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Note

Facile synthesis of 6-amino-6-deoxycellulose

Yoshiaki Matsui, Junya Ishikawa, Hiroshi Kamitakahara, Toshiyuki Takano* and Fumiaki Nakatsubo

Division of Forest and Biomaterials Science, Graduate School of Agriculture, Kyoto University, Sakyo-ku, Kyoto 606-8502, Japan

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Abstract—6-Amino-6-deoxycellulose (**4**) was synthesized from cellulose by three reaction steps, namely bromination at C-6, displacement of bromine by azide ion, and reduction of the azide group to amino group, in 67% overall yield. The ^{13}C NMR spectrum of compound **4** supports the expected structure for 6-amino-6-deoxycellulose. The degree of substitution of compound **4** was 0.96.

Keywords: 6-Amino-6-deoxycellulose; 6-Bromo-6-deoxycellulose; 6-Azido-6-deoxycellulose

Aminodeoxycellulose has potential medical, biological, and biotechnological applications.[1–4] It is generally understood that not only the DS but also the distribution of the functional groups may influence the properties of cellulose derivatives.[5] Therefore, in the case of aminodeoxycellulose, the high regioselective introduction of the amino group into the cellulose molecule is extremely important. 6-Amino-6-deoxycellulose is the most common regioselectively substituted aminodeoxycellulose studied so far.[6–11]

There are two major methods for the syntheses of 6-amino-6-deoxycellulose derivatives, either via a 6-azidodeoxycellulose derivative[7,8,10,11] (which can be prepared from a 6-tosylated cellulose derivative[12–14] or a 6-chlorodeoxycellulose derivative),[15] or by synthesis via a 6-oxidized cellulose derivative.[9] However, 6-amino-6-deoxycellulose with a high DS by the amino group at C-6 has been reported by only two groups, that is, by Teshirogi et al.[8] and by Liu and Baumann.[11]

Teshirogi et al. prepared 6-amino-6-deoxycellulose with a DS of 0.90 by using a 6-*O*-tosylcellulose derivative having protecting groups at C-2 and C-3 as an intermediate.[8] However, this method required eight steps from cellulose, and the yield after reduction of the azido group with $LiAlH_4$ was very low (23%).

However, Liu and Baumann recently described the synthesis of 6-amino-6-deoxycellulose of DS 1.0, without using protecting groups at C-2 and C-3, by synthesis via 6-*O*-tosylcellulose derivatives.[11] However the ^{13}C NMR spectrum of the 6-amino-6-deoxycellulose gave two broad peaks for C-1 around 105.5 ppm, and all other peaks were also broad, suggesting a possible side reaction at C-2 of the compound, although this was not mentioned. Thus, the structure of this 6-amino-6-deoxycellulose is still uncertain.

In these two reports,[8,11] 6-*O*-tosylcellulose derivatives were used as synthetic intermediates for 6-amino-6-deoxycellulose. However, it is well known that the regioselective tosylation of cellulose at C-6 with protecting groups at C-2 and C-3 is difficult, because the tosylation at C-2 and C-3 can occur at the same time.[11] It has also been reported that the tosyl group at C-6 is partially converted into the corresponding chloride in the reaction system of tosyl chloride–pyridine.[8,16]

Furuhata et al. reported that 6-bromo-6-deoxycellulose with a DS of 0.91 was produced by the reaction of cellulose with *N*-bromosuccinimide (NBS)–triphenylphosphine (Ph_3P), and that bromination at only C-6 took place.[17] Aoki et al. described that bromodeoxysaccharides are much more reactive than the corresponding chlorodeoxysaccharides in nucleophilic substitution of

* Corresponding author. Fax: +81 75 753 6300; e-mail: takatmys@kais.kyoto-u.ac.jp

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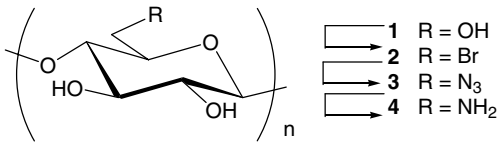
halogenated methyl glycosides.[18] Therefore, 6-bromo-6-deoxycellulose is considered to be an useful intermediate for the preparation of 6-amino-6-deoxycellulose.

Described here is the facile synthesis of 6-amino-6-deoxycellulose via 6-bromo-6-deoxycellulose.

The synthetic route for 6-amino-6-deoxycellulose (**4**) from cellulose (**1**) is shown in Scheme 1. 6-Bromo-6-deoxycellulose (**2**) was prepared by modification of the method of Furuhata et al.[17] Microcrystalline cellulose (DP = 114) was treated with NBS–Ph_3P in LiBr–Me_2N-COMe at 70 °C for 2 h to give 6-bromo-6-deoxycellulose (**2**) of DS 0.98 in 91% yield.

There are several reports about the preparation of 6-azido sugar from 6-haloro sugar. Horton et al. reported the preparation of 6-azido-6-deoxycellulose from 6-chloro-6-deoxycellulose by treatment with NaN_3 in Me_2SO at 100 °C for 48 h, although the DS by azide of the 6-azido-6-deoxycellulose under this conditions was not described.[15] Furuhata et al. reported the synthesis of 6-azido-6-deoxychitin of DS 0.69 from 6-bromo-6-deoxychitin by treating it with NaN_3 in Me_2SO at 60 °C for 5 h.[19] Cimecioglu et al. reported the synthesis of 6-azido-6-deoxyamylose of DS 0.37 from 6-chloro-6-deoxyamylose by treating with NaN_3 in Me_2SO at 70 °C for 48 h.[20] Thus, the method using NaN_3 was applied for the preparation of 6-azide-6-deoxycellulose (**3**).



Scheme 1.

6-Bromo-6-deoxycellulose (**2**) was treated with NaN_3 in the presence of tetra-*n*-butylammonium iodide in Me_2SO at 70 °C for 48 h. The reaction mixture became a clear solution after 24 h, although the bromocellulose (**2**) initially did not dissolve completely in Me_2SO at 60 °C. 6-Azido-6-deoxycellulose (**3**) was obtained in 81% yield, as expected. The ^{13}C NMR spectrum of **3**, measured in Me_2SO-d_6 at 50 °C, is shown in Figure 1. All peaks were assigned by *g*COSY, *g*HSQC spectroscopy. Azidocellulose **3** gives only a singlet peak for C-6-N_3 at 48.5 ppm. A peak at 59.4 ppm for C-6-OH[11] was not observed, indicating that hydrolysis at C-6 did not occur during substitution by azide. The IR spectrum of azidocellulose **3** also showed a strong peak for the azide group, at 2111 cm^{-1}. The complete elimination of bromine was confirmed by elemental analysis. These results indicate that the displacement of bromide by azide ion proceeded quantitatively. Thus, 6-azido-6-deoxycellulose (**3**) of DS 0.96 was obtained.

Reduction of the azido group to amino has been described in detail by Scriven and Turnbull, and a variety of procedures were described.[21] Liu et al. used $LiAlH_4$ to prepare 6-amino-6-deoxycellulose, but the yield was low (44%).[11] Furuhata et al. described that the reduction of 6-azido-6-deoxychitin with $NaBH_4$ gave 6-amino-6-deoxychitin in high yield (83%).[19]

6-Azido-6-deoxycellulose (**3**) was treated with $NaBH_4$ in Me_2SO at 60 °C for 48 h to give 6-amino-6-deoxycellulose (**4**) in 89% yield. The ^{13}C NMR spectrum of the aminocellulose (**4**) obtained is shown in Figure 1. All peaks, assigned by its *g*COSY, *g*HSQC spectroscopy,

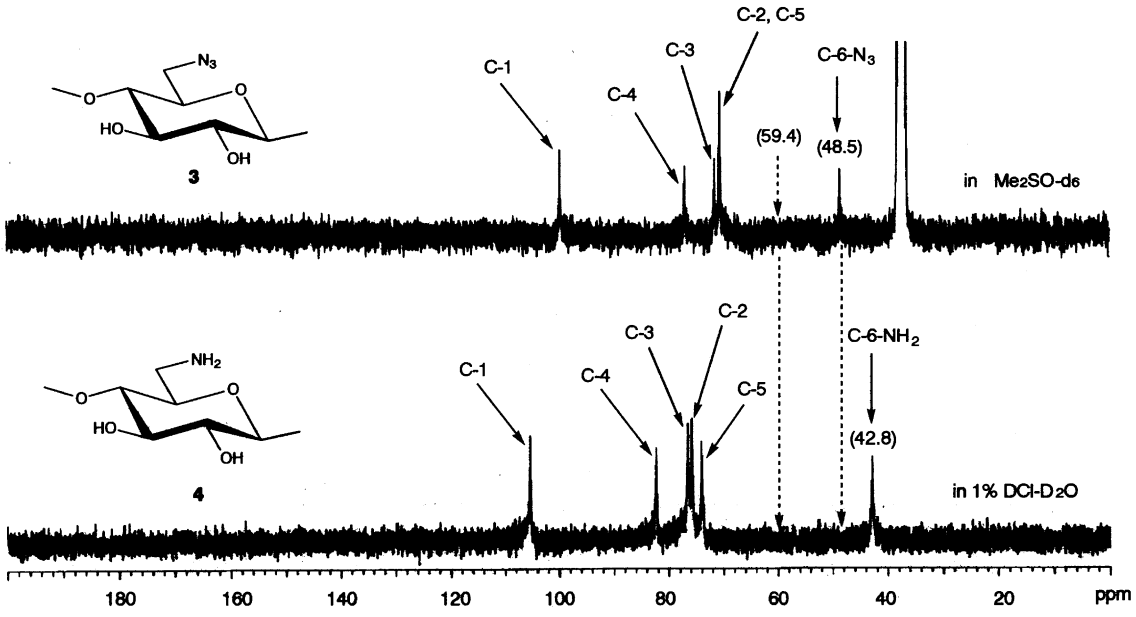


Figure 1. ^{13}C NMR spectra of 6-azido-6-deoxycellulose (**3**) and 6-amino-6-deoxycellulose (**4**).

appeared as singlets. The peak for C-6-N_3 at 48.5 ppm had completely disappeared, and a new peak for C-6-NH_2 appeared at 42.8 ppm. The spectrum gives only a singlet peak at 105.3 ppm for C-1, contrast to the spectrum by Liu and Baumann.[11] The infrared spectrum of aminocellulose **4**, showed that the typical azide absorption at 2111 cm^{-1} had disappeared, indicating that the azide group at C-6 had been reduced quantitatively to the amino group, and that the expected 6-amino-6-deoxycellulose (**4**) had been formed. The DS of **4** was found to be 0.96.

The DP_n (degree of polymerization) of the aminocellulose **4** was evaluated by gel permeation chromatography (GPC) measurements of its acetylated derivative, prepared by the reaction with Ac_2O–pyridine–Me_2N-COMe at 60 °C for 48 h. The DP_n of the aminocellulose **4** was found to be 66.

Although depolymerization occurred to some extent during the preparation, the 6-amino-6-deoxycellulose (**4**) was obtained in high yields (67%) by this sequence with only three steps.

1. Experimental

1.1. General methods

^{13}C NMR spectra were recorded with a Varian INO-VA300 FT-NMR (75 MHz) spectrometer in Me_2SO-d_6 or in 1% DCl–D_2O. Chemical shifts (δ) are given in δ values (parts per million). Infrared spectra were measured in KBr pellets with a Shimadzu FTIR-8600 spectrophotometer. Number-average molecular weights of the cellulose derivatives were measured by gel permeation chromatography (GPC) in $CHCl_3$ at 40 °C. Shodex columns (KF802, KF802.5, and K805), a Shimadzu liquid chromatography injector (LC-10ATvp), a Shimadzu column oven (CTO-10Avp), a Shimadzu UV–vis detector (RID-10A), a Shimadzu communication bus module (CBM-10A), and a Shimadzu LC workstation (CLASS-LC10) were used. Calibration curves were obtained by using polystyrene standards (Shodex). The flow rate was 1.0 mL/min. The DS of the cellulose derivatives were determined by elemental analysis.

Microcrystalline cellulose (Avicel®, DP = 114) and lithium bromide were purchased from Merck Co. and Sigma–Aldrich, respectively. The other reagents were purchased from Nakarai Tesque Inc. (Kyoto, Japan) or Wako Pure Chemical Industries, Ltd (Osaka, Japan). All chemicals and reagents, unless otherwise specified, were used without further purification. NBS was recrystallized from CCl_4–1,4-dioxane. Microcrystalline cellulose and lithium bromide were dried in vacuo at 100 °C for 1.5 h and at 130 °C for 3 h, respectively, before use.

1.2. Bromination of cellulose (1)

Microcrystalline cellulose (1.0 g, 6.2 mmol) was suspended in Me_2NCOMe (60 mL and stirred at 130 °C for 2 h. The temperature was lowered to 100 °C and LiBr (14.08 g, 162 mmol) was added. The mixture was kept for further 30 min at this temperature with stirring. The temperature was further lowered to room temperature. The mixture became a slightly yellow, viscous solution within 1 h.

The solution was stirred under cooling in an ice-water bath. Triphenylphosphine (4.05 g, 15.4 mmol) in Me_2COMe (30 mL) was added to the solution at 0 °C and then NBS (2.75 g, 15.4 mmol) in Me_2NCOMe (30 mL) was added dropwise at 0 °C. After stirring at 70 °C for 2 h, the mixture was poured into acetone. The resulting precipitate was filtered and washed three times with acetone. The residue was stirred in acetone for 2 h, filtered off and washed with distilled water. The residue was further stirred in $NaHCO_3$ solution (0.07 mol/L) at room temperature overnight, filtered, and washed with distilled water. The residue was stirred in distilled water at room temperature for 2 h, filtered, washed with distilled water several times, and freeze-dried to give 6-bromo-6-deoxycellulose (**2**) as a slightly brown powder (1.29 g, yield: 93%; DS = 0.98).

1.3. Nucleophilic displacement of 6-bromo-6-deoxycellulose (2) by sodium azide

6-Bromo-6-deoxycellulose (**2**) (200 mg, 0.89 mmol) was suspended in Me_2SO (20 mL). After addition of NaN_3 (578 mg, 8.89 mmol) and n-Bu_4NI (33 mg, 0.09 mmol), the mixture was stirred at 70 °C for 48 h, and poured into distilled water. The precipitate was filtered off and washed with distilled water. The residue was further stirred in distilled water for 2 h, filtered off, washed with distilled water and with CH_3OH, and dried in vacuo to afford 6-azido-6-deoxycellulose (**3**) as a slightly brown powder (134 mg, yield: 81%; DS = 0.96). IR (KBr): ν 3435 (OH), 2907 (CH), 2111 (N_3) cm^{-1}; ^{13}C NMR (Me_2SO-d_6, at 50 °C) δ 99.7 (C-1), 77.0 (C-4), 71.5 (C-3), 70.6 (C-5), 70.5 (C-2), 48.5 (C-6) ppm.

1.4. Reduction of the azido group of 6-azido-6-deoxycellulose (3) to the amino group

6-Azido-6-deoxycellulose (**3**) (200 mg, 1.1 mmol) was added to Me_2SO (40 mL). The mixture was stirred at 60 °C, and became a clear solution within 1 h. After the addition of $NaBH_4$ (809 mg, 21.4 mmol), the mixture was stirred at 60 °C for 48 h. HCl (1 M) was slowly added to the mixture at 0 °C until generation of gas ceased, and the mixture was neutralized by saturated aq $NaHCO_3$ centrifuged (10,000 rpm, 10 min), washed with distilled water 10 times and freeze-dried to give

6-amino-6-deoxycellulose (**4**) as a colorless powder (154 mg, yield; 89%; DS = 0.96). IR (KBr): *v* 3369 (OH and NH_2), 2907 (CH) cm^{-1}; ^{13}C NMR (1% DCl in D_2O, at 20 °C) δ: 105.3 (C-1), 82.2 (C-4), 76.5 (C-3), 75.7 (C-2) 74.0 (C-5) 42.8 (C-6) ppm.

6-Amino-6-deoxycellulose (**4**) (20 mg, 0.11 mmol) was added to Ac_2O (0.5 mL), pyridine (0.5 mL), and Me_2N-COMe (1 mL). The mixture was stirred at 60 °C for 48 h, and then poured into MeOH (50 mL). The precipitate was filtered off, washed with MeOH, and dried in vacuo to give the acetylated product for analysis by GPC.

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