Efficient Immobilization of Cellulose Phenylcarbamate Bearing Alkoxysilyl Group onto Silica Gel by Intermolecular Polycondensation and Its Chiral Recognition

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Cellulose 3,5-dimethylphenylcarbamate bearing a small amount of 3-(triethoxysilyl)propyl residues was synthesized and effectively immobilized onto silica gel support for high-performance liquid chromatography by the polycondensation of triethoxysilyl groups. The immobilized chiral packing material (CPM) showed high chiral recognition as well as the conventional CPM prepared by coating the derivative onto silica gel, and can be used with a variety of eluents.

Polysaccharide-based chiral stationary phases for high-performance liquid chromatography (HPLC) are known to show a broad applicability for the enantioseparation of a wide range of racemates.[1] These phases can also be used for supercritical fluid chromatography (SFC).[2] Among the many polysaccharide derivatives, cellulose tris(3,5-dimethylphenylcarbamate) (**1**) exhibits particularly high chiral recognition abilities for many racemates.[3] This type of chiral packing materials (CPMs) has usually been prepared by coating the polysaccharide derivatives onto a macroporous silica gel as the support. Therefore, the solvents, such as chloroform and tetrahydrofuran (THF), which swell or dissolve the polysaccharide derivatives, cannot be used with these CPMs, and rather limited solvents, such as a hexane–2-propanol mixture for normal phase separation and a water–acetonitrile mixture for reversed phase separation, have been used. Because the selection of a suitable eluent significantly improves the performance of both the analytical and preparative separations by HPLC, the immobilization of the derivatives onto silica gel without reducing ability is highly desirable.[4]

Until today, the polysaccharide derivatives have been immobilized onto silica gel by several methods.[5–8] However, the immobilization methods so far reported appear not to satisfy all of the necessary requirements for CPMs, i.e., high chiral recognition ability, high immobilization efficiency, high stability, simple process, and wide applicability to various polysaccharide derivatives.

Recently, Zou et al. examined the immobilization of the cellulose phenylcarbamate derivatives bearing a 3-(triethoxysilyl)propyl residue onto silica gel by the reaction between the triethoxysilyl group on the derivative and a silanol group on the silica surface.[9] However, they could introduce an almost undetectable amount of 3-(triethoxysilyl)propyl groups on the cellulose, therefore, the derivatives were not sufficiently immobilized.

In the present study, we successfully prepared cellulose 3,5-dimethylphenylcarbamate bearing a desired amount of 3-(triethoxysilyl)propyl residue as a cross-linkable group (**2** in Figure 1), and found that it was efficiently immobilized onto the silica gel via the intermolecular polycondensation of the triethoxysilyl groups under an acidic condition.

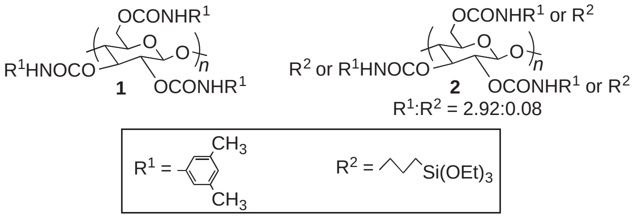

Figure 1. Structures of cellulose derivatives (**1** and **2**).

The cellulose derivative **2** bearing the 3-(triethoxysilyl)propyl residues was synthesized as mentioned below. First, the cellulose (Merck, Avicel) was dissolved in an *N*,*N*-dimethylacetamide–lithium chloride–pyridine mixture, and then allowed to react with 3,5-dimethylphenyl isocyanate (2.5 equiv. per glucose unit) for 6 h at 80 °C, and subsequently with 3-(triethoxysilyl)propyl isocyanate (0.11 equiv. per glucose unit) for 16 h. Finally, the remaining hydroxy groups were treated with an excess of 3,5-dimethylphenyl isocyanate for 7 h at 80 °C. The obtained cellulose derivative was isolated as a methanol-insoluble fraction. The introduction of the 3-(triethoxysilyl)propyl group was confirmed by the $SiCH_2$ peak in the ^{1}H NMR spectrum of the product, and the ratio of the (3,5-dimethylphenylcarbamate)/(3-(triethoxysilyl)propylcarbamate) was determined to be 2.92/0.08. The content of the 3-(triethoxysilyl)propylcarbamate groups can be controlled by the amount of the corresponding isocyanate.

The immobilization process is shown in Figure 2. The cellulose derivative **2** (0.35 g) dissolved in THF (8 mL) was coated on a macroporous silica gel (1.40 g, Daiso gel, 7-µm particle size, 100-nm pore size) based on previous methods.[3] In order to immobilize **2** onto the silica gel by the polycondensation of the triethoxysilyl groups, a mixture of ethanol (6 mL), water (1.5 mL), and trimethylsilyl chloride (0.1 mL) was then added to the coated silica gel and heated for 10 min at 110 °C. The remaining silanol groups on the silica surface are expected to be simultaneously end-capped with a trimethylsilyl group during the immobilization process. After the reaction, the **2**-immobilized CPM was thoroughly washed with THF and then dried.

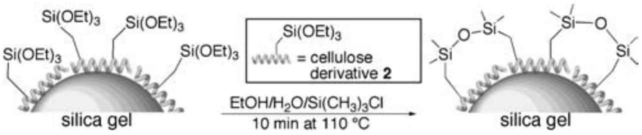

Figure 2. Scheme of immobilization of cellulose derivative **2**.

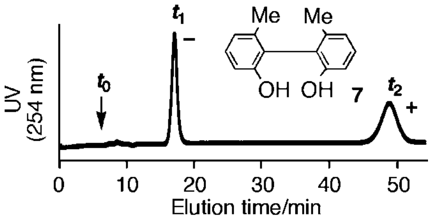

Figure 3. Chromatogram for the resolution of **7** on the **2**-immobilized CPM with hexane/2-propanol (9/1) as eluent.

The amount of the immobilized **2** was estimated to be 97% of the coated **2** based on the content of the organic materials on the CPM estimated by thermogravimetry.

The immobilization seems to be mainly attained by the polycondensation among the triethoxysilyl groups of **2**, because the immobilization efficiency was not decreased when 3-aminopropyl silica gel was used in place of the plain silica gel.

The **2**-immobilized CPM was packed in a stainless-steel tube (25 × 0.20 cm (i.d.)) by a slurry method.[3] The plate number of the column was about 1500 for benzene using hexane–2-propanol (90:10) as the eluent at the flow rate of 0.1 mL min^{-1}. 1,3,5-Tri-*t*-butylbenzene was used as the non-retained compound to estimate the dead time (t_0).[10]

Figure 3 shows the chromatogram for the resolution of the racemic 2,2′-dihydroxy-6,6′-dimethyl-1,1′-biphenyl (**7**) on the **2**-immobilized CPM. 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 7.36 min. The capacity factors, $k_1'[=(t_1 - t_0)/t_0]$ and $k_2'[=(t_2 - t_0)/t_0]$, were obtained as 1.29 and 5.64, respectively, which led to the separation factor α $(=k_2'/k_1')$ of 4.36.

The resolution results of ten racemates (**3**–**12**) (Figure 4) on the immobilized CPM with two eluents are given in Table 1 together with the data for the conventional CPM prepared by coating **1** onto the silica gel.[3] The immobilized CPM showed a high chiral recognition that was comparable to that of the **1**-coated CPM. The higher order structure of **2** after the immobilization seems to be similar to that of **1** coated onto the silica gel. The retention and chiral recognition on the **2**-immobilized CPM did not change even after washing the packed column with THF for 100 h, indicating that various eluents containing any proportion of chloroform and THF can be used without any dissolution of **2** from the column. Some racemates may be better resolved using these solvents.

We now present the facile synthesis of cellulose derivative bearing a controlled amount of a 3-(triethoxysilyl)propyl residue and the efficient immobilization of the derivative onto silica gel by a simple treatment. The immobilized packing material showed a chiral recognition comparable to those of the well-known coated packing material. The methods reported here must also be applicable for other polysaccharide derivatives. The polysaccharide derivatives bearing a controlled amount of the 3-(triethoxysilyl)propyl residue may also be used for the preparation of other types of chiral stationary phases, such as polysaccharide beads,[11] capillary columns, and monoliths.[12] The derivatives may also be used as an ingredient for organic and inorganic nanomaterials. These applications are now in progress.

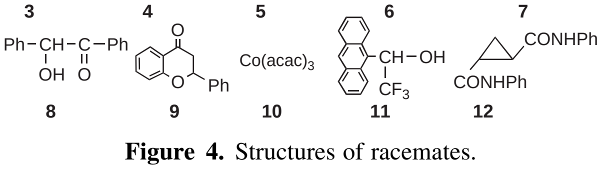

Figure 4. Structures of racemates.

Table 1. Separation factors (α) on the **2**-immobilized and **1**-coated CPMs

	2-immobilized CPM[a]		**1**-coated CPM[b]
	H/I (90/10)	H/C/I (90/10/1)	H/I (90/10)
3	1.31 (−)	1.30 (−)	1.15 (−)
4	1.56 (+)	1.39 (+)	1.32 (+)
5	1.30 (−)	1.82 (−)	1.68 (−)
6	1.18 (+)	1.13 (+)	1.34 (+)
7	4.36 (−)	1.96 (−)	1.83 (−)
8	1.31 (+)	1.34 (+)	1.58 (+)
9	1.19 (−)	1.22 (−)	1.41 (−)
10	ca. 1 (+)	1.0	ca. 1 (+)
11	2.29 (−)	2.77 (−)	2.59 (−)
12	1.48 (+)	1.44 (+)	3.17 (+)

[a]Column: 25 × 0.20 cm (i.d.). Flow rate: 0.1 mL/min. [b]Column: 25 × 0.46 cm (i.d). Flow rate: 0.5 mL/min. Eluent: H: hexane, I: 2-propanol, C: chloroform. The signs in parentheses represent the optical rotation of the first-eluted enantiomer.

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