Synthesis and Chiral Recognition of Novel Regioselectively Substituted Amylose Derivatives

Shunsuke Kondo,[1] Chiyo Yamamoto,[2] Masami Kamigaito,[1] and Yoshio Okamoto*[3]
[1]*Department of Applied Chemistry, Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8603*
[2]*Suzuka National College of Technology, Shiroko-cho, Suzuka 510-0294*
[3]*EcoTopia Science Institute, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8603*

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Two novel amylose derivatives **1a** and **1b** bearing different substituents at 2-, 3-, and 6-positions of a glucose ring have been successfully synthesized, and their abilities of enantiomer resolution in high-performance liquid chromatography (HPLC) have been evaluated. These derivatives exhibited the ability comparable or better to the commercial amylose-based column, Chiralpak AD.

Polysaccharides, such as amylose and cellulose, are readily converted to benzoate and phenylcarbamate derivatives by reaction with corresponding benzoyl chlorides and phenyl isocyanates, respectively, and some of the derivatives have been widely used as chiral stationary phases (CSP) for HPLC to resolve various chiral compounds.[1] These derivatives usually have the same substituent at the 2-, 3-, and 6-positions, and the derivatives with different substituents at the 6-position and 2, 3-positions are also well known.[2] However, the regioselective introduction of different substituents at 2- and 3-positions has not been attained.

Recently, Dicke reported that the reaction of amylose with vinyl benzoate in dimethyl sulfoxide (DMSO) could selectively esterify the 2-position to benzoate.[3] By using this method, we succeeded in synthesizing amylose derivatives with different substituents on each of the 2-, 3-, and 6-positions, and used them as the CSPs for HPLC (Figure 1).

In order to esterify only the 2-position, amylose was first dissolved in DMSO and reacted with vinyl benzoate in the presence of a catalyst, Na_2HPO_4, at 40 °C (Scheme 1).[3] The obtained mono ester was then allowed to react with 4-methoxytriphenylmethyl chloride to protect selectively 6-position as trityl ether.[4] The obtained 2-benzoyl-6-(4-methoxytrityl)amylose was treated with either 3,5-dimethylphenyl or 3,5-dichlorophenyl isocyanate to convert the 3-hydoxy group to the corresponding phenylcarbamate group. After deprotecting the 6-position with HCl/THF, it was converted to a carbamate group using the corresponding isocyanate to obtain the new amylose derivatives, **1a** and **1b**, whose yields from amylose were 81% and 83%, respectively.

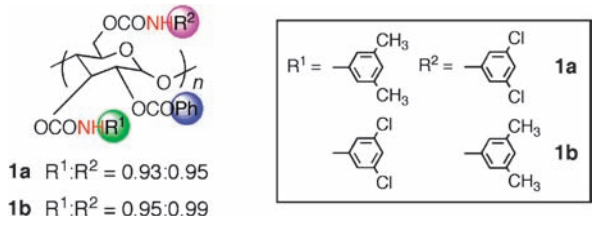
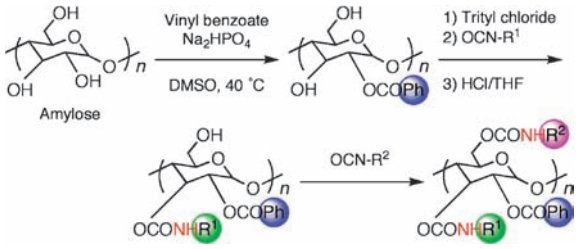


Figure 1. Structure of amylose derivatives, **1a** and **1b**.



Scheme 1. Synthesis of amylose derivatives.

The structures of the derivatives were confirmed by ^{1}H and ^{13}C NMR and also by elemental analysis.[5] The ^{1}H NMR spectrum of **1b** is shown in Figure 2. Two NH protons of carbamate residues are assigned to the peaks at 10.6 and 9.7 ppm, whose intensities are almost the same corresponding to the structure of **1b**. The ^{13}C NMR of **1b** in Figure 3 indicates three peaks due to carbonyl carbons and six peaks due to glucose carbons. Both the derivatives are soluble in THF and DMSO, and **1a** even in chloroform.

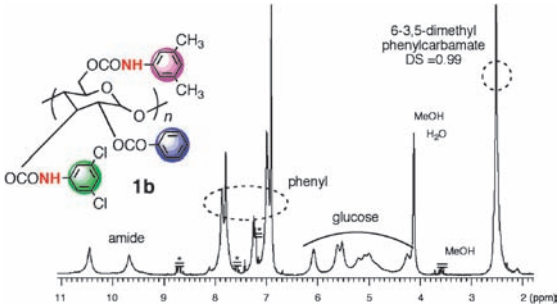


Figure 2. ^{1}H-NMR spectrum of **1b**/pyridine-d_5 at 80 °C. Asterisk is due to pyridine.

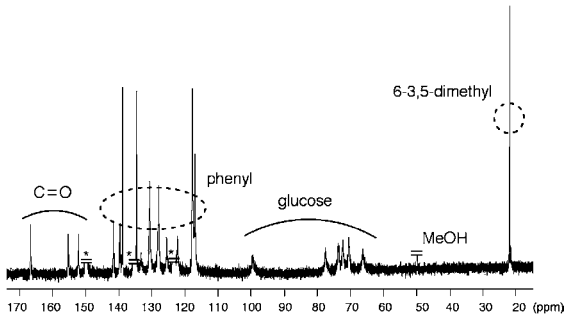


Figure 3. ^{13}C-NMR spectrum of **1b**/pyridine-d_5 at 80 °C. Asterisk is due to pyridine.

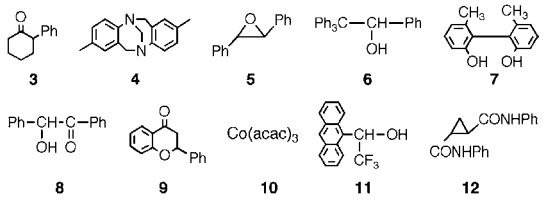


Figure 4. Structures of racemates.

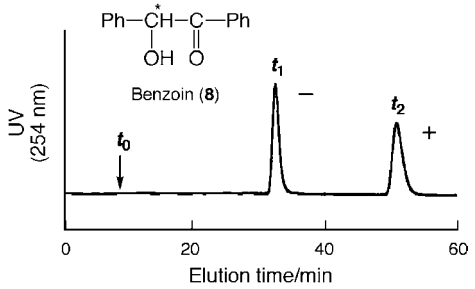


Figure 5. Chromatogram for the resolution of benzoin (**8**) on **1a**.

The derivatives **1a** and **1b** were coated on 3-aminopropyl silica gel (particle size 7 μm, pore size 100 nm, weight ratio of silica to derivative = 75:25) to be used as chiral packing materials. The packing materials were packed into a stainless-steel tube [25 × 0.20 (i.d.) cm] by a slurry method.[6] The plate numbers of the columns were about 1500 for benzene with a hexane–2-propanol (9/1, v/v) mixture as the eluent at the flow rate of 0.1 mL min^{-1}. The dead time (t_0) was estimated using 1,3,5-tri-*tert*-butylbenzene as the nonretained compound.[7]

The resolving ability was estimated using racemates **3**–**12** (Figure 4). Figure 5 shows a chromatogram of the resolution of the racemic benzoin (**8**) on **1a**. The enantiomers were eluted at retention times of t_1 and t_2 with complete separation. The dead time (t_0) was estimated to be 7.63 min. The retention factors, k_1' [$=(t_1 - t_0)/t_0$] and k_2' [$=(t_2 - t_0)/t_0$], were obtained as 3.27 and 5.66, respectively, which led to the separation factor α [$=(k_2'/k_1')$] of 1.73.

The results of the chromatographic resolutions are summarized in Table 1. For comparison, the resolution results on a commercial amylose-based chiral column, Chiralpak AD, which consists of the amylose tris(3,5-dimethylphenylcarbamate) and is known to be one of the most useful CSPs, are also included. The derivatives **1a** and **1b** having a benzoyl ester group at 2-position exhibited an equivalent or higher chiral recognition compared to Chiralpak AD, and racemates **3**, **9**, and **10**, which cannot be resolved effectively on Chiralpak AD, were resolved on both **1a** and **1b**. These phases also had a high recognition ability to racemate **10**, which is usually rather difficult to be resolved on commercially available columns.

The α values on **1a** and **1b** having reversed substituents at 3- and 6-positions are fairly different, indicating that the substituents have a large influence on chiral recognition. Particularly in the resolution of **3**, **9**, and **11**, the elution order of each enantiomer was reversed. The electronic effect of methyl and chloro groups significantly changed the chiral recognition of the CSPs,

Table 1. Separation factor (α) on the amylose derivatives[a]

	1a	1b	Chiralpak AD[b]
3	1.15 (−)	1.24 (+)	1.02 (−)
4	1.85 (+)	2.31 (+)	1.70 (+)
5	1.30 (−)	ca. 1 (−)	2.81 (+)
6	1.07 (+)	1.22 (+)	2.24 (+)
7	1.11 (−)	1.12 (−)	2.22 (−)
8	1.73 (−)	1.97 (−)	1.31 (−)
9	1.17 (−)	1.13 (+)	1.04 (+)
10	1.75 (−)	2.46 (−)	ca. 1 (−)
11	1.18 (−)	1.23 (+)	1.39 (+)
12	3.21 (+)	3.71 (+)	1.59 (+)

[a]Column: 25 × 0.20 (i.d.) cm. Flow rate: 0.1 mL/min. Eluent: hexane/2-propanol (9/1). [b]Column: 25 × 0.46 (i.d.) cm. Flow rate: 0.5 mL/min. Eluent: hexane/2-propanol (9/1). The signs in parentheses represent the optical ratation of the first-eluted enantiomers.

as well as the effect observed between the tris(3,5-dimethylphenylcarbamate) and tris(3,5-dichlorophenylcarbamate) of cellulose[6] and amylose.[8] All 10 racemates could be resolved on **1a**, which appears to be a very useful CSP with wide versatility.

In this study, novel amylose derivatives bearing three different substituents at 2-, 3-, and 6-positions were synthesized and evaluated as the CSPs in HPLC resolution of 10 racemates. The derivatives were stable in the solvents used as eluents and showed a similar or better chiral recognition compared to the Chiralpak AD. To our best knowledge, this is the first example of polysaccharide derivatives having different substituents regioselectively at all three hydroxy groups, and this method may be applicable to the synthesis of various amylose derivatives with different chiral recognitions and also with other functions.

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References and Notes

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5 Elemental analysis. **1a**: Calcd: C, 57.91; H, 4.36; N, 4.66%. Found: C, 57.85; H, 4.13; N, 4.63%. **1b**: Calcd: C, 57.91; H, 4.36; N, 4.66%. Found: C, 57.92; H, 4.35; N, 4.75%.
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