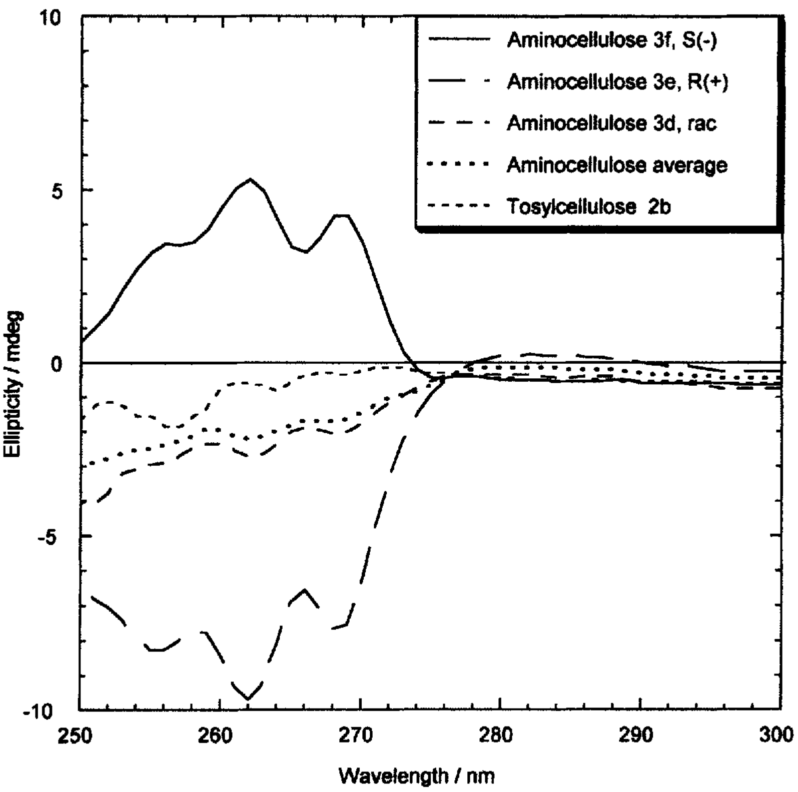


Fig. 3. CD spectra of the samples **3d-f** in DMSO

Notably, the reaction of cellulose with the racemic amine mixture produces a very similar CD-lineshape and intensity as the arithmetic average of the two chiral reaction products. Therefore, we conclude that the two enantiomeric amines possess the same reactivity towards optically active cellulose in the S_N reaction.The non-zero intensity of the arithmetic average of the two R(+)- and S(-)- forms and the very similar CD lineshape of the racemic reaction product must be attributed to the presence of the chiral cellulose C-atoms close to the chromophore. Likewise, the control spectrum of the tosyl cellulose used as a starting material shows a weak negative CD spectrum, albeit with a slightly different lineshape. Overall, we conclude that within experimental error and under the conditions used here, the initial chirality of the cellulose does not have any significant influence on its reactivity with either of the two enantiomeric amines.

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