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Synthesis and Characterization of Cellulose Carbamates Having α-Amino Acid Moieties

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Summary

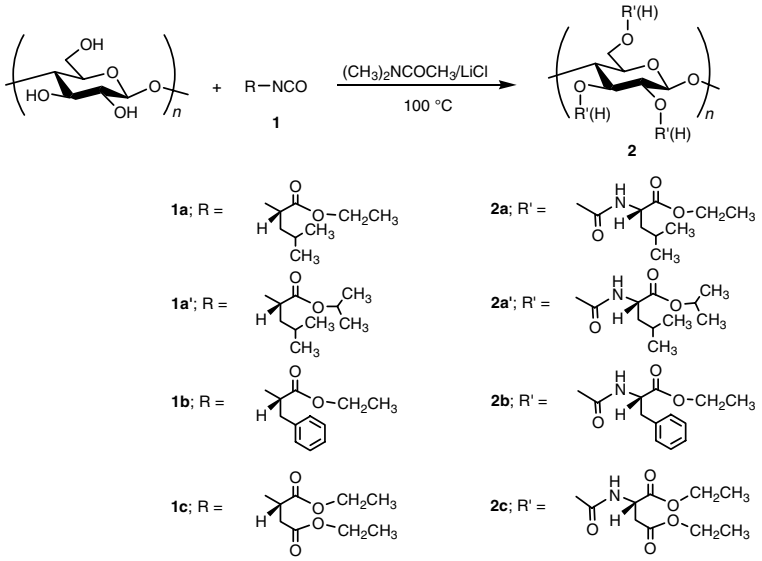
The reaction of cellulose with *N*-carbonyl α-amino acid ester **1** leading to cellulose carbamate **2** was carried out in *N*,*N*-dimethylacetamide at 100 °C. For *N*-carbonyl L-leucine ethyl ester (**1a**), the degree of the carbamate substituent (DS) in **2a** was 2.5 for [**1a**]/[glucose units in cellulose] = 3.0 and reached ca. 3.0 for [**1a**]/[glucose units in cellulose] = 4.0. Cellulose carbamate **2a** was highly soluble in not only aprotic polar solvents but also other organic solvents such as ethyl ether and methyl alcohol. The chiral discrimination ability of **2a** was higher than those of the cellulose carbamates having L-phenylalanine and L-aspartic acid moieties.

Introduction

Cellulose is crystalline, chemically and physically stable, biodegradable, and hydrophilic, but insoluble in water, alcohol, and other common solvents, which causes its poor processability [1]. Thus, in order to widely use cellulose as a raw material, cellulose is converted into various types of derivatives capable of dissolving in an appropriate solvent [2], for example, carboxymethyl cellulose and hydroxyethyl cellulose are soluble in water [3-4] and methyl cellulose, cellulose acetate, and cellulose nitrate are soluble in organic solvents [5-6]. Therefore, of great interest is efforts to design, synthesize, and characterize cellulose derivatives in order to develop the utilization of cellulose–based material.

In the last decade, the importance of cellulose carbamates, which are obtained from the reaction of cellulose with isocyanates, has been increasing, in particular, cellulose tris(phenylcarbamate) has a chiral discrimination property toward various racemates and is used as a chiral stationary phase for liquid chromatography from analytical to industrial scales [7-9]. Thus, it is interesting to expand the family of cellulose carbamate from a viewpoint of material science. In this study, we report the synthesis of cellulose carbamate **2** having α-amino acid moieties, such as L-leucine, L-phenylalanine, and L-aspartic acid from the carbamation of cellulose with *N*-carbonyl

α-amino acid ester **1**, as shown in Scheme 1. In order to control the degree of the carbamate substituent (DS) in **2**, the carbamation reaction is carried out by varying the molar ratio of **1** and the glucose units in cellulose, the kind of α-amino acid moieties, and the kind of ester groups of **1**. The effect of DS on the solubility of **2** is examined using various organic solvents. In addition, the optical resolution property of **2** is discussed as the chiral stationary phase in a high performance liquid chromatography (HPLC) system.



Scheme 1. Reaction of cellulose with *N*-carbonyl α-amino acid ester

Experimental

Materials

Cellulose (Avicel) was purchased from Merck and used after drying under vacuum at 80 °C for 24 h. *N*-Carbonyl L-leucine ethyl ester (**1a**), *N*-carbonyl L-leucine isopropyl ester (**1a'**), *N*-carbonyl L-phenylalanine ethyl ester (**1b**), and *N*-carbonyl L-aspartic acid ethyl ester (**1c**) were prepared according to a previously reported procedure [10].

Synthesis of cellulose carbamates

A solution of cellulose (1.0 g) and lithium chloride (4.2 g) in dry *N*,*N*-dimethylacetamide (45 mL) was heated with stirring at 100 °C for 24 h. To the solution was added *N*-carbonyl L-leucine ethyl ester (**1a**, 4.51 g, 24.3 mmol) and then the entire mixture was heated with stirring at 100 °C for 3 h. The reaction mixture was poured into a large amount of methanol and the precipitate was filtered off. The polymer was dissolved into acetone, this solution was poured into a large amount of methanol/water (1/10, v/v), and the collected precipitate was dried under vacuum to give **2a** as a white solid. Anal. Calcd for $(C_{33}H_{55}N_3O_{14})_n$: C, 55.22; H, 7.72; N, 5.85. Found: C, 55.06; H, 7.98; N, 5.84.

Chiral separation

A macroporous silica gel (10 g, Daiso gel, SP-1000, 7 μm) was refluxed with a large excess of 3-aminopropyl-triethoxysilane (35 mL) in dry toluene (270 mL) for 4 h. The mixture was filtered off and then washed several times with water and methanol, followed by drying under vacuum. Cellulose carbamate (0.75 g) was dissolved in DMAc (10 mL) and the silanized silica gel (3.0 g) was wetted with the solution as uniformly as possible. The solvent was then evaporated under reduced pressure. The remaining polymer solution was adsorbed on the silica gel using the same procedure. The polymer coated silica gel was packed in a stainless-steel tube (25 x 0.46 cm I.D.) by a conventional high-pressure slurry packing technique using a model CCP-085 Econo packer pump (Chemco Scientific Co.). The theoretical plate numbers of the columns were 1,200 – 1,900 for benzene with hexane/2-propanol (9/1) as the eluent at a flow rate of 0.5 mL·min^{-1}. Chromatographic resolution was accomplished on a Jasco HPLC system equipped with UV (Jasco UV-975) and circular dichroism (Jasco CD-1595) detectors at 23 °C. A solution of the racemate (1 – 5 μL) was injected into the chromatographic system using a Rheodyne Model 7725i injector.

Results and discussion

Cellulose was dissolved using a solution of lithium chloride in *N*,*N*-dimethyl-acetamide (DMAc), and then the cellulose was reacted with *N*-carbonyl α-amino acid ester, **1**. In order to study the effect of the ester group in **1** on the degree of the carbamate substitution (DS) of **2**, the reaction using *N*-carbonyl L-leucine ethyl ester (**1a**) and *N*-carbonyl L-leucine isopropyl ester (**1a'**) was carried out under the condition of the ratio of **1** and the glucose units in cellulose ([**1**]/[glucose units in cellulose]) of 5.0 at 100 °C for 24 h. Figure 1 shows the results of the DS vs. reaction time. For all the reaction cases, the yield of the obtained polymer was as high as > 90 %. For **1a**, the DS value, which was estimated using elemental analysis, was 2.2

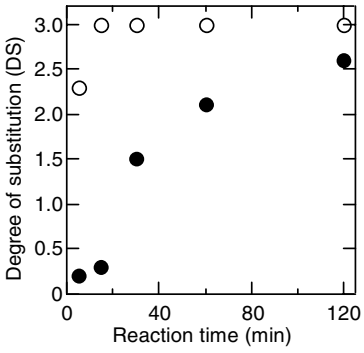


Figure 1. Degree of substitution for the reaction of cellulose with (○) *N*-carbonyl L-leucine ethyl ester (**1a**) and (●) *N*-carbonyl L-leucine isopropyl ester (**1a'**) in DMAc/LiCl at 100 °C for 24 h ([**1**]/[glucose units in cellulose] = 5.0).

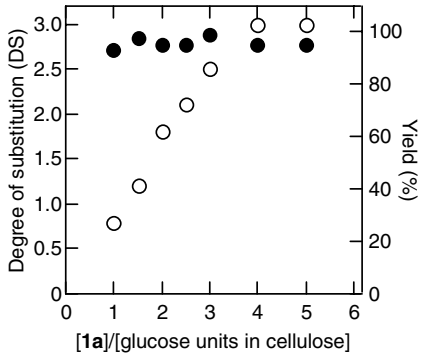


Figure 2. Effect of [*N*-carbonyl L-leucine ethyl ester (**1a**)]/[glucose units in cellulose] on (○) degree of substitution (DS) and (●) yield for the reaction of cellulose with **1a** in DMAc/LiCl at 100 °C for 24 h.

for a 5 min reaction time and reached ca. 3.0 after 30 min. On the contrary, the DS value using **1a'** gradually increased with the reaction time and was 2.6 even after 2 h. The ester group in **1** affected the DS, and thus the following experiments were carried out using the ethyl ester of the *N*-carbonyl α-amino acid.

In order to study the effect of [**1**]/[glucose units in cellulose] on the DS and yield, the reaction of cellulose with **1a** carried out in DMAc/LiCl at 100 °C for 24 h. The yields of the obtained carbamated cellulose were 93 ~ 99 %, as shown in Figure 2. Although the DS value proportionally increased with the increasing [**1a**]/[glucose units in cellulose], the excess amount of **1a** was needed for the preparation of **2a** with a DS of 3.0; the DS value was 2.5 for [**1a**]/[glucose units in cellulose] = 3.0 and reached ca. 3.0 for [**1a**]/[glucose units in cellulose] = 4.0.

Table 1 lists the carbamation results using *N*-carbonyl L-phenylalanine ethyl ester (**1b**) and *N*-carbonyl L-aspartic acid ethyl ester (**1c**). The reactivity of **1b** for the carbamation was very similar to that of **1a**, for example, the DS value was 2.6 and ca. 3.0 for [**1b**]/[glucose units in cellulose] = 3.0 and 4.0, respectively. On the contrary, the reactivity of **1c** was extremely low when the DS value was 1.1 for [**1c**]/[glucose units in cellulose] = 3.0 and 2.7 even though [**1c**]/[glucose units in cellulose] = 6.0. Although **2c** with a DS of 2.7 reacted with **1c** in order to prepare the fully carbamated **2c**, the DS vale of 3.0 was not realized.

The carbamation of cellulose was confirmed by the characteristic absorption due to the carbamate groups in the ^{1}H NMR and IR spectra of **2a**-**c**. In addition, science Knölker reported that the *in situ* derivatization of *N*-carbonyl α-amino acid ester with amines and alcohols afforded the corresponding enantiopure ureas and carbamates, respectively [10], the stereochemistry of the carbamate linkage in **2** should be maintained.

The cellulose carbamates with certain DS values could be obtained by varying [**1**]/[glucose units in cellulose]. Thus, the solubility characteristics of the cellulose carbamates **2a**-**c** were examined using various organic solvents and these results are

Table 1. Synthesis of cellulose carbamate **2** by the reaction of cellulose with *N*-carbonyl L-phenylalanine ethyl ester (**1b**) and *N*-carbonyl L-aspartic acid ethyl ester (**1c**) [a].

	[**1**]/[glucose units in cellulose]	Yield, %	DS [b]
1b	1.5	96	1.0
	2.5	92	2.4
	3.0	94	2.6
	4.0	99	ca. 3.0
1c	1.5	97	0.51
	2.5	96	0.90
	3.0	99	1.1
	4.0	99	2.1
	6.0	98	2.7

a) Cellulose, 1.0 g; solvent; 45 mL of dry *N*,*N*-dimethylacetamide (DMAc) with 4.2 g of lithium chloride (LiCl); temp., 100 °C. b) Degree of substitution in **2** determined by elemental analysis.

listed in Table 2. Although there is an obvious difference in the solubility depending on the α-amino acid moiety and its substitution degree (DS), all samples were soluble in dimethyl sulfoxide (DMSO). The solubility of the aliphatic carbamate (L-leucine and L-aspartic acid) cellulose was higher than that of the aromatic one (L-phenylalanine), and the solubility of **2** increased with the increasing DS value. In addition, **2a** is highly soluble not in only aprotic polar solvents, but also in other organic solvents such as ethyl ether and methyl alcohol.

Table 2. Solubility of cellulose carbamate **2** in various solvents [a].

	2a			**2b**			**2c**		
	DS			DS			DS		
	0.95	2.1	ca. 3.0	1.0	2.4	ca. 3.0	0.90	2.1	2.7
ethyl ether	–	+–	+	–	–	–	–	–	–
ethyl acetate	–	+–	+	–	–	–	–	+	+
MeOH	+	+	+	–	–	–	+	+	+
acetone	+–	+	+	–	+	+	–	+	+
$CHCl_3$	+–	+	+	–	+	+	+–	+	+
THF	+–	+	+	+–	+	+	+–	+	+
DMSO	+	+	+	+	+	+	+	+	+

a) Examined by using 5 mg of **2** in 0.5 mL of solvent at room temperature for 24 h (**+,** soluble; –, insoluble; **+**–, swelling).

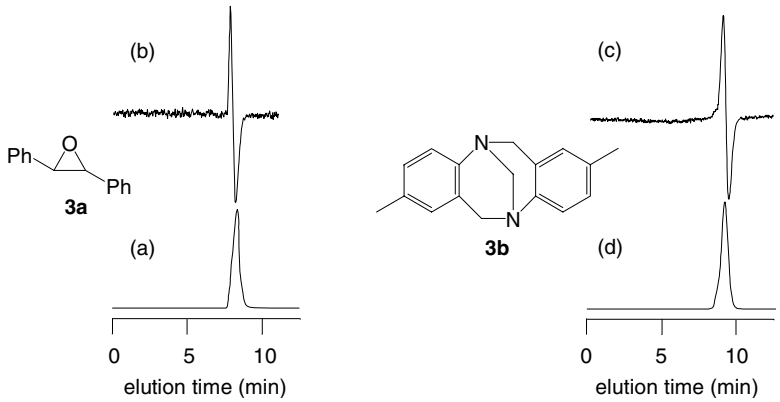
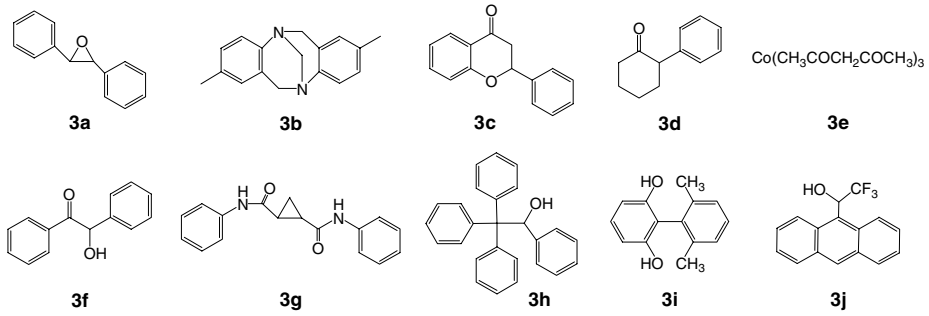


Figure 3. UV- and CD-detected chromatograms for the optical resolution of *trans*-stilbene oxide (**3a**) and Tröger's base (**3b**) using **2a** with an eluent of hexane/2-propanol (v/v, 9/1).

In order to estimate the chiral discrimination property, the optical resolution of the racemates using **2** as a chiral stationary phase was examined in high performance liquid chromatography (HPLC) with hexane/2-propanol (v/v, 9/1) using ultraviolet (UV) and circular dichroism (CD) detectors. Figure 3 shows the chromatograms for the resolution of *trans*-stilbene oxide (**3a**) and Tröger's base (**3b**) using a column

packed with **2a**. Although one peak is only observed at an elution time (e.t.) of 8.0 min for **3a** and 9.2 min for **3b** using a UV detector, there are two peaks consisting of plus and minus sign ones using a CD detector. Flavanone (**3c**, e.t. = 9.7), 2-phenylcyclo-hexanone (**3d**, e.t. = 8.0), cobalt(III) tris(acetylacetonate) (**3e**, e.t. = 8.0), and 1,2,2,2-tetraphenylethanol (**3h**, e.t. = 10.0) are partially resolved as well as **3a**, but benzoin (**3f**), *trans*-cyclopropanedicarboxylic acid dianilide (**3g**), 2,2′-dihydroxy-6,6′-dimethylbiphenyl (**3i**), and 2,2,2-trifluoro-1-(9-anthyl)ethanol (**3j**). On the contrary, the chiral discrimination abilities of **2b** and **2c** are lower than that of **2a**; **3a** (e.t. = 8.5), **3b** (e.t. = 11.2), **3e** (e.t. = 10.8), and **3i** (e.t. = 18.1) are partially resolved using **2b** and **3b** (e.t. = 8.9), **3c** (e.t. = 10.8), and **3e** (e.t. = 8.6) using **2c**.



3a **3b** **3c** **3d** **3e**

3f **3g** **3h** **3i** **3j**

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