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Organic-Inorganic Hybrid Materials for Efficient Enantioseparation Using Cellulose 3,5-Dimethylphenylcarbamate and Tetraethyl Orthosilicate

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Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday

Abstract: The hybrid bead-type chiral packing material (CPM) for preparative enantioseparation has been prepared from the cellulose 3,5-dimethylphenylcarbamate containing a small number of 3-(triethoxysilyl)propyl groups in the presence of tetraethyl orthosilicate, by a sol-gel reaction in an aqueous surfactant solution. The obtained hybrid bead-type CPM was packed into a column and evaluated by high-performance liquid chromatography. When compared with the commercially available Chiralpak IB, which is prepared by the immobilization of cellulose 3,5-dimethylphenylcarbamate on silica gel, the hybrid bead-type CPM was shown to exhibit a similar chiral recognition and possess a higher loading capacity.

Keywords: chiral packing material · chiral resolution · organic-inorganic hybrid composites · silicon · sol-gel processes

Introduction

The preparation of optically active compounds has become increasingly important in the fields of drugs, agrochemicals, foods, and functional materials, such as ferroelectric liquid crystals and organic nonlinear optical molecules. Over the past few decades, the direct enantioseparation in high-performance liquid chromatography (HPLC) has significantly advanced as a practical method for obtaining both enantiomers,[1] and has become an indispensable technology particularly for the development of new chiral drugs.[2]

Among the large number of chiral selectors already reported,[3] polysaccharide derivatives, such as cellulose 3,5-dimethylphenylcarbamate (**1** in Figure 1), have been recognized as the most powerful for both analytical and preparative separations.[4] These polysaccharide-based chiral packing materials (CPMs) have been conventionally prepared by coating or immobilizing the polysaccharide derivatives (approximately 20 wt%) on a macroporous silica gel support. This means that a major portion of the CPMs (80 wt%) consists of an achiral silica gel, which is inactive for chiral recognition. Thus, the current CPMs require improvement for large-scale preparative separation.

Although the polysaccharide content in the CPMs needs to be high in order to perform efficient preparative separa-

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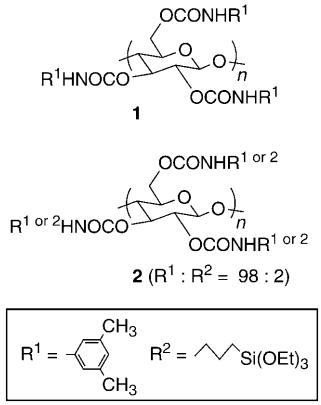

Figure 1. Structures of the cellulose derivatives **1** and **2**.

tions, it is difficult to increase the content obtained by the conventional method without compromising the performance. In order to increase the enantioselective sites in the CPMs, the bead-type CPMs, which are prepared from only polysaccharide derivatives without silica gel, have been developed and shown to have a higher loading capacity than the conventional coated-type CPMs.[5–8] However, these bead-type CPMs suffer from a low mechanical resistance against high pressure arising from the absence of solid inorganic supports.

In the present study, we propose the hybrid bead-type CPM for preparative separation, which is prepared from cellulose 3,5-dimethylphenylcarbamate **2** containing a small number of 3-(triethoxysilyl)propyl groups in the presence of tetraethyl orthosilicate (TEOS), by a sol-gel reaction. The obtained hybrid bead was packed into an HPLC column and its recognition ability was compared to the commercially available immobilized-type CPM, Chiralpak IB, which is prepared by the immobilization of derivative **1** on a silica gel.

Results and Discussion

Preparation of the Hybrid Bead-Type CPM-1 Using Cellulose Derivative 2 and TEOS

The cellulose derivative **2** was synthesized by the stepwise additions of 3,5-dimethylphenyl isocyanate and 3-(triethoxysilyl)propyl isocyanate according to a previous method (Figure 2).[9,10] The ratio of the (3,5-dimethylphenylcarbamate)/(3-(triethoxysilyl)propylcarbamate) was determined to be 98:2 from the ratio of the (aromatic proton)/($SiCH_2$) in the ^1H NMR spectrum.

Figure 3 shows the preparation method and scanning electron microscope (SEM) image of the hybrid bead-type CPM-**1**. Preparation was by the dissolution of **2** (0.25 g) and TEOS (2.0 mL) in a mixture of tetrahydrofuran (THF), 1-heptanol, H_2O, and trimethylsilyl chloride(24/6/1/0.5, *v/v/v/v* = 31.5 mL), and then heating for 9 h at 80 °C. The pretreated solution was then added dropwise to a 0.2% aqueous solution (500 mL) of sodium lauryl sulfate with mechanical stirring (1100 rpm) at 80 °C. After the sol-gel reaction for 1 h at 80 °C, the hybrid beads were isolated by filtration of the suspension. Spherical-shaped hybrid beads with a mean particle size less than 20 μm were obtained (Figure 3). The organic and inorganic contents in the obtained hybrid bead-type CPM-**1** were estimated to be 69 wt% and 31 wt%, respectively, from thermogravimetric (TG) analysis (Code 2 in Table 1).

The hybrid bead-type CPM-**1** could be packed into an HPLC column at a pressure of 400 kg/cm^2 without any change in its spherical shape. This behavior is different from the previous bead-type CPMs prepared from only organic components, namely, polysaccharide derivatives and diisocyanates.[7,8] These could not be packed under high pressure, because the beads were crushed in the column and the eluents could not flow. These results indicate that the inorganic component in the hybrid bead provides a supporting role and confers sufficient mechanical resistance to the CPM.

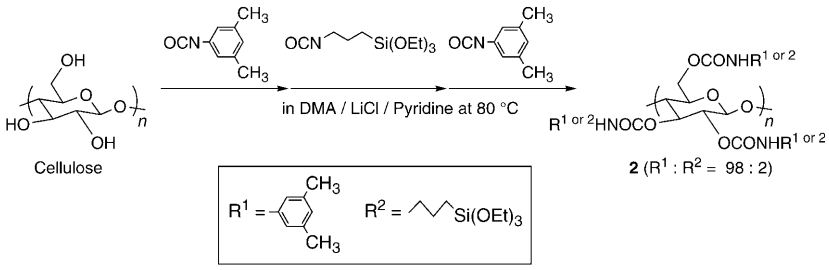

Figure 2. Synthesis of the cellulose derivative **2** bearing a triethoxysilyl group.

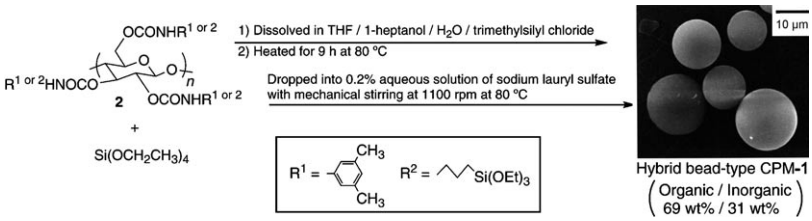

Figure 3. Preparation and SEM image of the hybrid bead-type CPM-**1**.

Table 1. The organic and inorganic contents in the hybrid beads prepared from **2** and TEOS by sol-gel reaction.[a]

Code	**2** [g]	TEOS [mL]	Organic/inorganic [wt%/wt%]
1	0.25	1.0	80:20
2	0.25	2.0	69:31
3	0.25	3.0	57:43

[a] The organic and inorganic contents in the hybrid beads were determined by thermogravimetric (TG) analysis.

Abstract in Japanese:
多糖誘導体を固定相に用いた高速液体クロマトグラフィー用キラル充填剤として、側鎖の一部にトリエトキシシリル基を有するセルロース 3,5-ジメチルフェニルカルバメート誘導体とテトラエトキシシランを用いたゾル-ゲル反応により、セルロース誘導体とシリカゲルからなる有機-無機ハイブリッドビーズを調製した。このハイブリッドビーズ型キラル充填剤は、セルロース 3,5-ジメチルフェニルカルバメート誘導体をシリカゲルに固定化して調製される市販のキラル充填剤 Chiralpak IB と同程度の光学分割能を示し、単位時間あたりに分割できるラセミ体の量が 2 倍程度増加することが明らかとなった。

When the amount of TEOS was decreased from 2.0 mL to 1.0 mL (Code 1 in Table 1), the inorganic content in the hybrid material was decreased to 20 wt%. This hybrid did not possess enough mechanical strength to endure a pressure of 400 kg/cm^2 and could therefore, not be used as a CPM. Although the inorganic content was increased to 43 wt% using 3.0 mL of TEOS (Code 3 in Table 1), most of the obtained hybrid material had no spherical shape. In order to prepare a stable micelle and a spherical hybrid bead, an appropriate lipophilicity in the pretreated solution of **2** and TEOS may be necessary. With respect to mechanical strength and the shape of the hybrid materials, the hybrid bead-type CPM-**1** (Code 2 in Table 1) seems to be preferable.

The solid-state ^{29}Si CP/MAS NMR (59.6 MHz) spectrum of the hybrid bead-type CPM-**1** is shown in Figure 4. Besides

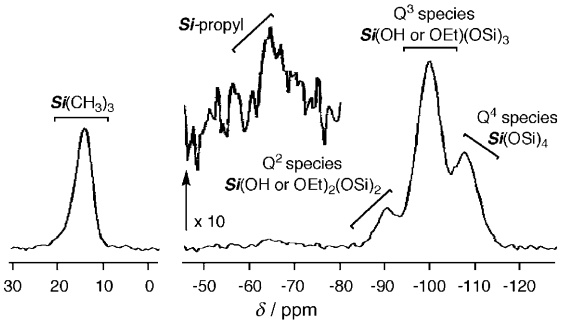

Figure 4. Solid-state ^{29}Si CP/MAS NMR spectrum of the hybrid bead-type CPM-**1** at RT.

a small peak around −65 ppm, which was derived from the 3-(triethoxysilyl)propylcarbamate residue in the cellulose derivative, four intense peaks were observed at 13, −91, −101, and −109 ppm, which were assigned to the trimethylsilyl group ($Si(CH_3)_3$), Q^2 ($Si(OH\ or\ OEt)_2(OSi)_2$), Q^3 ($Si(OH\ or\ OEt)(OSi)_3$), and Q^4 species ($Si(OSi)_4$), respectively.[11] The presence of the Q^2 and Q^3 species indicates that the polycondensation of TEOS did not proceed to completion and the silanol or ethoxysilyl groups remained in the hybrid bead-type CPM-**1**.

In order to investigate the distribution of the organic and inorganic components in the hybrid bead, elemental mapping analysis of the hybrid bead-type CPM-**1** was carried out. Figure 5 shows the energy-dispersive X-ray (EDX) mapping patterns of the hybrid bead-type CPM-**1**. The area of the EDX mappings completely corresponds to that of the SEM image in Figure 3. The bright spots in Figures 5a and 5b represent the distribution of nitrogen in the organic component and silicon in the inorganic component, respectively. These results suggest that no phase separations occurred at least in the micrometer scale range and both the organic and inorganic components were well dispersed on the surface of the hybrid bead-type CPM-**1**.

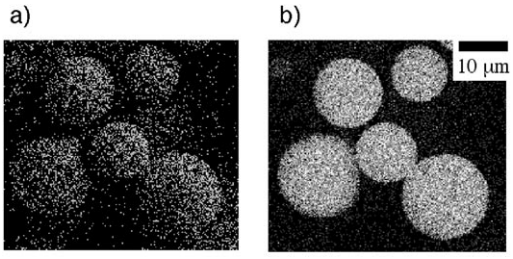

Figure 5. Energy-dispersive X-ray (EDX) mapping patterns of nitrogen (a) and silicon (b) in the hybrid bead-type CPM-**1**.

Chiral Recognition Ability of the Hybrid Bead-Type CPM-1

The chiral recognition ability of the hybrid bead-type CPM-**1** was evaluated using the ten racemates shown in Figure 6. Figure 7 shows the chromatogram for the resolution of the

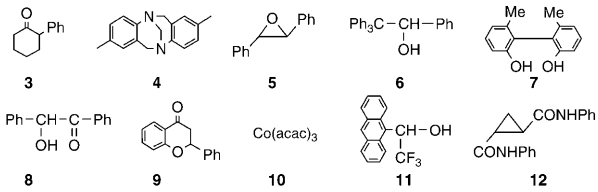

Figure 6. Structures of the racemates.

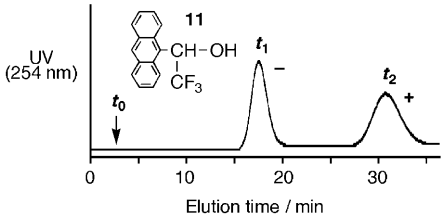

Figure 7. Chromatogram for the resolution of **11** on the hybrid bead-type CPM-**1** with hexane/2-propanol (90:10) as eluent.

racemic 2,2,2-trifluoro-1-(anthryl)ethanol **11** on the hybrid bead-type CPM-**1**. The enantiomers were eluted at the retention times of t_1 and t_2 with baseline separation. The dead time (t_0) was estimated to be 2.82 min. The capacity factors, $k_1'[=(t_1\text{-}t_0)/t_0]$ and $k_2'[=(t_2\text{-}t_0)/t_0]$, were determined to be 5.19 and 9.89, respectively, which led to the separation factor α ($=k_2'/k_1'$) of 1.91. The resolution results on the hybrid bead-type CPM-**1** are summarized in Table 2 together with the results on the coated-type CPM-**2** and the commercially available Chiralpak IB,[12] which were prepared by coating **2** and immobilizing **1** on silica gel, respectively.

Although the elution orders of the enantiomers on both the hybrid bead-type CPM-**1** and the coated-type CPM-**2** were the same using a hexane/2-propanol (90:10) mixture as the eluent, the hybrid bead-type CPM-**1** showed a lower chiral recognition than the coated one, especially for racemates **4** and **7**. The low enantioselectivity may be caused by the non-enantioselective adsorption on the silanol groups remaining in the hybrid bead and the slightly different higher order structure of the cellulose derivative in both the CPMs.

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Table 2. Resolution of racemates **3**–**12** on the hybrid bead-type CPM-**1**, coated-type CPM-**2**, and Chiralpak IB.[a]

	Eluents	Hybrid bead-type CPM-**1** H/I (90:10)		H/C/I (90:10:1)		Coated-type CPM-**2** H/I (90:10)		Chiralpak IB H/I[b] (90:10)		H/C/I (90:10:1)	
Racemates		k_1'	α	k_1'	α	k_1'	α	k_1'	α	k_1'	α
3		3.84 (−)	1.21	3.92 (−)	1.21	1.20 (−)	1.31	1.00 (−)	1.14	1.09 (−)	1.16
4		6.00 (+)	1.33	6.02 (+)	1.27	0.94 (+)	1.63	0.96 (+)	1.22	1.16 (+)	1.22
5		2.15 (−)	1.76	2.63 (−)	2.16	0.73 (−)	1.52	0.55 (−)	1.77	0.71 (−)	2.37
6		3.71 (+)	1.23	6.83 (+)	~1	1.49 (+)	1.21	1.12 (+)	1.22	2.12 (+)	1.15
7		4.45 (−)	2.38	18.3 (−)	1.44	1.58 (−)	4.49	1.48 (−)	2.72	6.38 (−)	1.57
8		7.91 (+)	1.26	12.0 (+)	1.29	2.62 (+)	1.30	2.00 (+)	1.33	3.05 (+)	1.39
9		4.44 (−)	1.18	4.71 (−)	1.17	1.49 (−)	1.17	1.13 (−)	1.26	1.30 (−)	1.37
10		2.67 (+)	~1	1.09	1.0	0.68 (+)	~1	3.15 (+)	~1	1.26	1.0
11		5.19 (−)	1.91	34.9 (−)	2.29	1.78 (−)	2.19	1.54 (−)	2.42	11.6 (−)	2.96
12		3.11 (+)	1.16	–		1.15 (+)	1.41	0.86 (+)	1.89	–	

[a] The signs in parentheses represent the optical rotation of the first-eluted enantiomer. Eluent: H, hexane; I, 2-propanol; C, chloroform. Column: 25 cm by 0.46 cm I.D. Flow rate: 1.0 mL min^{-1}. [b] Data from Ref. [12]. Flow rate: 0.5 mL min^{-1}.

However, the hybrid bead-type CPM-**1** exhibited a chiral recognition similar to Chiralpak IB with the hexane/2-propanol mixture, except for racemates **11** and **12**.

While the cellulose derivative **2** was soluble in THF, the major part (80 wt%) of the hybrid bead-type CPM-**1** was insoluble. This suggests that molecules of **2** in the hybrid bead partly formed cross-links with themselves or with the silica component through the polycondensation of alkoxysilyl groups during the sol-gel reaction. The eluents containing less than 20% chloroform or 10% THF could be used with the hybrid bead-type CPM-**1**. However, the eluents containing higher contents of chloroform and THF could not be used, because the CPM-**1** was highly swollen or partly soluble in the eluents, and the column pressure became too high. After the additional treatment of the hybrid bead-type CPM-**1** under an acidic condition (see Experimental Section),[10] the cross-linking reaction proceeded in the hybrid bead and the content of the insoluble part increased to 94 wt%. Even in this case, the hybrid bead was still swollen in chloroform and THF, and therefore, could not be used.

The resolution results of the hybrid bead-type CPM-**1** and Chiralpak IB with the eluents containing 10% chloroform are listed in Table 2. It was found that some racemates could be more efficiently resolved with the eluent containing chloroform than with the eluent consisting of the hexane/2-propanol mixture and the α values obtained on the hybrid bead-type CPM-**1** were close to those obtained on the coated one.[13] The hybrid bead-type CPM-**1** also showed a similar or slightly lower chiral recognition compared to Chiralpak IB.

The polysaccharide contents in the conventional CPMs, such as the coated-type CPM-**2** and Chiralpak IB, are usually less than 20 wt%, while the organic components of the hybrid bead-type CPM-**1** are 69 wt%, mainly composed of the cellulose derivative. Because the amount of the cellulose derivative in the CPMs significantly influences the capacity factors, the hybrid bead-type CPM-**1** showed a much higher capacity factor than the other two.

Comparison of Loading Capacity Between the Hybrid Bead-Type CPM-1 and Chiralpak IB

The loading capacity of a chiral column is a particularly important factor for preparative separation, because this determines the maximum amount of racemates resolved on a column. In order to demonstrate the potential of the hybrid bead-type CPM-**1** for preparative separation, the loading capacities on the hybrid bead-type CPM-**1** and Chiralpak IB were compared using 2,2,2-trifluoro-1-(anthryl)ethanol **11** and *trans*-stilbene oxide **5** racemates.

Figure 8a shows the results of the preparative separation of **11** on the hybrid bead-type CPM-**1** with a hexane/2-propanol (90:10) mixture as the eluent at the flow rate of 1.0 mL min^{-1}. Although the individual enantiomers eluted

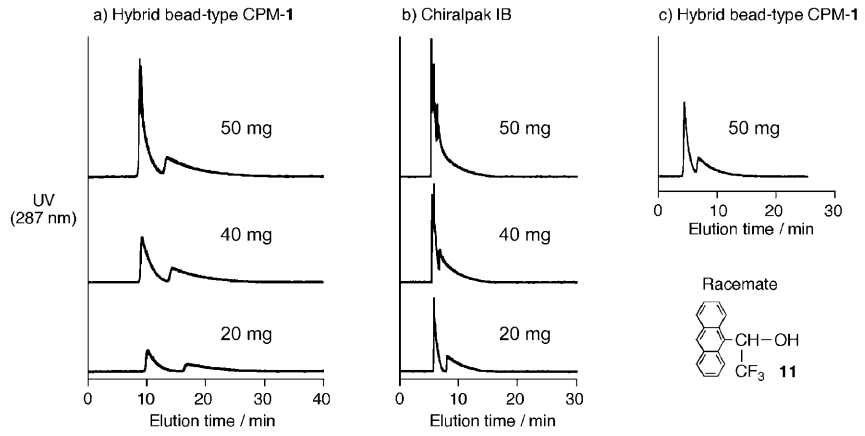

Figure 8. Preparative separation of *rac*-2,2,2-trifluoro-1-(anthryl)ethanol **11** with hexane/2-propanol (90:10) as eluent: a) hybrid bead-type CPM-**1** at flow rate of 1.0 mL min^{-1}; b) Chiralpak IB at flow rate of 1.0 mL min^{-1}; c) hybrid bead-type CPM-**1** at flow rate of 2.0 mL min^{-1}.

faster and the two peaks became closer with an increase in the loading sample from 20 mg to 50 mg, the hybrid bead-type CPM-**1** could almost completely resolve 50 mg of the racemate, whereas Chiralpak IB showed overlapping peaks for the 50 mg loading (Figure 8b). In the case of the preparative separation of **5** with a hexane/chloroform (80:20) mixture as the eluent at a flow rate of 0.5 mL min^{-1}, a larger amount of the sample could also be resolved on the hybrid bead-type CPM-**1** than on Chiralpak IB (Figures 9a and 9b).

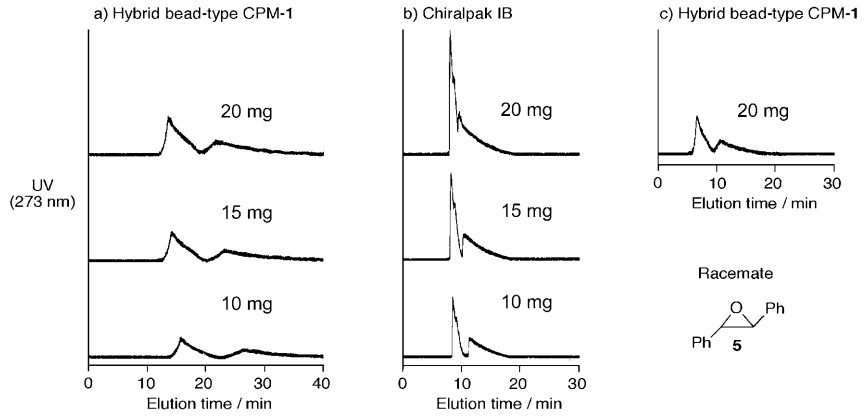

Figure 9. Preparative separation of *rac-trans*-stilbene oxide **5** with hexane/chloroform (80:20) as eluent: a) hybrid bead-type CPM-**1** at flow rate of 0.5 mL min^{-1}; b) Chiralpak IB at flow rate of 0.5 mL min^{-1}; c) hybrid bead-type CPM-**1** at flow rate of 1.0 mL min^{-1}.

Under the same chromatographic condition, however, the amount of pure enantiomers obtained per unit time on the hybrid bead-type CPM-**1** did not increase, arising from the higher retention time compared to Chiralpak IB. Therefore, the eluting time on the hybrid bead-type CPM-**1** was set to that on Chiralpak IB by adjusting the flow rate, and the efficiency of the preparative separations was reevaluated for **11** and **5** (Figures 8c and 9c). These results clearly indicate that a higher throughput preparation of optically active compounds could be achieved using the hybrid bead-type CPM-**1** compared to Chiralpak IB.

Conclusions

An organic-inorganic hybrid material as a CPM for preparative separation by HPLC was prepared from the cellulose 3,5-dimethylphenylcarbamate having a small number of 3-(triethoxysilyl)propyl groups in the presence of TEOS, by a sol-gel reaction in an aqueous surfactant solution. Because the inorganic component provided a supporting role, the obtained hybrid bead possessed a high mechanical strength. The hybrid bead-type CPM-**1** exhibited a chiral recognition similar to the commercially available Chiralpak IB, and possessed a higher loading capacity. Using the hybrid bead-type CPM-**1**, a high throughput preparation of optically active compounds could be achieved. We are now optimizing the preparation conditions of the hybrid bead-type CPM by controlling the ratio of (polysaccharide derivative)/(TEOS), changing the type and amount of surfactants, and treating the residual silanol groups. Through these modifications, the performance of the hybrid bead-type CPM is expected to be improved. This preparation method of the hybrid bead can be applied to other polysaccharide derivatives with a high chiral recognition.

Experimental Section

Chemicals

Cellulose (Avicel, DP ~ 200) was purchased from Merck (Darmstadt, Germany). 3,5-Dimethylphenyl isocyanate was a gift from Daicel (Tokyo, Japan). Tetraethyl orthosilicate, 3-(triethoxysilyl)propyl isocyanate, and trimethylsilyl chloride were purchased from Tokyo Kasei (Tokyo, Japan). Lithium chloride and 1-heptanol were obtained from Wako (Tokyo, Japan). Sodium lauryl sulfate was from Kishida (Osaka, Japan). The wide-pore silica gel (Daiso gel SP-1000) with a mean particle size of 7 μm and a mean pore diameter of 100 nm was kindly supplied by Daiso Chemical (Osaka, Japan). The dehydrated *N,N*-dimethylacetamide and pyridine were from Kanto (Tokyo, Japan). HPLC grade solvents were used in the chromatographic experiments. Chiralpak IB (25 cm by 0.46 cm I.D.) was kindly supplied from Daicel. The racemates were commercially available or were prepared by the usual methods.[14]

Synthesis of Cellulose 3,5-Dimethylphenylcarbamate with Attached 3-(Triethoxysilyl)propyl Groups

The cellulose 3,5-dimethylphenylcarbamate **2** with affixed 3-(triethoxysilyl)propyl groups was synthesized according to a previously reported method (Figure 2).[9,10] First, cellulose was dissolved in a mixture of *N,N*-dimethylacetamide, lithium chloride, and pyridine. 3,5-Dimethylphenyl isocyanate (83 mol% to the hydroxyl groups of cellulose) was then added and the mixture was stirred for 8 h at 80 °C. Subsequently, 3-(triethoxysilyl)propyl isocyanate (2 mol% to the hydroxyl groups of cellulose) was added and allowed to react for 12 h at 80 °C. Finally, the remaining hydroxyl groups were treated with an excess amount of 3,5-dimethylphenyl isocyanate (116 mol% to the hydroxyl groups of cellulose) for 8 h at 80 °C. The cellulose derivative **2** mainly bearing 3,5-dimethylphenylcarbamate and a small amount of 3-(triethoxysilyl)propylcarbamate was isolated as the methanol-insoluble fraction. The ratio of the (3,5-dimethylphenylcarbamate)/(3-(triethoxysilyl)propylcarbamate) was determined from the ratio of the (aromatic proton)/($SiCH_2$) in the ^{1}H NMR spectrum.

Preparation of the Hybrid Bead-Type CPM-1

The hybrid bead-type CPM-**1** was prepared as shown in Figure 3. The cellulose derivative **2** (0.25 g) and TEOS (1.0, 2.0, or 3.0 mL) were first dissolved in a THF/1-heptanol/H_2O/trimethylsilyl chloride (24:6:1:0.5 *v/v/v/v* = 31.5 mL). This solution was then heated for 9 h at 80 °C and added dropwise into water (500 mL) containing sodium lauryl sulfate (0.2%) at 80 °C with mechanical stirring at 1100 rpm using a multidisperser (SMT PB95), which has a shaft bearing six blades (PH-4) (SHIMADZU, Kyoto). The stirring and temperature were maintained for 1 h.

The obtained suspension was filtered to separate the hybrid bead-type CPM-**1**, which was then washed with water, ethanol, and hexane, and dried in vacuo at room temperature for 12 h. For comparison, the coated-type CPM-**2** was separately prepared by coating **2** (20 wt% of silica gel) on plain silica gel according to previously reported methods.[15,16]

Preparation of the Packed Column

The hybrid bead-type CPM-**1** and coated-type CPM-**2** were packed in a stainless-steel tube (25 cm by 0.46 cm ID) at a pressure of 400 kg/cm^2 by a slurry method. The plate numbers of the packed columns were approximately 1800 for benzene using a hexane/2-propanol (90:10) mixture as the eluent at the flow rate of 1.0 mL min^{-1}. 1,3,5-Tri-tert-butylbenzene was used as the non-retained compound for estimating the dead time (t_0).[17]

Acid Treatment of the Hybrid Bead-Type CPM-1

The hybrid bead-type CPM-**1** (0.30 g) was dispersed into a mixture of ethanol (6 mL), water (1.5 mL) and trimethylsilyl chloride (0.1 mL), and heated for 10 min in an oil bath at 110 °C.[10] After the reaction, the obtained beads were washed with water, ethanol, and hexane, and then dried.

Instrumentation

SEM image and EDX mappings of the hybrid beads were recorded using a JEOL JSM-5600 instrument (JEOL, Tokyo, Japan) with an acceleration voltage of 20 kV. The chromatographic experiments were performed using a JASCO PU-980 chromatograph equipped with UV (JASCO MD-2010) and polarimetric (JASCO OR-990, Hg–Xe without filter) detectors (JASCO, Tokyo, Japan) at room temperature. A solution of the racemate was injected into the chromatographic system using a Rheodyne Model 7125 injector. The TG analysis was carried out on a Seiko EXSTRA 6000 system (Seiko, Chiba, Japan). The ^{1}H NMR (400 MHz) and solid-state ^{29}Si CP/MAS NMR (59.6 MHz) spectra were obtained using a Varian Gemini-2000 spectrometer (Varian, California, USA) and a Bruker DSX-300 spectrometer (Bruker BioSpin, Rheinstetten, Germany), respectively.

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