



Immobilization of helical poly(phenylacetylene)s having L-phenylalanine ethyl ester pendants onto silica gel as chiral stationary phases for HPLC



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ABSTRACT

Novel one-handed helical copoly(phenylacetylene)s bearing a small amount of 3-(triethoxysilyl)propyl residues (CPAs 1–4) were synthesized, and efficiently chemically immobilized onto silica gel by the intermolecular polycondensation of the triethoxysilyl groups. Their chiral recognition abilities were evaluated as immobilized-type chiral stationary phases (CSPs) for high performance liquid chromatography (HPLC). These immobilized-type CSPs showed different chiral recognition abilities from the corresponding coated-type CSPs, which may be ascribed to the conformational change in the copoly(phenylacetylene)s during the immobilization process according to the diffuse reflectance circular dichroism (DRCD) measurement of the copolymer. In addition, the immobilized-type CSPs showed a universal solvent tolerability, for instance, CHCl₃-containing eluents that cannot be used with the corresponding coated-type CSPs could now be used for the immobilized-type CSPs so that the chiral recognition of *i*-CSP-2 for the racemic 1-(9-anthyl)-2,2,2-trifluoroethanol (5) was improved with separation factors comparable or higher than those obtained on the popular polysaccharide-based CSPs. The intermolecular polycondensation of the triethoxysilyl groups of the copoly(phenylacetylene)s is a valuable immobilization method for poly(phenylacetylene)-based CSPs.

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1. Introduction

Enantiomers are often recognized as different compounds in biosystems [1,2]. Therefore, the preparation and acquisition of enantiomerically-pure isomers are often requested to develop new biologically-active compounds such as drugs. The direct separation of enantiomers by HPLC using chiral stationary phases (CSPs) is one of the efficient techniques for these purposes [3–5]. The chiral recognition ability of chiral stationary phases (CSPs) is one of the key points of this separation technique [6,7]. Polysaccharide-based CSPs have been widely investigated and used in both the analytical

and preparative separations of enantiomers [8–11]. Besides polysaccharide derivatives, some artificial optically-active polymers also showed high chiral recognition abilities as CSPs [12–17]. Among these synthetic polymers, the one-handed helical poly(-phenylacetylene)s have drawn much attention due to their unique performances [17–27].

In the previous study, we found that the coated-type CSPs derived from one-handed helical poly(phenylacetylene)s bearing L-amino acid pendants showed a good chiral recognition ability for several racemates [17,25–29]. However, the coated polymers can be dissolved or swelled by some solvents, such as chloroform (CHCl₃), tetrahydrofuran (THF), acetone, ethyl acetate, etc., which limits the selection of the eluent and the application of the polymers as CSPs [30,31]. If the polymers are immobilized on silica-gel, the polymers on the surface of the silica gel cannot be washed away by the prohibited solvents, and sometimes the polymer may show a better resolution using the prohibited solvents as eluents. In

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addition, the high solubility of the samples is also an important factor for the efficient preparative separation of enantiomers by HPLC. Therefore, the immobilized-type CSPs based on one-handed helical poly(phenylacetylene)s are strongly requested for the efficient separation of enantiomers by HPLC.

In this study, inspired by the efficient immobilization approach of the polysaccharide-based CSPs [31–33], in order to enhance the solvent tolerance and the chiral recognition ability of the poly(phenylacetylene)-based CSPs, a novel phenylacetylene derivative having a 3-(triethoxysilyl)propyl group (PA-TES) was synthesized and copolymerized with a chiral phenylacetylene having an *l*-phenylalanine ethyl ester substituent (PA-Phe), and the resulting copolymers were immobilized on the silica gel by intermolecular polycondensation of the triethoxysilyl groups. The chiral recognition ability of the resulting immobilized-type CSPs was carefully evaluated by HPLC.

2. Material and methods

2.1. Materials

l-Phenylalanine (purity 99%) was purchased from Shanghai Jingchun Reagent Co., Ltd. (Shanghai, China). Hydrogen chloride in ethanol (30–40%) was purchased from Chengdu Xiya Chemistry Technology Co., Ltd. (Chengdu, China). 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methyl morpholinium chloride (DMT-MM) (purity 98%) and 3-aminopropyltriethoxysilane (APTES) (purity 98%) were purchased from Sahn Chemical Technology Co., Ltd. (Shanghai, China). Triphenylphosphine (purity 99%) and trimethylsilyl chloride (purity 99%) were purchased from J&K Chemical Co., Ltd. (Beijing, China). 4-Ethynylbenzoic acid and the *N*-(4-ethynylbenzoyl)-*l*-phenylalanine ethyl ester (PA-Phe) were synthesized according to previously reported methods [17,34]. $\text{Rh}^+(2,5\text{-norbornadiene})[(\eta^6\text{-C}_6\text{H}_5)\text{B}(\text{C}_6\text{H}_5)_3]$ ($\text{Rh}(\text{nbdb})\text{BPh}_4$) was synthesized based on a previous report [35]. All solvents used in the reactions were of analytical grade, carefully dried, and distilled before use. Silica gel with a mean particle size of 37–56 μm for the column chromatography was purchased from Qingdao Haiyang Chemical Co., Ltd. (Qingdao, China). The porous spherical silica gel with a mean particle size of 7 μm and a mean pore diameter of 100 nm (Daiso gel SP-1000-7) for HPLC was kindly supplied by Daiso Chemicals (Osaka, Japan), and was silanized with 3-aminopropyltriethoxysilane in toluene at 80 °C before use. All solvents used in the preparation of the chiral stationary phases were of analytical grade. Hexane, 2-propanol and CHCl_3 used in the chromatographic experiments were of HPLC grade. The racemates were commercially available or were prepared by the usual methods.

2.2. Synthesis of 4-ethynyl-*N*-(3-(triethoxysilyl)propyl)benzamide (PA-TES)

4-Ethynyl-*N*-(3-(triethoxysilyl)propyl)benzamide (PA-TES) was synthesized via the amidation reaction between 4-ethynylbenzoic acid and 3-aminopropyltriethoxysilane (Scheme 1). The synthesis procedure is described as follows. To a solution of 4-ethynylbenzoic acid (0.831 g, 5.68 mmol) and DMT-MM (1.737 g, 6.28 mmol) in dry methanol (MeOH) (30.0 mL) was added the 3-aminopropyltriethoxysilane (1.60 mL). After stirring at room temperature for 19 h, the reaction mixture was purified by silica gel chromatography (eluent: hexane/ethyl acetate (3/1, v/v)) followed by recrystallization in hexane to produce PA-TES as a white solid. Yield: 0.988 g (49.7%). Anal. Calcd for $\text{C}_{18}\text{H}_{27}\text{O}_4\text{NSi}$ (349): C, 61.89; H, 7.74; N, 4.01; Si, 8.02. Found: C, 61.76; H, 7.63; N, 4.09; Si, 8.48.

2.3. Copolymerization of PA-Phe and PA-TES

The typical procedure is described as follows. PA-Phe (0.650 g, 2.03 mmol) and PA-TES (7.0 mg, 0.020 mmol) were weighed into a flask and dissolved in dry *N,N*-dimethylformamide (DMF) (185.0 mL) under a nitrogen atmosphere before a solution of $\text{Rh}(\text{nbdb})\text{BPh}_4$ (0.024 g, 0.046 mmol) in dry DMF (19.5 mL) was added. After stirring at room temperature under a nitrogen atmosphere for 24 h, triphenylphosphine (36.5 mg, 0.14 mmol) was added to the reaction mixture. The solution was concentrated and then poured into a large amount of hexane. The precipitates were dissolved in DMF and precipitated in hexane. After filtration, the precipitates were dried under reduced pressure to form a copolymer (CPA-1) as a yellow solid (0.647 g, 98.5%). $M_n = 3.24 \times 10^5$; $M_w/M_n = 6.4$.

The copoly(phenylacetylene)s CPA-2–4 were synthesized by a similar procedure as already described.

2.4. Immobilization of the copolymers onto silica gel by intermolecular polycondensation of triethoxysilyl groups

A typical immobilization procedure is described as follows. A copolymer solution in CHCl_3 (0.40 g in 10.0 mL) was coated on the aminopropyl silanized silica gel (1.60 g) according to the reported approach [31]. The copolymer-coated silica gel (2.00 g) was then mixed with ethanol (18.0 mL), water (4.50 mL) and trimethylsilyl chloride (0.40 mL). After stirring for 24 h at 35 °C, the immobilized CSPs were sufficiently washed with CHCl_3 and dried at 60 °C in vacuo. The immobilization efficiency was estimated by a thermogravimetric analysis (TGA).

2.5. Preparation of the packed HPLC columns

The copolymer-immobilized silica gels were packed in a stainless-steel tube (25 cm \times 0.20 cm I.D.) by a slurry method. The plate numbers of the packed columns were 1800–3300 for benzene using a hexane/2-propanol (95/5, v/v) mixture as the eluent at the flow rate of 0.1 mL/min at 25 °C. The results of the HPLC separation were evaluated using the retention factors k_1' and k_2' and the separation factor α as follows. If a pair of enantiomers are eluted at the retention times t_1 and t_2 , respectively, and the dead time (t_0) of the column is estimated using 1,3,5-tri-*tert*-butylbenzene as the non-retained compound, the retention factors, k_1' and k_2' , are estimated as $(t_1 - t_0)/t_0$ and $(t_2 - t_0)/t_0$, respectively, which leads to the separation factor $\alpha (k_2'/k_1')$ [30].

2.6. Instrumentation

The ^1H NMR spectra (500 MHz) were recorded using a Bruker AVANCE III-500 (Fällanden, Switzerland) instrument at 20 °C or 80 °C. The number-average molecular weight (M_n), the weight-average molecular weight (M_w), and the polydispersity (M_w/M_n) of the polymers were determined by size exclusion chromatography (SEC) calibrated with standard polystyrenes at 40 °C using a JASCO SEC system (Tokyo, Japan) (PU-980 Intelligent pump, CO-965 column oven, RI-930 Intelligent RI detector, and Shodex (Tokyo, Japan) DEGAS KT-16) equipped with a Shodex Asahipak GF-310 HQ column (linear, 7.6 mm \times 300 mm; pore size, 20 nm; bead size, 5 μm ; exclusion limit, 4×10^4) and a Shodex Asahipak GF-7 M HQ column (linear, 7.6 mm \times 300 mm; pore size, 20 nm; bead size, 9 μm ; exclusion limit, 4×10^7) in DMF containing lithium chloride (LiCl) (0.01 M) at the flow rate of 0.4 mL/min. The circular dichroism (CD) and ultraviolet visible (UV-Vis) spectra were measured in a 1-mm path length cell using a Jasco J-815 spectropolarimeter (Tokyo, Japan). The diffuse reflectance circular dichroism (DRCD) and

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