Titanized or Zirconized Porous Silica Modified with a Cellulose Derivative as New Chiral Stationary Phases

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Spherical porous silica supports modified with titanium or zirconium alkoxides were prepared, and allyl groups were chemically attached to the titanized or zirconized silica supports, and the product was cross-polymerized with a double bond containing cellulose derivative to yield new CSPs (chiral stationary phases). Magic angle spinning ^{13}C solid state NMR and elemental analysis were used to characterize the CSPs. The performances of the chiral stationary phases were examined in comparison with a conventional chiral stationary phase. Spherical porous silica particles modified with 3,5-dimethylphenylcarbamate of cellulose were prepared and used as the conventional chiral stationary phase. Chromatographic data were collected for a few pairs of enantionmers in heptane/2-propanol mixed solvents of various compositions with the three chiral columns and the results were comparatively studied. The separation performance of the chrial phase made of the titanized silica was better than the others, and the separation performance of the chiral phase of the zirconized silica was comparable to that of the conventional chiral phase. The superiority of titanized silica over bare or zirconized silica in chiral separation seemed to be owing to the better yield of crosslinking (monitored by increase of carbon load) for titanized silica than for the others.

Key Words : Allyltitanized silica, Allylzirconized silica, Cellulose derivative, Crosslinking, Chiral stationary phases

Introduction

Cellulose-based phases have been known to be very versatile chiral phases. The wide applicability and usefulness of the polysaccharide-based CSPs have been demonstrated in a couple of comprehensive reviews.[1,2] The cellulose derivatives were physically coated on porous silica particles in the early stage of development, but such chiral phases suffered from limited lifetimes due to loss or swelling of cellulose derivatives by mobile phase solvents.[2] Efforts to overcome such troubles have been reported. 10-Undecenoyl-3,5-dimethylphenylaminocarbonyl derivatives of cellulose were synthesized and chemically bonded on allylsilica gel by crosslinking.[3,4] Other chiral phases with chemical bonding between the silica support and various cellulose derivatives[5-9] have been recently developed.

Preparation and application of titinia or titanized silica[10-15] as well as zirconia or zirconized silica[16-20] have been reported in the literature. However, there has been no trial to make chiral stationary phases based on titanized silica or zirconized silica so far. In this study, new chiral stationary phases were prepared by bonding the 10-undecenoyl-3,5-dimethylphenyl-aminocarbonyl derivative of cellulose to allyl titanized silica and allyl zirconized silica via crosslinking, and the chromato-graphic performances of the new chrial phases were examined in comparison with the conventional stationary phase made by bonding the same ligand to allylsilica.[3,4]

Experimental Section

Chemicals and Apparatus. Allyltrimethoxysilane, 1,1,1,3,3,3-hexamethyldisilazane (HMDS), 10-undecenoyl chloride, 3,5-dimethylphenylisocyanate, titanium(IV) butoxide, zirconium (IV) isopropoxide, toluene, pyridine(anhydrous), Tröger base, trans-stilbene oxide, benzoin, warfarin were purchased from Aldrich (Milwaukee, IL, USA). 1,1'-Azoisobutyronitrile (AIBN) was obtained from Junsei Chemical (Tokyo, Japan). Microcrystalline cellulose was from Merck (Darmstadt, Germany), and silica gel (Adsobosphere, 5 μm particle size, 80 Å pore size), from Alltech (Deerfield, IL, USA). Methanol, tetrahydrofuran, chloroform, acetone, heptane were of HPLC grade and purchased from Fisher (Pittsburg, PA, USA).
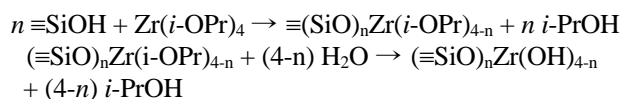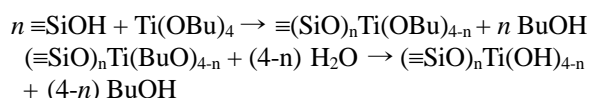
A Shimadzu (Tokyo, Japan) 10AD pump, a Shimadzu DGU-14A membrane degasser, a Rheodyne (Cotati, CA, USA) 7520 injector with a 0.5 μL injection loop, a Jasco (Tokyo, Japan) UV-2075 UV/Vis capillary window detector, and the home-made 0.5 mm ID glass-lined microcolumn were combined to compose the HPLC system. The chromatographic data were obtained by a PC system, and a software Multichro 2000 from Youlin-Gisul (Sungnam, Korea) was used to acquire and process the data. An Alltech (Deerfield, IL, USA) slurry packer was used to pack the microcolumns used.

A Varian (Palo Alto, CA, USA) UnityINOVA400 (400 MHz) NMR was used for acquisition of ^{13}C solid state NMR

spectra of the phases, and a Thermo Scientific (Waltham, MA, USA) Flash EA1112 Automatic Elemental Analyzer was used to obtain carbon load data of the phases.

Synthesis of 10-undecenoyl 3,5-dimethylcarbamate of Cellulose. The cellulose derivative was prepared according to the literature.[3] Thus, cellulose 1 g was dispersed in 30 mL pyridine, and 350 mg 10-undecenoyl chloride was added and stirred for 1 h at 100 °C. Then 3,5-dimethylphenyl isocyanate 3.0 g was added and stirred for 16 h at 100 °C. Methanol was added to precipitate the product. The product was filtered, dissolved in chloroform, and recrystallized with methanol twice.

Synthesis of Titanized Silica and Zirconized Silica. Titanized silica or zirconized silica was prepared basically according to the literature[10,20] with some modification. Silica gel 1 g was dehydrated at 300 °C for 3 h. Titanium(IV) butoxide 3.0 mmol (or zirconium(IV) iso-propxide 0.6 mL) was dissolved in 50 mL toluene and sonicated for 10 min, then the dehydrated silica was added and stirred for 8 h at 120 °C. The reaction product was thoroughly washed with toluene, 2-propanol, and water in sequence, and put in a 10^{-3} M HNO_3 solution with stirring for 4 h at room temperature to hydrolyze the residual alkoxy groups. The relevant chemical reactions are given below.[10,20]

$$n \equiv\!SiOH + Ti(OBu)_4 \rightarrow \equiv\!(SiO)_nTi(OBu)_{4\text{-}n} + n\ BuOH$$
$$(\equiv\!SiO)_nTi(BuO)_{4\text{-}n} + (4\text{-}n)\ H_2O \rightarrow (\equiv\!SiO)_nTi(OH)_{4\text{-}n} + (4\text{-}n)\ BuOH$$

$$n \equiv\!SiOH + Zr(i\text{-}OPr)_4 \rightarrow \equiv\!(SiO)_nZr(i\text{-}OPr)_{4\text{-}n} + n\ i\text{-}PrOH$$
$$(\equiv\!SiO)_nZr(i\text{-}OPr)_{4\text{-}n} + (4\text{-}n)\ H_2O \rightarrow (\equiv\!SiO)_nZr(OH)_{4\text{-}n} + (4\text{-}n)\ i\text{-}PrOH$$

Preparation of Allylsilica, Allyltitanized Silia, and Allylzirconized Silica. The porous silica was baked at 300 °C (150 °C for allyltitanized silica and allylzirconized silica) for 3 h to remove adsorbed water completely. The porous silica 1 g was dispersed in toluene and reacted with 0.7 mL allyltrimethoxysilane for 4 h at 110 °C while stirring. Then, 0.4 mL HMDS was added for endcapping of residual silanol groups and the reaction mixture was stirred for 2 h at the same temperature. After completion of reaction, the silica was filtered, thoroughly washed with toluene, THF, 50/50 (v/v %) methanol/water, and methanol, and dried. Allyltitanized silica and allylzirconized silica were prepared by the same procedure by replacing silica with titanized silica or zirconized silica while other experimental setups being the same.

Preparation of the Stationary Phases (CSP-1, CSP-2, and CSP-3) *via* Cross Polymerization. Allylsilica 200 mg, 10-undecenoyl-3,5-dimethylcarbamate of cellulose 40 mg, and 10 mL THF were added to a small round bottom flask and stirred well and evaporated in a rotavapor. Then 4 mg AIBN were dissolved in 10 mL toluene and the solution was added to the flask, stirred, and evaporated. The bath temperature was raised to 100 °C and maintained for 4 h while rotating the bottle. The stationary phase was thoroughly washed with chloroform and methanol in sequence and dried to give CSP-1. When allylsilica was replaced by the same amount of allyl
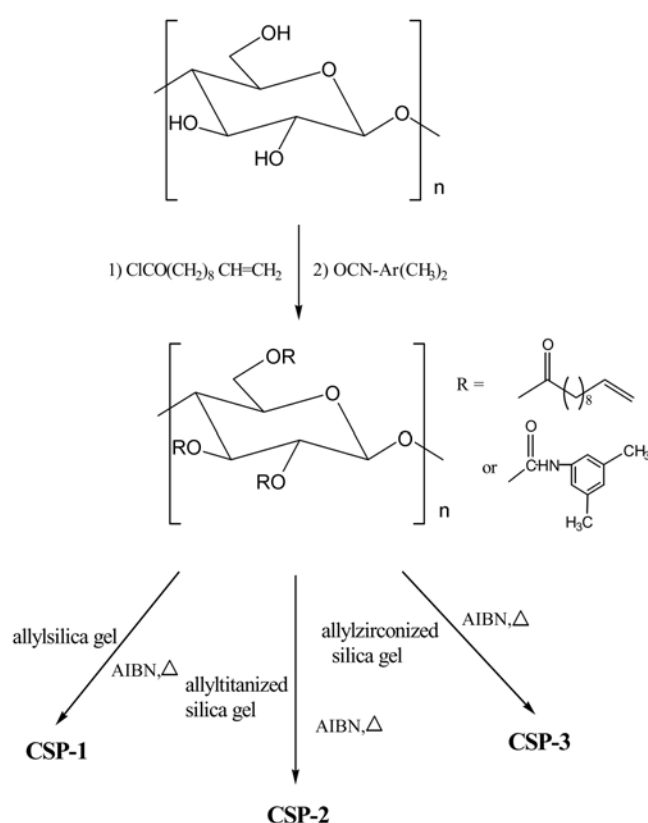

Figure 1. The summarized scheme of synthesis of the chiral stationary phases CSP1, CSP2, and CSP3.

titanized silica or allyl zirconized silica while other experimental setups being the same, CSP-2 and CSP-3 were obtained, respectively. The overall scheme of preparation of the three stationary phases is summarized in Figure 1. Each stationary phase packed in a microcolumn (0.5 mm × 300 mm) for study of chromatographic performance according to the procedure of previous studies.[21-23]

Results and discussion

Comparison of Typical Chromatograms of Three Phases (CSP-1, CSP-2, CSP-3). Four optical isomer pairs (Tröger base, trans-stilbene oxide, benzoin, and warfarin) were used in this study. Their chemical structures are shown in Figure 2. The separation data were obtained in 98/2, 95/5, 90/10, 85/15, and 80/20 (v/v %) heptane/2-propanol for Tröger base, trans-stilbene oxide, benzoin, and the data of warfarin were obtained in 90/10, 85/15, 80/20, and 70/30 (v/v %) heptane/2-propanol. This adjustment was necessary since retention times of warfarin were abnormally long in eluents of low 2-propanol content. The typical chromatograms of the solutes in 90/10 (v/v %) heptane/2-propanol obtained by CSP-1, CSP-2, and CSP-3 were assembled in Figures 3, 4, and 5, respectively. In general, good chiral sepration was observed except for Tröger base. Chiral separation by CSP-2 (titanized silica phase, Figure 4) is generally better than that by CSP-1(silica phase, Figure 3) or CSP-3 (zirconized silica phase, Figure 5), and such situation is a general trend in
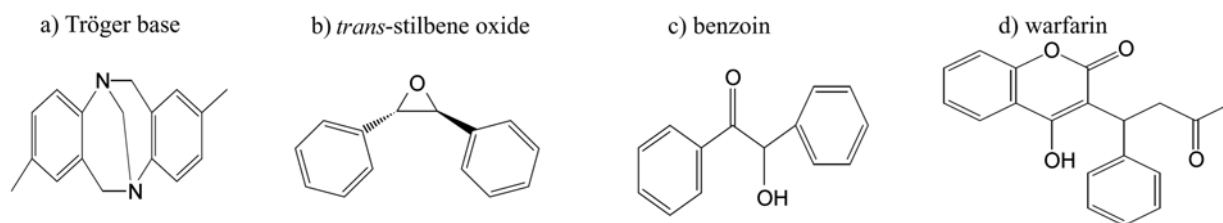
Figure 2. The chemical structures of the chiral compounds used in this study.
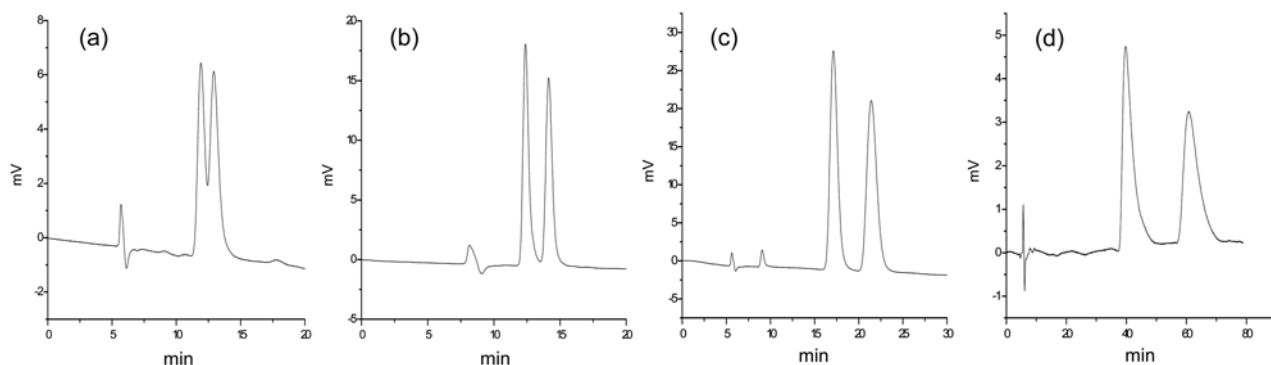
Figure 3. Chromatograms of (a) Tröger base, (b) *trans*-stilbene oxide, (c) benzoin and (d) warfarin isomers separated on CSP-1. The mobile phase is heptane/2-propanol (90/10 v/v%), the flow rate, 0.01 mL/min, and the UV wavelength, 254 nm.
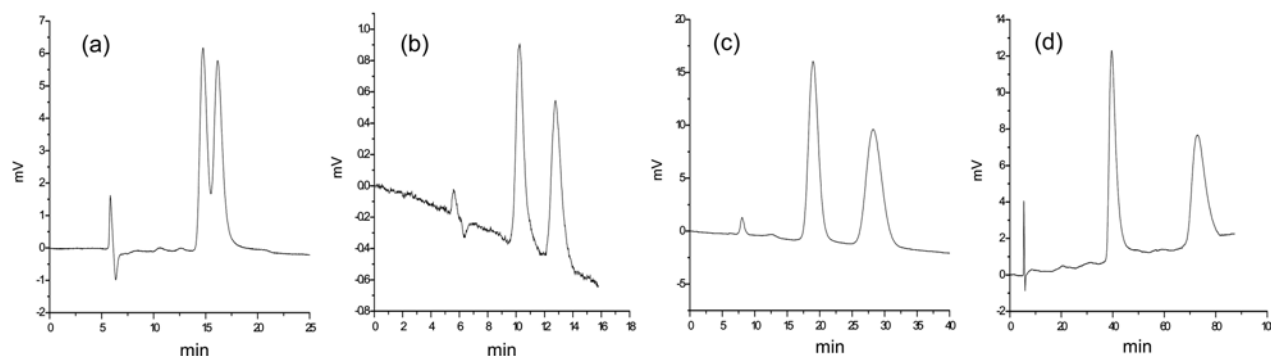
Figure 4. Chromatograms of a) Tröger base, b) *trans*-stilbene oxide, c) benzoin and d) warfarin isomers separated on CSP-2. The mobile phase is heptane/2-propanol (90/10 v/v%), the flow rate, 0.01 mL/min, and the UV wavelength, 254 nm.
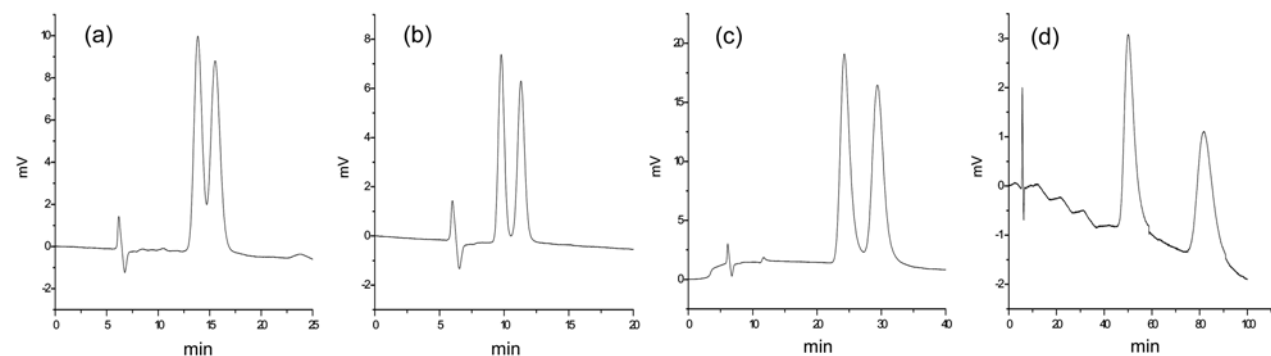

Figure 5. Chromatogram of (a) Tröger base, (b) *trans*-stilbene oxide, (c) benzoin and (d) warfarin isomers separated on CSP-3. The mobile phase is heptane/2-propanol (90/10 v/v%), the flow rate, 0.01 mL/min, and the UV wavelength, 254 nm.

eluents of various compositions as discussed in later sections.

Comparison in Selectivity and Its Variation Trend with Respect to Mobile Phase Composition. The chiral selectivity values (a) obtained by the three stationary phases and their variation trends with mobile phase composition were com-

paratively plotted in Figure 6 for all the solutes. The variation trends over the given mobile phase composition range were entirely arbitrary and dependent upon character of chiral phase and type of solute. For example, a minimum was observed for trans-stilbene oxide(b) at 90/10 (v/v %) heptane/
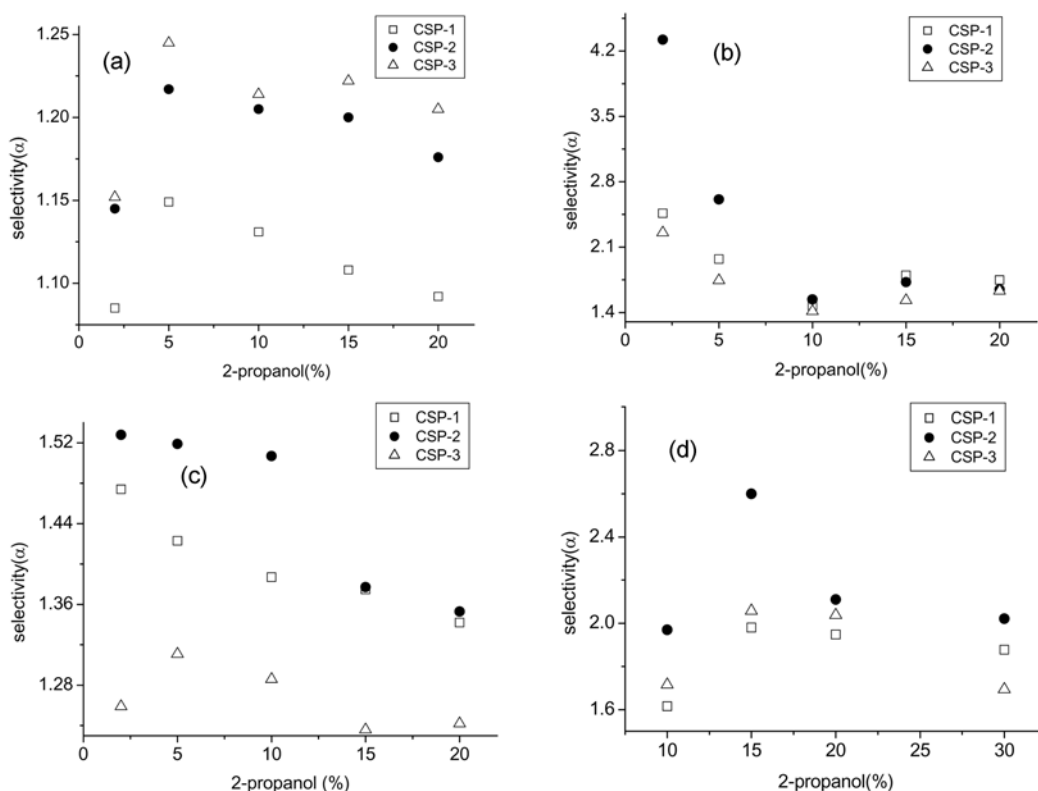
Figure 6. Comparison of variation trends of selectivity values of Tröger base (a), *trans*-stilbene oxide (b), benzoin (c), and warfarin (d) as a function of volume % of 2-propanol in the eluent for the three CSPs.
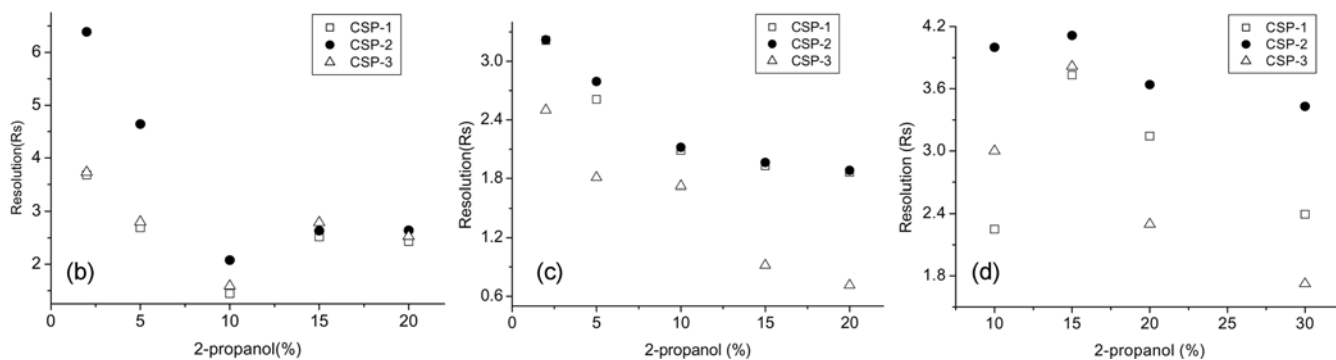
Figure 7. Comparison of variation trends of resolution values of *trans*-stilbene oxide (b), benzoin (c), and warfarin (d) as a function of volume % of 2-propanol in the eluent for the three CSPs. The resolution values of Tröger base (a) were not obtained because of poor separation of its R- and S-isomers.

2-propanol while a maximum was observed for Tröger base(a) at 95/5 (v/v %) heptane/2-propanol and for warfarin(d) at 85/ 15 (v/v %) heptane/2-propanol. For benzoin(c), a maximum was observed with CSP-3 while a monotonic decrease was observed with increase of 2-propanol content with CSP-1 and CSP-2, and the variation curve shapes were still different between CSP-1 and CSP-2. No good explanation can be suggested for these observations since chiral recognition is governed by a very complicated mechanism influenced by many factors. However, it is clear that CSP-2 generally showed higher α values than CSP-1 and CSP-3. It is true for trans-stilbene oxide, benzoin, and warfarin. CSP-3 was a little better than CSP-2 for Tröger base. Performances of CSP-1 and CSP-3 were comparable in general. They showed

similar values for trans-stilbene oxide and warfarin. CSP-1 was much better for benzoin while CSP-3 was much better for Tröger base.

Comparison in Resolution and Its Variation Trend with Respect to Mobile Phase Composition. The chiral resolution values (Rs) obtained by the three chiral phases and their variation trends with mobile phase composition were comparatively plotted in Figure 7 for trans-stilbene oxide, benzoin, and warfarin. The resolution values of Tröger base (a) were not obtained because of poor separation of its optical isomers. The variation trends of Rs with mobile phase composition were in general consistent with the variation trends of α. Again, it is clear that CSP-2 (titanized silica phase) was better than CSP-1(silica phase) and CSP-3 (zirconized silica

Table 1. Elemental analysis results of allylsilica gel, allyltitanized silica gel, allylzirconized siliga gel, CSP-1, CSP-2 and CSP-3

Phase	Element content (%)		
	N	C	H
Allylsilica gel	0	2.39	0.45
CSP-1	0.71	11.03	1.31
Allyltitanized siliga gel	0	3.08	0.67
CSP-2	1.03	15.80	1.82
Allylzirconized siliga gel	0	4.43	0.89
CSP-3	0.73	11.43	1.36
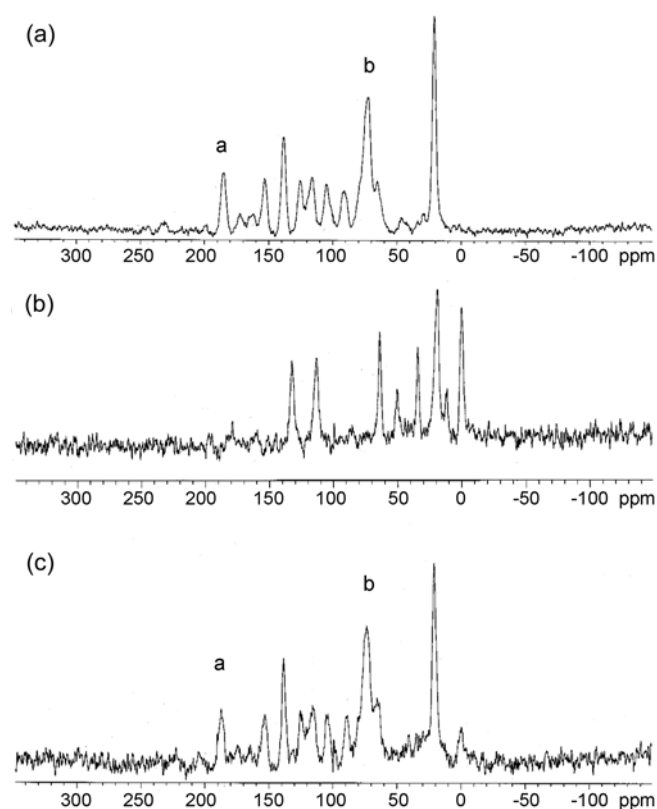
Figure 8. Magic angle spinning ^{13}C solid state NMR spectra of a) 10-undecenoyl-3,5-dimethylcarbamate of cellulose, b) allyltitanized silica gel, and c) CSP-2. The characteristic peaks of the cellulose derivative such as a and b are also observed in the chiral phase CSP2, which proves chemical bonding of the ligand to the allyltitanized silica.

phase).

Characterization of the Chiral Phases based on Elemental Analysis and ^{13}C NMR Data. A clue to the reason why CSP-2 showed better chiral separation than CSP-1 and CSP-3 was provided by the elemental analysis data (Table 1). According to Table 1, the yields of allyl group incorporation were in the order of zirconized silica, titanized silica, and bare silica, and the reaction yields of crosslinking (carbon load increase) was in the order of allyltitanized silica, allylsilica, and allylzirconized silica. A high reaction yield of crosslinking is, of course, a requirement for good chiral separation. Thus the phase of titanized silica showed the best performance in chiral separation. The ^{13}C NMR spectra of

CSP-2 is, for example, given in Figures 8 together with the spectra of its precursors and the chiral ligand[10-undecenoyl 3,5-dimethylcarbamate of cellulose]. The characteristic peaks of the chiral ligand (denoted "a" for carbonyl carbon and "b" for cellulose backbone carbon) were also observed in CSP-1, CSP-2, and CSP-3, which proves chemical attachment of the ligand to the porous support. It is noted that the relative peak heights of "a" and "b" peaks to the highest reference peak in CSP-3 were smaller than those in CSP-2.

The characteristic allyl double bond carbon peaks (doublet, 110-140 ppm) were simultaneously observed in allylsilica, allyltitanized silica, and allylzirconized silica, and their relative intensities were reduced in CSP-1, CSP-2, and CSP-3. Similar double bond carbon peaks were observed in 10-undecenoyl cellulose (3,5-dimethylcarbamate) and their relative intensities were also reduced when the ligand was incorporated in the supports to give CSP-1, CSP-2, and CSP-3. It adds to the evidences of chemical bonding of the ligand to the support. The poor yield of crosslinking of allylzirconized silica despite the presence of more allyl groups (compared to other supports) was also monitored by ^{13}C NMR data.

The reason why the reaction yield of cross polymerization for titanized silica was better than that of bare or zirconized silica is not clear at present. Comprehensive investigation of chemistry of titanized silica and zirconized silica is necessary, and such study is under way.

Conclusion

New chiral stationary phases were prepared by cross polymerization of 10-undecenoyl cellulose (3,5-dimethyl-carbamate) with allyltitanized silica and allylzirconized silica. A conventional chiral phase was also made by crosslinking of the same ligand with allylsilica for comparison purpose. Chemical attachment of the ligand to the supports was verified by elemental analysis and ^{13}C NMR. It was found that more chiral ligands were attached to allyltitanized silica than to allylzirconized silica. The separation performance of the chrial phase made of the titanized silica was better than the others, and the separation performance of the chiral phase of the zirconized silica was comparable to that of the silica based chiral phase.

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