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Short communication

Development of an improved ligand exchange chiral stationary phase based on leucinol for the resolution of proton pump inhibitors

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ABSTRACT

As an effort to develop improved ligand exchange chiral stationary phases (CSPs) for the resolution of chiral drugs, the residual silanol groups on the silica surface of a CSP based on sodium *N*-[(*S*)-1-hydroxymethyl-3-methylbutyl]-*N*-undecylaminoacetate, a (*S*)-leucinol derivative, were protected with *n*-octyl groups. The residual silanol group-protected CSP was applied to the resolution of proton pump inhibitors (PPIs) such as omeprazole, pantoprazole, lansoprazole and rabeprazole. The resolution of PPIs on the residual silanol group-protected CSP was excellent with the separation factors (α) in the range of 4.32–6.42 and the resolution factors (R_S) in the range of 6.70–7.15. The improved chiral recognition ability of the residual silanol group-protected CSP was rationalized to be originated from the protection of the non-enantioselective interaction sites on the silica surface and the improved lipophilicity of the stationary phase.

1. Introduction

Liquid chromatographic chiral stationary phases (CSPs) have been known to be very effective for the determination of enantiomeric purity or enantiomeric composition of chiral compounds including chiral drugs [1–3]. Among various CSPs, ligand exchange CSPs have been known to be useful for the determination of enantiomeric purity or enantiomeric composition of chiral bidentate or tridentate substrates [4–9]. Ligand exchange CSPs have been prepared by covalently bonding or dynamically coating a bidentate or tridentate chiral selector onto column supporting material. Proline, hydroxyproline or other amino acids have been successfully utilized as chiral selectors for the preparation of ligand exchange CSPs [4–7]. Amino alcohol derivatives such as (*S*)-leucinol derivative, sodium *N*-[(*S*)-1-hydroxymethyl-3-methylbutyl]-*N*-undecylaminoacetate, and (*R*)-phenylglycinol derivative, sodium *N*-[(*R*)-2-hydroxy-1-phenylethyl]-*N*-undecylaminoacetate, covalently bonded to silica gel [10,11] or dynamically coated on octadecylsilica gel [12] were also quite successful as ligand exchange CSPs for the resolution of α- and β-amino acids and α-hydroxycarboxylic acids [10–17]. Especially, a CSP (CSP **1**, Fig. 1) based on (*R*)-phenylglycinol derivative covalently bonded to silica gel was quite successful in the resolution of proton pump inhibitors (PPIs) including omeprazole, pantoprazole, lansoprazole and rabeprazole shown in Fig. 2 [18], which are drugs for the treatment of diseases related to gastric acid secretion disorders [19]. When the residual silanol groups on the silica surface of CSP **1** were protected with *n*-octyl groups, the resulting CSP (CSP **2**, Fig. 1) was found to afford improved chiral recognition ability for α-amino acids and PPIs [20]. The improved lipophilicity of CSP **2** was proposed to be responsible for its improved chiral recognition ability.

Previously, the improvement in the lipophilicity of crown ether-based CSPs has also been reported to improve the chiral recognition ability and this effect has been found to be more significant with more lipophilic analytes [21,22]. Ligand exchange CSP based on L-proline was also reported to show higher chiral recognition ability when its lipophilicity was improved [23]. CSP **3** (Fig. 1) derived from (*S*)-leucinol derivative has been proposed to be more lipophilic than CSP **1** from the chromatographic trends for the resolution of α- and β-amino acids on the two CSPs [14]. Consequently, CSP **3** is expected to show greater chiral recognition ability than CSP **1** especially for PPIs, which are predicted to be highly lipophilic from their structures [19]. However, CSP **3** has not been applied to the

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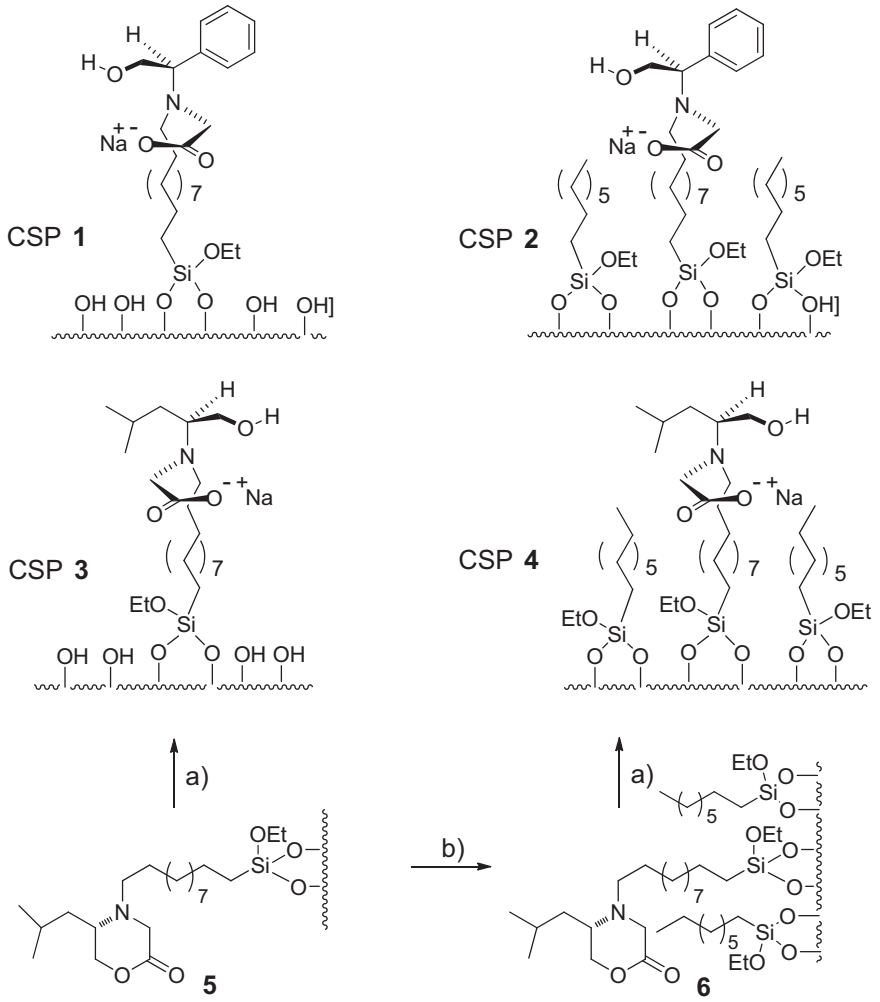

Fig. 1. Structures of CSP **1**, CSP **2**, CSP **3** and CSP **4** and the synthetic route for the preparation of CSP **3** and CSP **4**. (a) 1 N NaOH solution, methanol, room temperature, 24 h. (b) *n*-Octyltriethoxysilane, Dean–Stark trap, toluene, reflux, 72 h.

resolution of PPIs. Another CSP (CSP **4**), which can be prepared by introducing *n*-octyl groups on the silica surface of CSP **3**, is expected to show even greater chiral recognition ability for PPIs because of the additional lipophilic *n*-octyl groups. In this study, we prepared CSP **3** and CSP **4** from the identical source of silica gel modified with (*S*)-leucinol derivative to minimize the effect of the loading level of chiral selector on the chiral recognition ability and apply them to the resolution of PPIs. The comparison of the chromatographic results for the resolution of PPIs on CSP **3** and CSP **4** with those on CSP **1** and CSP **2** is expected to explore the importance of the lipophilicity of the stationary phase for the resolution of PPIs.

2. Experimental

2.1. Chromatography

Chromatography was performed with an HPLC system consisting of a Waters model 515 HPLC pump (Milford, MA, USA), a Rheodyne model 7725i injector (Rohnert Park, CA, USA) with a 20 μl sample loop, a Waters 484 tunable absorbance UV detector (Milford, MA, USA) and a YoungLin Autochro data module (Software: YoungLin Autochro-WIN 2.0 plus, Seoul, Korea). The temperature of the chiral column was controlled by using a JEIO TECH VTRC-620 cooling circulator (Daejeon, Korea). All analytes including racemic and optically active PPIs such as omeprazole, pantoprazole, lansoprazole and rabeprazole and PPI analogues **7**, **8** and **9** shown in Fig. 2 were available from the prior studies [18,20]. Injection samples were prepared by dissolving each analyte in methanol or ethanol (usually 1.0 mg/ml). The usual injection volume was 2.0 μl.

2.2. Preparation and column packing of CSP 3 and CSP 4

CSP **3** and CSP **4** were prepared via the procedure shown in Fig. 1. Modified silica gel **5** (4.6 g) was prepared starting from (*S*)-leucinol via the procedure we reported previously [10]. Based on the elemental analysis of modified silica gel 5 (C 4.31%, N 0.24%, H 0.90%), 0.17 mmol (based on C) of (*S*)-leucinol derivative was calculated to be loaded on 1 g of modified silica gel. Modified silica gel **5** was divided into two portions. One portion (2.3 g) was suspended into methanol (10 ml) and 1 N NaOH solution (0.4 ml) and then stirred for 24 h at room temperature. Then the modified silica gel was filtered and washed with methanol and then dried to afford CSP **3**. CSP **3** was slurried in methanol and packed into stainless steel HPLC column (150 × 4.6 mm) by using a conventional column packing method with an Alltech HPLC slurry packer.

Another portion (2.3 g) of modified silica gel **5** was suspended into toluene (100 ml) in a flask equipped with a Dean–Stark trap. The mixture was heated to reflux until water was removed completely (azeotropic removal of water). And then *n*-octyltriethoxysilane (6 ml, 19.1 mmol) was added. The whole mixture was refluxed for 72 h. After cooling, the modified silica