# Synthesis of Natural- and Non-natural-type Aminopolysaccharides: 2-Acetamido-2-deoxy-β-D-glucopyranan Derivatives by Acid-Catalyzed Polymerization of 2-Methyl(3,6- and 3,4-di-*O*-benzyl-1,2-dideoxy-α-D-glucopyrano)-[2,1-*d*]-2-oxazolines Involving Stereoregular Glycosylation

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ABSTRACT: This paper describes the acid-catalyzed polymerization of two saccharide monomers, 2-methyl(3,6-di-*O*-benzyl-1,2-dideoxy-α-D-glucopyrano)-[2,1-*d*]-2-oxazoline (**1**) and 2-methyl(3,4-di-*O*-benzyl-1,2-dideoxy-α-D-glucopyrano)-[2,1-*d*]-2-oxazoline (**3**). The polymerization of **1** and **3** proceeded by stereoregular glycosylation to give natural- and non-natural-type aminopolysaccharides **2** and **4**, respectively. The polymer structures were determined by means of $^1$H NMR, $^{13}$C NMR, and IR spectra as well as elemental analyses. The molecular weight of **2** was at most 4900, whereas the highest molecular weight of **4** was 13 100. Debenzylation of **2** and **4** was carried out by the catalytic hydrogenation in the presence of 10% Pd−C to give free aminopolysaccharides.

## Introduction

The synthesis of polysaccharides is one of the important research projects to elucidate the biological mechanism of naturally occurring polysaccharides. For synthetic approaches to polysaccharides with well-defined structures, the control of stereoregularity at the anomeric position is most difficult.[1] A few methods, therefore, such as the trityl−cyanoethylidene method,[2] ring-opening polymerization,[3] and enzymatic polymerization[4] have been available to solve this problem so far.

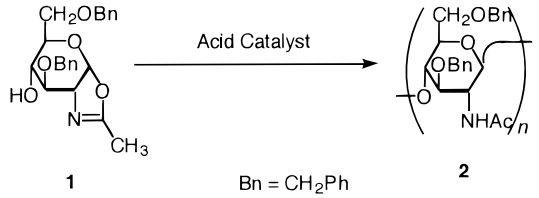
In carbohydrate chemistry, stereospecific glycosylation is still a topic of current research. The oxazoline method is one of the excellent glycosylations for high stereoselectivity, in which the stereospecific glycosylation of alcohol with an oxazoline derivative of an amino sugar is achieved in the presence of an acid catalyst to give β-glycoside.[5]

Recently, we have reported a stereoregular polymerization of an oxazoline-type monomer, 2-methyl(3,6-di-*O*-benzyl-1,2-dideoxy-α-D-glucopyrano)-[2,1-*d*]-2-oxazoline (**1**) by means of an acid catalyst to give the dibenzylchitin-type polysaccharide, 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-(1→4)-β-D-glucopyranan (**2**) (Scheme 1).[6]

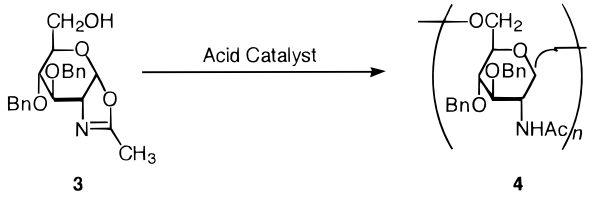
In relation to this polymerization approach, only one example of the synthesis of a polysaccharide by means of an orthoester glycosylation method has been previously reported.[7]

In this paper, we report the comprehensive and extended results of this type of polymerization using oxazoline-type saccharide monomers. Two monomers **1** and 2-methyl(3,4-di-*O*-benzyl-1,2-dideoxy-α-D-glucopyrano)-[2,1-*d*]-2-oxazoline (**3**) were polymerized by an acid catalyst to give two kinds of aminopolysaccharides, 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-(1→4)-β-D-glucopyranan (**2**) and 2-acetamido-3,4-di-*O*-benzyl-2-deoxy-(1→6)-β-D-glucopyranan (**4**), respectively (Schemes 1 and 2).

**Scheme 1**




**Scheme 2**




The former has the natural (chitin-type) structure in the main chain, whereas the latter has a non-natural structure. Furthermore, deprotection of the obtained polymers is described.

## Results and Discussion

**Polymerization of 1.** As previously reported by us,[6] the polymerization of **1** was carried out with an acid catalyst in 1,2-dichloroethane solvent at reflux temperature. The structure of the isolated polymer was determined by means of $^1$H NMR, $^{13}$C NMR, and IR spectra as well as elemental analysis.

The $^1$H NMR spectrum of the polymer in $CDCl_3$ showed broad peaks at δ 1.75−2.20 due to methyl protons of the acetamido group (3H), peaks at δ 3.24−3.97 ascribable to the sugar protons of positions 2−6 (6H), broad peaks at δ 4.40−4.90 assignable to the methylene protons of the benzyl groups and an anomeric proton of the β-glycosidic linkage (5H), and a large peak at δ 7.29 due to aromatic protons (10H). If the α-anomer exists, the peak due to the corresponding anomeric proton generally appears at around δ 5.0−5.5. No peak was observed at that region, indicating that the polym-

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**Table 1. Polymerization of 1 under Various Conditions[a]**

| entry | catalyst (mol % **1**) | time (h) | yield[b] (%) | $M_n$[c] |
|---|---|---|---|---|
| 1 | CSA (10) | 5 | 46 | 2500 |
| 2 | CSA (10) | 20 | 45 | 3600 |
| 3 | CSA (10) | 100 | 44 | 4900 |
| 4 | CSA (10) | 120 | 40 | 4200 |
| 5 | CSA (1) | 5 | 50 | 3000 |
| 6 | TsOH (10) | 5 | 47 | 3400 |
| 7 | TfOH (10) | 120 | 49 | 3900 |

[a] At reflux temperature in 1,2-dichloroethane as solvent. [b] Part insoluble in hexane. [c] Determined by GPC with chloroform eluent.

erization proceeded by the stereoregular glycosylation to give (1→4)-$\beta$-glucopyranan **2**.

The following $^{13}C$ NMR data of the same sample also supported structure **2**.[8] Peaks at $\delta$ 99.75, 81.00, 77.67, 72.11, 70.40, and 52.18−56.48 are assignable to sugar carbons of positions 1, 4, 3, 5, 6, and 2, respectively. Peaks at $\delta$ 170.40 and 23.24 are ascribable to a carbonyl carbon and a methyl carbon of the acetamido group, respectively. Peaks at $\delta$ 127.51−138.35 and 73.39 are assignable to aromatic carbons and methylene carbons of the benzyl groups, respectively. Specifically, as there was no peak attributable to C1 of an α-glycoside (below $\delta$ 100), only the $\beta$-configuration was tenable.

The IR spectrum of the product polymer showed the disappearance of the absorption at 1668 $cm^{-1}$ due to C═N of monomer **1** and the appearance of the new absorption at 1654 $cm^{-1}$ due to C═O of acetamido, indicating that the polymerization proceeded with the formation of an acetamido group via the glycosylation between the oxazoline ring and alcohol to give polymer **2**.

Anal. Calcd for $[C_{22}H_{25}NO_5(H_2O)]_n$: C, 65.82; H, 6.78; N, 3.49. Found: C, 65.53; H, 6.09; N, 3.18. All above spectroscopic and elemental analysis data support the polymer structure **2**.

Table 1 shows the polymerization results under various conditions. Three kinds of sulfonic acids, 10-camphorsulfonic acid (CSA), *p*-toluenesulfonic acid (TsOH), and trifluoromethanesulfonic acid (TfOH), were used as acid catalysts. These acids have already been employed in glycosylation using an oxazoline-type glycosyl donor.[9−11] All the acids catalyzed the polymerization of **1** to produce aminopolysaccharide **2**. A longer reaction time gave polymer with higher molecular weight (entries 1−3). The molecular weight, however, decreased with further extension of the reaction time to 120 h (entry 4). Under the same reaction time and temperature, the use of a smaller ratio of catalyst toward monomer **1** gave polymer with higher molecular weight (entries 1 and 5). The highest molecular weight was 4900 (degree of polymerization ca. 13) under the conditions of entry 3.

**Polymerization of 3.** The polymerization of **3** was also carried out with CSA (10 mol % for **3**) in 1,2-dichloroethane at reflux temperature. Figure 1a shows the gel permeation chromatographic (GPC) profile of the reaction mixture obtained with a reaction time of 3 h without a work-up procedure. The chart shows the bimodal profile consisting of a peak in the polymer region and a peak in the low molecular weight region; the former corresponds to the molecular weight of ca. 10 000 and the latter is located in the same region as the peak of monomer **3**. These GPC data indicate that the reaction mixture contains two kinds of products. In order to separate these two materials, the reaction mixture was poured into a large amount of 1,2-

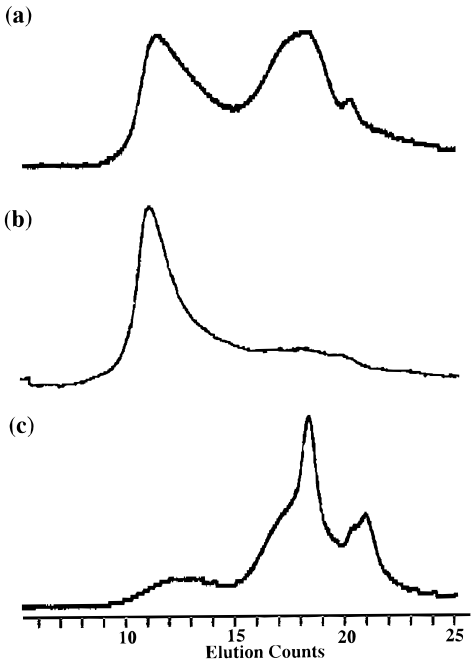



**Figure 1.** GPC charts of the crude reaction product (a), 1,2-dimethoxyethane insoluble part (b), and 1,2-dimethoxyethane soluble part (c).

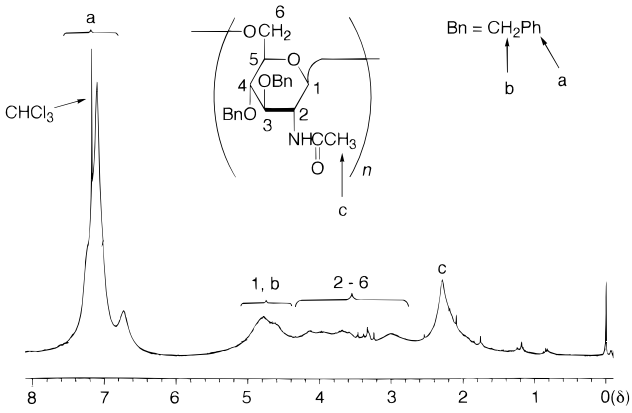



**Figure 2.** $^1H$ NMR spectrum of polymer **4** in $CDCl_3$.

dimethoxyethane (DME). Parts b and c of Figure 1 show the GPC profiles of DME insoluble and soluble parts, respectively. The GPC profile of the DME insoluble part (Figure 1b) shows one peak in the polymer region, indicating that the product polymer can be isolated by pouring the reaction mixture into DME. The molecular weight of this peak was calculated to be 12 600 by using a calibration curve with polystyrene standards. On the other hand, the GPC profile of the DME soluble part (Figure 1c) shows mainly the peak in the low molecular weight region accompanied by a small peak in the polymer region. This polymer peak appears at a higher elution volume compared with that in the GPC profile of the DME insoluble part in Figure 1b, indicating that the lower molecular weight part of the product polymer is soluble in DME.

The structure of the DME insoluble polymer was determined by $^1H$ NMR, $^{13}C$ NMR, and IR spectra as well as elemental analysis. Figure 2 shows the $^1H$ NMR spectrum of the DME insoluble polymer ($CDCl_3$). Peak c at $\delta$ 2.24 is due to methyl protons of the acetamido group (3H). Peaks at $\delta$ 3.02−4.15 are ascribable to sugar protons of positions 2−6 (6H). Peaks at $\delta$ 4.41−5.10 are assignable to methylene protons of benzyl groups and the anomeric proton of the $\beta$-glycosidic

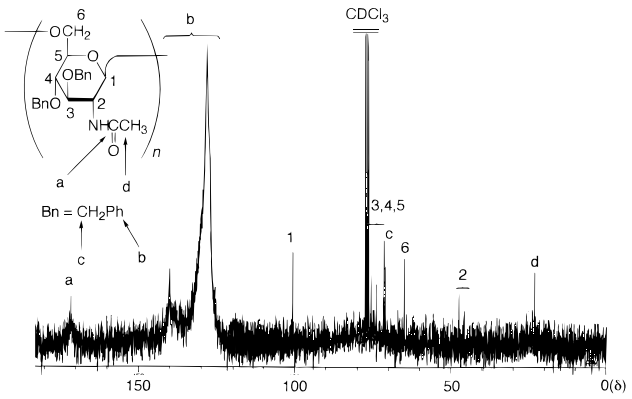
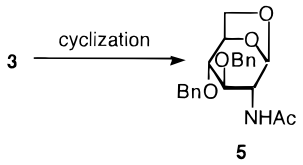



**Figure 3.** $^{13}C$ NMR spectrum of polymer **4** in $CDCl_3$.

**Scheme 3**




**5**

linkage (5H). The large peak a at $\delta$ 6.75−7.30 is due to aromatic protons (10H).

The $^{13}C$ NMR spectrum of the same sample is shown in Figure 3. The peaks' assignments are as follows. The peak at $\delta$ 100.67 is due to an anomeric sugar carbon. Peaks at $\delta$ 77.20, 75.63, and 71.18 are assignable to sugar carbons of positions 3−5. Peaks at $\delta$ 65.02 and 45.79−47.50 are ascribable to positions 6 and 2, respectively. Peaks a and d at $\delta$ 172.33 and 23.25 are due to a carbonyl carbon and a methyl carbon of the acetamido group, respectively. Peaks b and c at $\delta$ 119.43−142.82 and 71.75 are assignable to aromatic carbons and methylene carbons of the benzyl groups, respectively. Only one peak due to the anomeric carbon corresponding to $\beta$-glycoside appears, indicating that the polymerization proceeded by stereoregular glycosylation to give (1→6)-$\beta$-glucopyranan **4**.

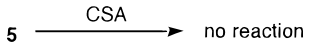
The IR spectrum of the product polymer showed the disappearance of the absorption at 1670 $cm^{-1}$ due to C═N of monomer **3** and the appearance of the new absorption at 1654 $cm^{-1}$ due to C═O of acetamido. These data indicate that the polymerization proceeded with the formation of an acetamido group via the reaction between the oxazoline ring and alcohol to give polymer **4**.

Anal. Calcd for $(C_{22}H_{25}NO_5)_n$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.99; H, 6.81; N, 3.51. All above mentioned spectroscopic data and the elemental analysis data can be taken to support polymer structure **4**.

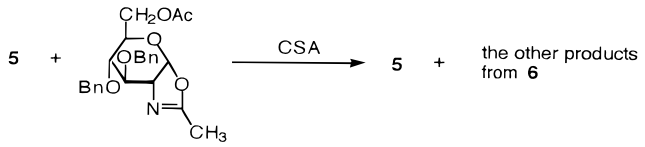
On the other hand, the low molecular weight product was isolated from the reaction mixture by using silica gel column chromatography. The structure of the product was determined as 1,6-anhydro-2-acetamido-2-deoxy-3,4-di-*O*-benzyl-$\beta$-D-glucopyranose (**5**) by $^1H$ and $^{13}C$ NMR spectra as well as elemental analysis. These data indicate that the intramolecular cyclization of monomer **3** occurred during the reaction (Scheme 3).

To confirm the reactivity of **5** under the reaction conditions, the following two model reactions were carried out. When **5** was refluxed in 1,2-dichloroethane solvent in the presence of CSA, no product was obtained by thin layer chromatographic (TLC) analysis and **5** was recovered in 79.4% yield from the reaction mixture (Scheme 4). This result shows that CSA did not induce any reaction of **5** such as ring-opening polymerization.

**Scheme 4**




**Scheme 5**




**6**

**Table 2. Polymerization of 3 with CSA Catalyst (10 mol % for 3) under Various Conditions[a]**

| entry | temp (°C) | time (h) | yield[b] (%) | $M_n$[c] |
|---|---|---|---|---|
| 1 | reflux | 1 | 19 | 12 600 |
| 2 | reflux | 3 | 17 | 12 600 |
| 3 | reflux | 5 | 17 | 11 800 |
| 4 | reflux | 8 | 21 | 13 100 |
| 5 | 60 | 3 | 17 | 10 000 |
| 6[d] | reflux | 15 | 12 | 12 800 |
| 7[e] | reflux | 3 | 32 | 12 600 |
| 8[e] | 60 | 3 | 28 | 4000 |

[a] Monomer (0.20 mmol) in 1.0 mL of 1,2-dichloroethane. [b] Part insoluble in DME. [c] Determined by GPC with chloroform eluent. [d] Monomer (0.20 mmol) in 2.0 mL of 1,2-dichloroethane. [e] Monomer (5.0 mmol) in 8.0 mL of 1,2-dichloroethane.

Furthermore, **5** was refluxed with 2-methyl(6-*O*-acetyl-3,4-di-*O*-benzyl-1,2-dideoxy-α-D-glucopyrano)-[2,1-*d*]-2-oxazoline (**6**) in 1,2-dichloroethane solvent in the presence of CSA (Scheme 5).

The TLC analysis of the reaction mixture showed the presence of **5** in the mixture, and **5** was recovered in 97.5% yield from the mixture together with the other products formed from **6**. The result of the above reaction indicates that **5** did not react with the oxazoline ring in the presence of CSA. All above results of two model reactions support that the polymerization and the intramolecular cyclization of **3** took place as a parallel reaction to each other and formed **5** was not related with the polymerization reaction.

Table 2 summarizes the polymerization results of **3** catalyzed by CSA under various conditions. The molecular weights of the polymers obtained by the reflux temperature of 1,2-dichloroethane using CSA of 10 mol % for monomer are around 12 000 (entries 1−4). A lower reaction temperature gave polymers with lower molecular weights (entries 5 and 8). Under higher concentration conditions, the yield of the polymer was higher (entries 7 and 8). This is attributed to the prevention of the intramolecular cyclization under the higher concentration condition. The molecular weight of **4** is higher than that of **2** obtained by the similar reaction condition. This is probably due to the higher reactivity of a primary alcohol at position 6 of **3** than that of a secondary alcohol at position 4 of **1**.

**Debenzylation of Polymers 2 and 4.** Debenzylation of polymers **2** and **4** obtained above was carried out to give free aminopolysaccharides **8** and **9**, respectively. Previously, debenzylation of the synthetic polysaccharide derivatives has been carried out by Birch reduction (sodium in liquid ammonia).[12] In the case of debenzylation of **2** and **4**, however, Birch reduction was not effective. Instead of that, hydrogenation in the presence of Pd−C was useful for the debenzylation of **2** and **4**.

The catalytic hydrogenation of **2** (entry 3 in Table 1) was carried out in the presence of 10% Pd−C and a small amount of hydrochloric acid in a mixed solvent of DMF and water (3:1, v/v) at 40 °C (Scheme 6).

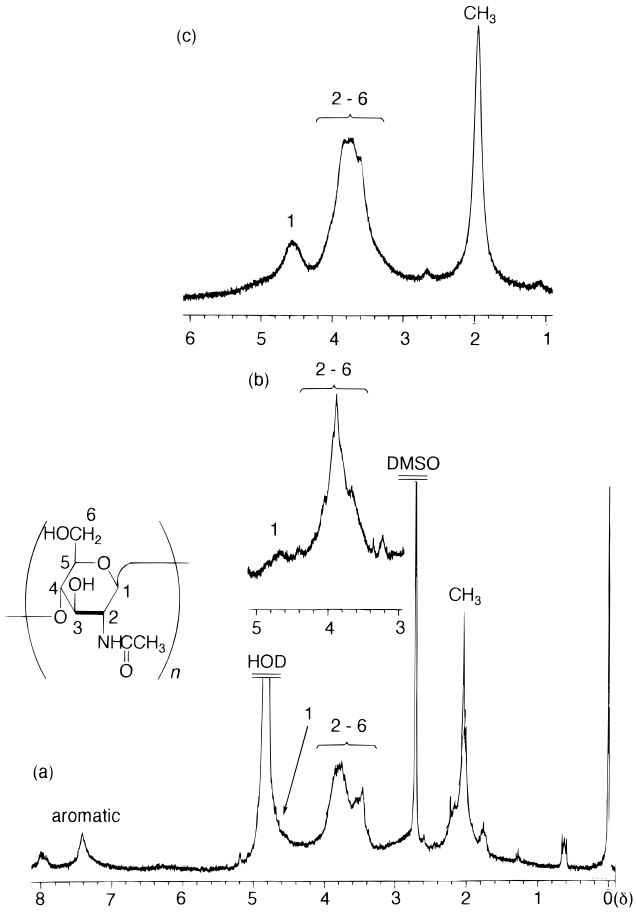
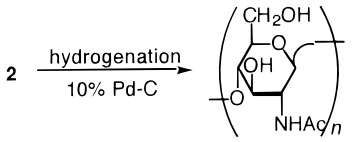



**Figure 4.** $^1$H NMR spectra of debenzylated polymer from **2** in a mixed solvent of $D_2O$ and DMSO-$d_6$ (a) and in acetic acid-$d_4$ (b) and of natural chitin in formic acid-$d_2$ (c).

**Scheme 6**




**7**

Figure 4a shows the $^1$H NMR spectrum of the obtained polymer in a mixed solvent of $D_2O$ and DMSO-$d_6$. A peak at $\delta$ 2.16 is due to the methyl protons of the acetamido group (3H). Broad peaks at $\delta$ 3.36−4.20 are assignable to the sugar protons of positions 2−6 (6H). A peak due to the $\beta$-anomeric proton is overlapping with a peak of water. When the $^1$H NMR spectrum was measured in acetic acid-$d_4$ solvent (Figure 4b), the anomeric peak appeared at $\delta$ 4.50−5.00. The sugar peaks' pattern in Figure 4b is very similar to that of natural chitin in Figure 4c measured in formic acid-$d_2$, supporting the oligochitin structure of the debenzylated polymer. Absorption of aromatic protons, however, is still present at $\delta$ 7.42, indicating the incomplete debenzylation of the polymer. From the integrated ratio between this aromatic peak and the methyl peak of the acetamido, it can be calculated that ca. 90% of the benzyl groups were cleaved by the catalytic hydrogenation. The molecular weight of the debenzylated polymer was estimated to be 2800 by the GPC measurement with water eluent. This value is in very good agreement with the calculated value (2600) based on the molecular weight of polymer **2** before the debenzylation. The debenzylated polymer is relatively soluble in water,

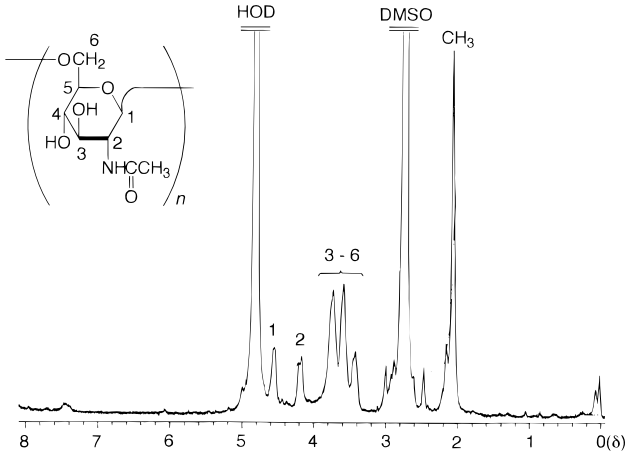
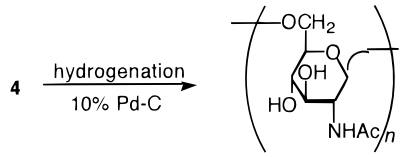



**Figure 5.** $^1$H NMR spectrum of debenzylated polymer from **4** in a mixed solvent of $D_2O$ and DMSO-$d_6$.

**Scheme 7**




**8**

acetic acid, DMSO, DMF, and a water/DMF mixed solvent (the solvent of the hydrogenation) in spite of its oligochitin structure, in which natural chitin is insoluble in such solvents. The X-ray diffraction (XRD) measurement of the debenzylated polymer did not show any peaks, indicating no crystallinity of the polymer. This XRD result is completely different from that of natural chitin, which has shown the characteristic peaks due to the crystallinity of natural chitin.[13] This is probably due partly to the existence of benzyl groups in the product polymer, and no crystallinity may cause the higher solubility compared with natural chitin.

The hydrogenation of **4** (entry 7 in Table 2) was carried out in an experimental manner similar to that of **2** (Scheme 7).

The $^1$H NMR spectrum of the product polymer ($D_2O$ + DMSO-$d_6$) is shown in Figure 5. Peak assignments are as follows. A peak at $\delta$ 2.09 is due to the methyl protons of the acetamido group (3H). Multiplet peaks at $\delta$ 3.36−3.89 are assignable to the sugar protons of positions 3−6 (5H). Peaks at $\delta$ 4.18 and 4.55 are ascribable to the sugar protons of positions 2 and 1, respectively (1H and 1H). The $^{13}$C NMR spectrum of the product polymer in $D_2O$ shows $\delta$ 20.86 ($CH_3$), 53.93 (C2), 66.96, 68.50, 72.22, 74.30 (C3−6), 100.01 (C1), and 172.87 (C═O). No observation of the aromatic peak in those $^1$H and $^{13}$C NMR spectra indicates the occurrence of the perfect debenzylation, giving rise to polysaccharide **8**. The molecular weight determined by GPC with water eluent was 5600, which is in good agreement with the calculated value (6200). The solubility of **8** in water, DMSO, and DMF is higher than that of **7**.

## Conclusions

Acid-catalyzed polymerization of oxazoline-type saccharide monomers **1** and **3** proceeded by stereoregular glycosylation to give natural- and non-natural-type aminopolysaccharides **2** and **4**, respectively. The debenzylation of **2** and **4** by the catalytic hydrogenation was carried out to give free aminopolysaccharides. The

debenzylation of **2** was incomplete, whereas the perfect debenzylation of **4** took place to produce polysaccharide **8**.

## Experimental Section

**Materials.** Monomer **1** and compound **6** were prepared according to the literature.[6,14] Acid catalysts, 10-camphorsulfonic acid, *p*-toluenesulfonic acid, and trifluoromethanesulfonic acid were purified according to the usual manners. Solvents, 1,2-dichloroethane and DMF, were purified by distillation. Other reagents and solvents were commercially available and used without further purification.

**Synthesis of Monomer 3.** To a solution of **6** (1.47 g, 3.45 mmol) in dry methanol (10 mL) was added sodium methoxide (0.085 g, 1.57 mmol) at 0 °C under argon, and the mixture was stirred for 1 h at room temperature. The reaction mixture was poured into ice-water and extracted twice with ethyl acetate. The extract was washed with water, dried over sodium sulfate, and evaporated. The residual syrup was dried under reduced pressure at room temperature to give **3** (1.15 g, 3.00 mmol) in 87.0% yield. $^1$H NMR ($CDCl_3$): $\delta$ 1.92 (br s, 1H, OH), 2.04 (s, 3H, $CH_3$), 3.36−3.42 (m, 1H, H5), 3.53−3.64 (m, 2H, H6), 3.72−4.04 (m, 2H, H3 and H4), 4.25 (m, 1H, H2), 4.35, 4.56, 4.59, 4.68 (d, d, d, d, 1H, 1H, 1H, 1H, respectively, $J$ = 11.88 Hz, 12.15 Hz, C$H_2$C$_6$H$_5$), 5.97 (d, 1H, $J$ = 7.29 Hz, H1), 7.23−7.37 (m, 10H, aromatic). $^{13}$C NMR ($CDCl_3$): $\delta$ 13.46 ($CH_3$), 61.94, 64.84, 71.43, 74.68, 76.21 (C2, C6, C5, C3, C4), 70.84, 70.94 (*C*H$_2$C$_6$H$_5$), 127.39, 127.48, 127.53, 127.62, 127.92, 128.03, 138.29 (aromatic), 165.71 (N=C−O). IR (neat): 1670 cm$^{-1}$ (N=C). Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.18; H, 6.71; N, 3.59.

**Polymerization of 1.** A typical example was as follows (entry 4 in Table 1). Under argon, monomer **1** (0.945 g, 2.46 mmol) and CSA (0.057 g, 0.246 mmol) were dissolved in 30 mL of 1,2-dichloroethane at room temperature. Then, the mixture was refluxed for 120 h and cooled to room temperature. The reaction mixture was diluted with chloroform and poured into water. The extract with chloroform was washed successively with aqueous sodium hydrogen carbonate and water, dried over sodium sulfate, filtered, and evaporated. The concentrated solution was poured into a large amount of hexane to precipitate a polymeric product. The precipitate was isolated by filtration and dried in vacuo to give 0.369 g of the product polymer (40.0% yield).

**Polymerization of 3.** A typical run was as follows (entry 7 in Table 2). Under argon, monomer **3** (1.91 g, 5.00 mmol) and CSA (0.116 g, 0.500 mmol) were dissolved in 8.0 mL of 1,2-dichloroethane at room temperature. Then, the mixture was refluxed for 3 h and cooled to room temperature. The reaction mixture was diluted with chloroform and poured into water. The extract with chloroform was washed successively with aqueous sodium hydrogen carbonate and water, dried over sodium sulfate, filtered, and evaporated. The concentrated solution was poured into a large amount of DME to precipitate a polymeric product. The precipitate was isolated by filtration and dried in vacuo to give 0.611 g of the product polymer (32.0% yield).

**Isolation of 5.** 1,6-Anhydro-2-acetamido-2-deoxy-3,4-di-*O*-benzyl-$\beta$-D-glucopyranose (**5**) was isolated from the reaction mixture obtained by the conditions of entry 7 in Table 2. To a solution of **3** (1.16 g, 3.01 mmol) in 1,2-dichloroethane (5.0 mL) was added CSA (0.0660 g, 0.300 mmol) at room temperature under argon. After refluxing for 3 h, the reaction mixture was poured into a large amount of water and extracted twice with chloroform. The extract was successively washed with aqueous sodium hydrogen carbonate and water. The solution was dried over sodium sulfate, filtered, and evaporated. The concentrated solution was poured into a large amount of DME, and the precipitate was filtered off. The filtrate was chromatographed on silica gel (Wakogel C-200) with 3:2 (v/v) ethyl acetate/hexane as the eluent to give 1,6-anhydrosugar **5** (0.159 g, 0.416 mmol) in 13.8% yield. $^1$H NMR ($CDCl_3$): $\delta$ 1.96 (s, 3H, $CH_3$), 3.40, 3.45 (s, s, 2H, H6), 3.78 (d, 1H, $J$ = 4.78 Hz, H2), 4.20−4.30 (m, 2H, H3 and H4), 4.40−4.82 (m, 4H, C$H_2$C$_6$H$_5$), 4.60 (d, 1H, $J$ = 3.05 Hz, H5), 5.28 (s, 1H, H1), 7.20−7.40 (m, 10H, aromatic). $^{13}$C NMR ($CDCl_3$): $\delta$ 22.87 ($CH_3$), 47.15, 64.44, 70.53, 70.93, 73.35 (C2, C6, C5, C3, C4), 75.11, 75.15 (*C*H$_2$C$_6$H$_5$), 100.87 (C1), 127.15, 127.19, 127.51, 127.85, 128.01, 136.86, 137.29 (aromatic), 168.84 (C=O). IR (KBr): 1648 cm$^{-1}$ (C=O), Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 69.28; H, 6.68; N, 3.61.

**Model Reaction of 5 in the Presence of CSA.** Under argon, **5** (0.0408 g, 0.107 mmol) and CSA (0.00750 g, 0.0323 mmol) were dissolved in 1,2-dichloroethane (1.0 mL) and the solution was refluxed for 3 h. The mixture was poured into a large amount of water and extracted with chloroform. The extract was successively washed with aqueous sodium hydrogen carbonate and water. The solution was dried over sodium sulfate, filtered, and evaporated. The residual syrup was dried under reduced pressure to give unreacted **5** (0.0324 g, 0.0848 mmol) in 79.4% recovery yield.

**Model Reaction of 5 with 6 in the Presence of CSA.** Under argon, **5** (0.0550 g, 0.143 mmol), **6** (0.122 g, 0.286 mmol), and CSA (0.0200 g, 0.0560 mmol) were dissolved in 1,2-dichloroethane (4.0 mL), and the solution was refluxed for 3 h. Then, the reaction mixture was poured into a large amount of water and extracted twice with chloroform. The extract was successively washed with aqueous sodium hydrogen carbonate and water. The chloroform solution was dried over sodium sulfate, filtered, and evaporated. The residual syrup was dried in vacuo to give products. The recovery yield of **5** was determined to be 97.5% by the $^1$H NMR analysis of the products.

**Debenzylation of 2.** A solution of **2** (entry 3 in Table 1; 0.144 g, 0.377 mmol) in DMF and water (3:1 v/v; 16.0 mL) was hydrogenated in the presence of 10% Pd−C (0.150 g) and a small amount of hydrochloric acid at 40 °C for 24 h under a hydrogen atmosphere. After the residue was filtered off and washed well with DMF and water, the filtrate was concentrated, and acetone was added to the residue. The insoluble product was isolated by filtration and dried in vacuo to give debenzylated product (0.0579 g) in 81.5% yield.

**Debenzylation of 4.** Debenzylation of **4** (entry 7 in Table 2; 0.255 g, 0.666 mmol) was carried out in a mixed solvent of DMF and water (3:1 v/v; 27.0 mL) in the presence of 10% Pd−C (0.250 g) and a small amount of hydrochloric acid at 40 °C for 24 h under a hydrogen atmosphere. After the residue was filtered off and washed well with DMF and water, the filtrate was concentrated and acetone was added to the residue. The insoluble product was isolated by filtration and dried in vacuo to give the debenzylated product (0.0413 g) in 32.5% yield.

**Measurements.** $^1$H and $^{13}$C NMR spectra were recorded on a JEOL EX-270 spectrometer. IR spectra were recorded on a HORIBA FT-200 spectrometer. GPC analyses with chloroform eluent were performed by using a Tosoh HLC-802UR with a UV detector under the following conditions: TSKgel G4000H8 column at a flow rate of 1.0 mL/min with polystyrene standards. GPC analyses with water eluent were performed by using a Hitachi L-7100 with RI detector under the following conditions; TSKgel G3000PW$_{XL}$ column at a flow rate of 1.0 mL/min with pullulan standards. Powder XRD spectra were recorded on a Rigaku powder diffractometer unit using Cu K$\alpha$ (filtered) radiation at 40 kV and 20 mA.

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## References and Notes

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