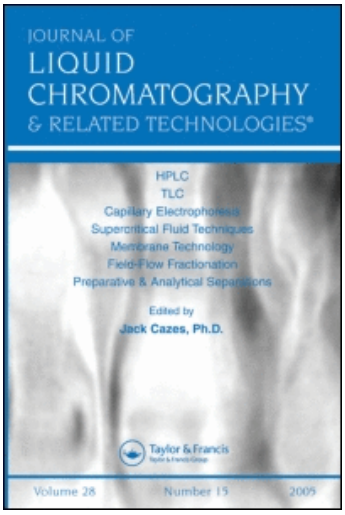

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Liquid Chromatographic Resolution of 1,1′-Bi-2-Naphthol and 3,3′-Diaryl-1,1′-bi-2-Naphthols on Pirkle-Type Chiral Stationary Phases Based on Leucine and Phenylglycine

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Abstract: Pirkle-type chiral stationary phases (CSPs) based on (*S*)-leucine and (*S*)-phenylglycine were applied in the resolution of 1,1′-bi-2-naphthol and 3,3′-diaryl-1,1′-bi-2-naphthols. Among the two Pirkle-type CSPs, the one based on (*S*)-*N*-(3,5-dinitrobenzoyl)leucine *N*-propylamide was found to be excellent and most widely applicable. Interestingly, the elution orders for the resolution of 1,1′-bi-2-naphthol on the CSPs based on (*S*)-*N*-(3,5-dinitrobenzoyl)leucine *N*-propylamide and (*S*)-*N*-(3,5-dinitrobenzoyl)phenylglycine *N*-propylamide were opposite to those for the resolution of 3,3′-diaryl-1,1′-bi-2-naphthols. In order to rationalize the reversed elution orders, we proposed two different chiral recognition mechanisms based on the chromatographic resolution behaviors, with the aid of the CPK molecular model study.

Keywords: Enantiomer separation, chiral stationary phase, 1,1′-bi-2-naphthol, 3,3′-diaryl-1,1′-bi-2-naphthols

INTRODUCTION

While optically active 1,1′-bi-2-naphthol (1, R = H, Figure 1) has been utilized as a ligand of chiral catalyst in asymmetric synthesis,[1,2] various efforts have been devoted to the development of more effective optically active 1,1′-bi-2-naphthol

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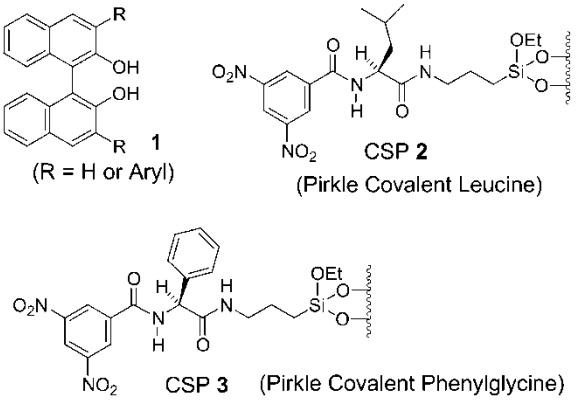

Figure 1. Structures of analytes (1) and CSPs (2 and 3) used in this study.

analogs and, as a result, various 3,3′-diaryl-1,1′-bi-2-naphthol (1, R = aryl, Figure 1) have been developed and successfully utilized as chiral ligands.[3–6] Optically active 1,1′-bi-2-naphthol and 3,3′-diaryl-1,1′-bi-2-naphthols have also been incorporated into chiral crown ethers, useful as stereoselective complexing agents or liquid chromatographic chiral stationary phases (CSPs), after being bonded to column solid support material.[7–11] During the process of developing or utilizing optically active 1,1′-bi-2-naphthol and 3,3′-diaryl-1,1′-bi-2-naphthols, the accurate determination of their enantiomeric purity is essential. Among various methods, liquid chromatographic separation of enantiomers on CSPs has been known to be the most accurate and convenient means of determining the enantiomeric purity of optically active compounds.[12–14]

Previously, racemic 1,1′-bi-2-naphthol has been resolved on various CSPs based on, for example, helical polymers,[15] cellulose derivatives,[16] network polymers,[17] macrocyclic antibiotics,[18] and Pirkle-type low molecular weight $\pi-\pi$ complex forming agents.[19,20] However, the systematic studies on the liquid chromatographic resolution of racemic 1,1′-bi-2-naphthol and 3,3′-diaryl-1,1′-bi-2-naphthols are quite rare. In this study, we wish to explore the chromatographic behaviors for the resolution of racemic 1,1′-bi-2-naphthol and 3,3′-diaryl-1,1′-bi-2-naphthols on Pirkle-type CSPs based on (*S*)-leucine and (*S*)-phenylglycine (CSPs 2 and 3, Figure 1) more systematically, and propose a chiral recognition mechanism based on the chromatographic resolution behaviors.

EXPERIMENTAL

Chromatography was performed with an HPLC system consisting of a Waters model 510 pump, a Rheodyne model 7125 injector with a 20 μL sample loop, a YoungLin M720 absorbance detector with a 254 nm UV filter, and a

YoungLin Autochro Data Module (Software: YoungLin Autochro-WIN 2.0 plus). Chiral columns packed with CSP 2 and CSP 3 were commercially available from Regis Chemical Company (Morton Grove, IL, USA). All chromatographic data were collected using a mixed solvent of 2-propanol–hexane (10 : 90, v/v) as a mobile phase with a flow rate of 2 mL/min at 20°C. The void volume was determined by the injection of 1,3,5-tri-*tert*-butyl benzene.

Racemic and optically active 1,1′-bi-2-naphthol (1, R = H, Figure 1) were purchased from Aldrich. 3,3′-Diaryl-1,1′-bi-2-naphthols (1, R = aryl, Figure 1) were prepared from racemic or optically active 1,1′-bi-2-naphthol by Suzuki coupling reaction as described previously.[5,6] 3,3′-Diaryl-1,1′-bi-2-naphthols, thus prepared, were consistent with the spectroscopic structural data such as ^{1}H NMR spectra.

Each of racemic and optically active 1,1′-bi-2-naphthol and 3,3′-diaryl-1,1′-bi-2-naphthols was dissolved in methylene chloride (usually 2.5 mg/mL) and then used as an injection sample. The usual injection volume was 0.5 μL.

RESULTS AND DISCUSSION

Chromatographic separation of the enantiomers of 1,1′-bi-2-naphthol and 3,3′-diaryl-1,1′-bi-2-naphthols was performed on CSP, 2 and 3 and the results are summarized in Table 1. The representative chromatograms are presented in Figure 2. The elution order shown in Table 1 was obtained by injecting configurationally known samples.

Table 1. Resolution of 1,1′-bi-2-naphthol and 3,3′-diaryl-1,1′-bi-2-naphols (1) on CSP 2, and 3)[a]

	Analytes 1	CSP 2		CSP 3	
Entry	R	k_1'[b]	α[c]	k_1'[b]	α[c]
a	H	1.63 (R)	1.33	3.25 (R)	1.41
b	C_6H_5	1.33 (S)	1.38	4.72 (S)	1.16
c	4-(C_6H_5)-C_6H_4	2.10 (S)	1.19	11.08 (S)	1.09
d	4-tert-Butyl-C_6H_4	0.42 (S)	1.19	1.26	1.00
e	2,6-Dimethyl-C_6H_3	0.40 (S)	1.18	1.19 (S)	1.14
f	3,4-Dimethyl-C_6H_3	1.47 (S)	1.29	4.91 (S)	1.15
g	1-Naphthyl	3.26 (S)	1.40	15.58 (S)	1.11
h	2-Naphthyl	6.93 (S)	1.30	46.03 (S)	1.19

[a]Chromatographic condition is given in the experimental part.

[b]Capacity factor of the first eluted enantiomer. Absolute configuration of the first eluted enantiomer is given in parentheses.

[c]Separation factor.

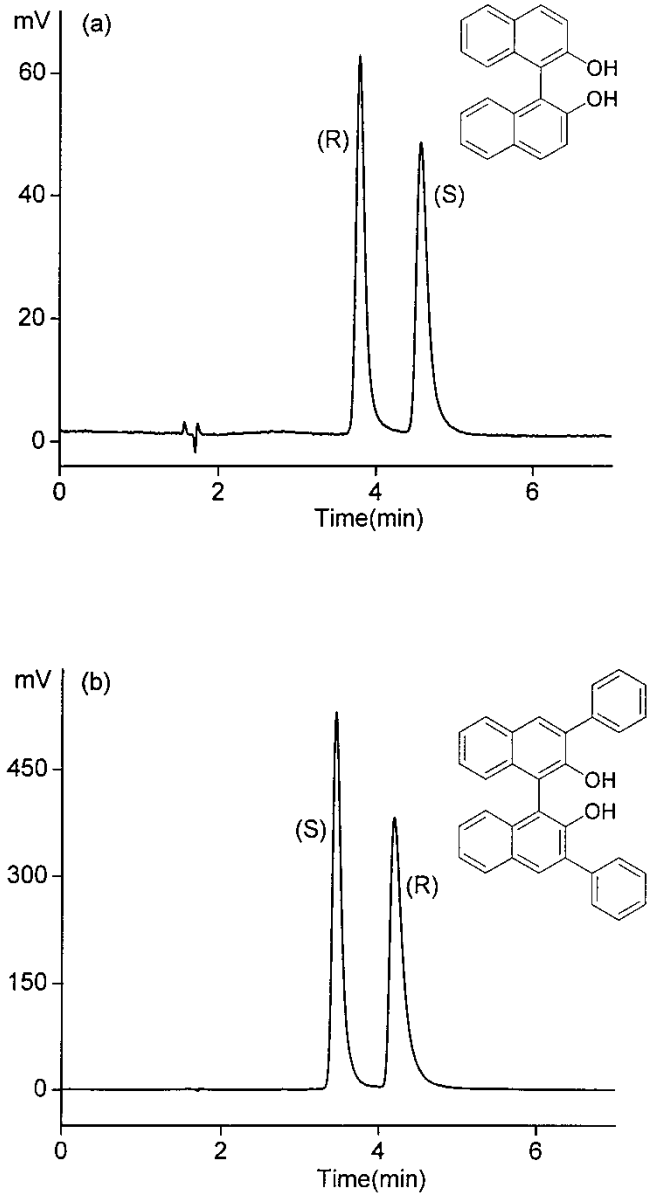

Figure 2. Representative chromatograms for the resolution of (a) 1,1′-bi-2-naphthol (1, R = H) and (b) 3,3′-diphenyl-1,1′-bi-2-naphthol (1, R = phenyl) on CSP 2. Mobile phase; 10% isopropyl alcohol in hexane; flow rate; 2 mL/min, detection, 254 nm UV; temperature, 20°C.

As shown in Table 1, CSP 2 based on (*S*)-*N*-(3,5-dinitrobenzoyl)leucine *N*-propylamide is quite useful in the resolution of 1,1′-bi-2-naphthol and 3,3′-diaryl-1,1′-bi-2-naphthols. CSP 3 based on (*S*)-*N*-(3,5-dinitrobenzoyl)-phenylglycine *N*-propylamide is also useful in the resolution of 1,1′-bi-2-naphthol and 3,3′-diaryl-1,1′-bi-2-naphthols. Between the two CSPs, CSP 2 turns out to be better than CSP 3 in the resolution of 3,3′-diaryl-1,1′-bi-2-naphthols, even though CSP 3 is slightly better than CSP 2 in the resolution of 1,1′-bi-2-naphthol.

The most surprising results for the resolution of 1,1′-bi-2-naphthol and 3,3′-diaryl-1,1′-bi-2-naphthols on CSPs 2 and 3 are the elution orders. As shown in Table 1, the (*R*)-enantiomer eluted first in the resolution of 1,1′-bi-2-naphthol on CSPs 2 and 3. However, the (*S*)-enantiomers eluted always first in the resolution of all of 3,3′-diaryl-1,1′-bi-2-naphthols on CSPs 2 and 3.

The reversed elution orders for the resolution of 1,1′-bi-2-naphthol and 3,3′-diaryl-1,1′-bi-2-naphthols on CSPs 2 and 3 indicate that the chiral recognition mechanism for the resolution of 1,1′-bi-2-naphthol on CSPs 2 and 3 should be different from that for the resolution of 3,3′-diaryl-1,1′-bi-2-naphthols on CSPs 2 and 3. Previously, a chiral recognition mechanism for the resolution of 1,1′-bi-2-naphthol on ionically bonded *N*-(3,5-dinitrobenzoyl)phenylglycine CSP was proposed.[19] According to that chiral recognition mechanism, the preferentially bound enantiomer undergoes a minimum of three simultaneous interactions with the CSP. The three simultaneous interactions were proposed to consist of a $\pi-\pi$ interaction between the dinitrobenzoyl group of the CSP and one naphthyl π-system of the analyte, a hydrogen bond between the amide hydrogen of the CSP and the oxygen of the non-π-complexed naphthyl ring of the analyte, and a hydrogen bond between the carboxylate group of the CSP and the hydroxy group of the π-complexed naphthyl ring of the analyte. Based on the observed chromatographic results, with the aid of CPK molecular models, we assumed that the chiral recognition mechanism for the resolution of 1,1′-bi-2-naphthol on CSP 2 or 3 might be identical to that proposed previously by Pirkle for the resolution of 1,1′-bi-2-naphthol on ionically bonded *N*-(3,5-dinitrobenzoyl)phenylglycine CSP, except for the utilization of the amide carbonyl oxygen of the tethering group of CSP 2 or 3 instead of the carboxylate oxygen of ionically bonded *N*-(3,5-dinitrobenzoyl)phenylglycine CSP for the second hydrogen bond. The chiral recognition mechanism proposed in this study for the resolution of 1,1′-bi-2-naphthol on CSP 2 is presented in Figure 3 (the identical chiral recognition mechanism is expected to be applicable on CSP 3).

As shown in Figure 3, we can easily recognize the face-to-face $\pi-\pi$ interaction between the dinitrobenzoyl group of the CSP and one naphthyl π-system of 1,1′-bi-2-naphthol and the two simultaneous hydrogen bonds between the CSP and the analyte. However, in the resolution of 3,3′-diaryl-1,1′-bi-2-naphthols on CSP 2 or 3, we found from the CPK molecular model studies, that the 3,3′-diaryl groups, which are orthogonal to the naphthyl group, sterically hinder the face-to-face $\pi-\pi$ interaction between the dinitrobenzoyl group of the CSP and one naphthyl group of 3,3′-diaryl-1,1′-bi-2-naphthols, and the chiral recognition

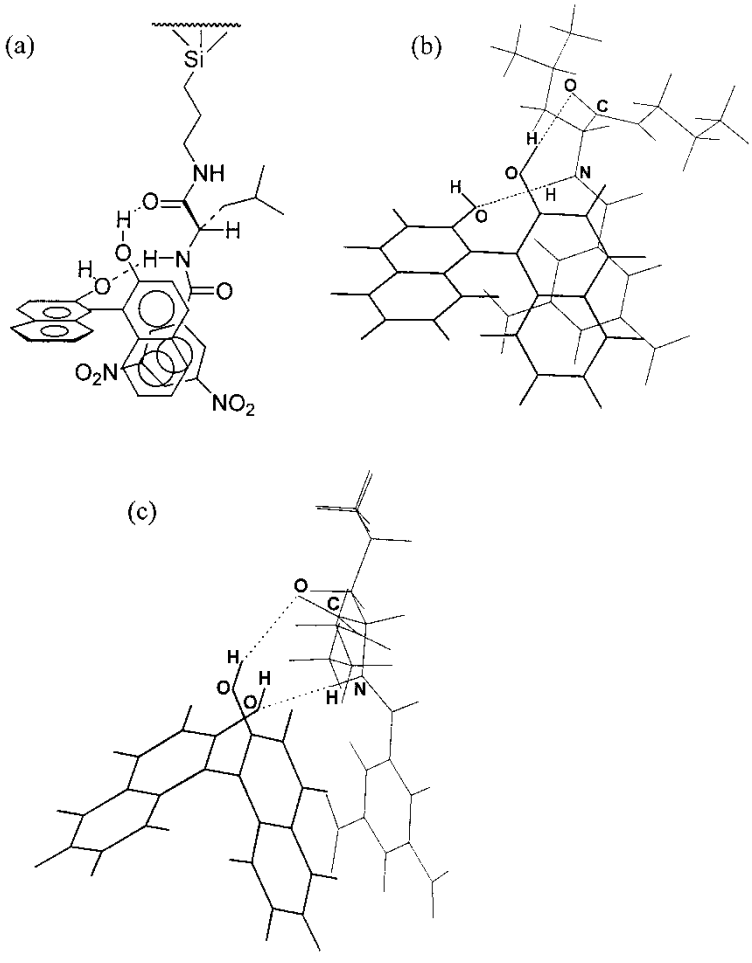

Figure 3. Proposed chiral recognition mechanism for the more stable (*S*, *S*)-complex formed between the chiral selector of (*S*)-CSP 2, (*S*)-*N*-(3,5-dinitrobenzoyl)leucine *N*-propylamide, and the (*S*)-enantiomer of 1,1′-bi-2-naphthol (1, R = H). (a) Schematic presentation of the chiral recognition model. (b) Computer generated (Hyper Chem 4.0) stick molecular models viewed from the angle showing the face-to-face $\pi-\pi$ interaction between the chiral selector of the CSP (thin lines) and the analyte (thick lines). (c) The same stick molecular models as in (b) viewed from different angle.

mechanism shown in Figure 3 can not be applicable. Consequently, in the resolution of 3,3′-diaryl-1,1′-bi-2-naphthols on CSP 2 or 3, we herein propose a different chiral recognition mechanism, which can rationalize the non-consistent elution orders for the resolution of 1,1′-bi-2-naphthol and 3,3′-diaryl-1,1′-bi-2-naphthols on CSP 2 and 3.

The chiral recognition mechanism proposed herein for the resolution of 3,3′;-diaryl-1,1′-bi-2-naphthols on CSP 2 is presented in Figure 4 (again the identical chiral recognition mechanism is applicable on CSP 3). In Figure 4, the chiral selector of CSP 2, (*S*)-*N*-(3,5-dinitrobenzoyl)leucine *N*-propylamide, interacts with (*R*)-3,3′-diphenyl-1,1′-bi-2-naphthol through

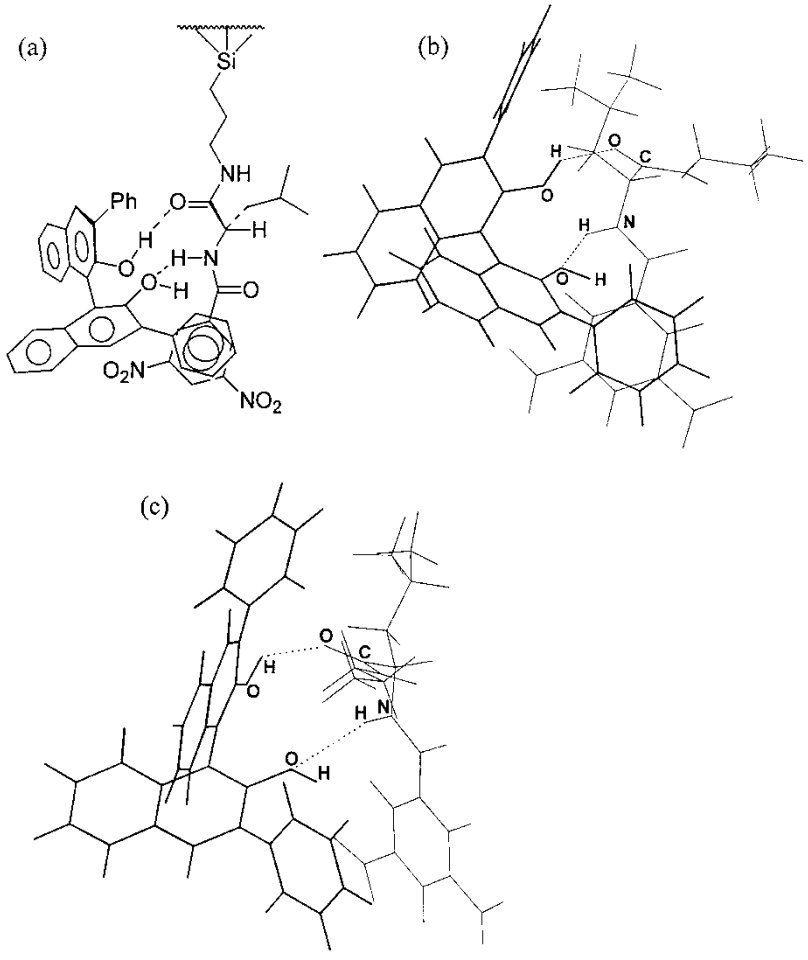

Figure 4. Proposed chiral recognition mechanism for the more stable (*S*, *R*)-complex formed between the chiral selector of (*S*)-CSP 2, (*S*)-*N*-(3,5-dinitrobenzoyl)leucine *N*-propylamide and the (*R*)-enantiomer of 3,3′-1,1′-bi-2-naphthol (1, R = phenyl). (a) Schematic presentation of the chiral recognition model. (b) Computer generated (HyperChem 4.0) stick molecular models viewed from the angle showing the face-to-face $\pi-\pi$ interaction between the chiral selector of the CSP (represented with thin lines) and the analyte (represented with thick lines). (c) The same stick molecular models as in (b) viewed from different angle.

the face-to-face $\pi-\pi$ interaction between the 3,5-dinitrobenzoyl group of the CSP and the phenyl group at the 3- or 3′-position of the analyte. Simultaneously, the chiral selector of CSP 2 interacts with (*R*)-3,3′-diphenyl-1,1′-bi-2-naphthol through two hydrogen bondings. One hydrogen bonding is presumed to be formed between the *N*-(3,5-dinitrobenzoyl)amide N═H hydrogen of the CSP and the hydroxy oxygen at the 2-position of the naphthyl ring neighboring with the π-complexed phenyl ring of the analyte. The other hydrogen bonding is formed between the *N*-propylamide carbonyl oxygen of the CSP and the hydroxy hydrogen at the 2′-position of the other naphthyl ring of the analyte. The three simultaneous interactions of the chiral selector of CSP 2 (or CSP 3) with (*S*)-3,3′-diphenyl-1,1′-bi-2-naphthol are energetically less favorable because of the inadequate three dimensional positions of the interaction sites. In this instance, the (*R*)-enantiomers are retained longer on the column.

In summary, in this study, we demonstrated that two Pirkle-type CSPs based on (*S*)-leucine or (*S*)-phenylglycine can be successfully applied in the determination of the enantiomeric composition of racemic or optically active 1,1′-bi-2-naphthol and 3,3′-diaryl-1,1′-bi-2-naphthols. Especially, CSP 2 based on (*S*)-*N*-(3,5-dinitrobenzoyl)leucine *N*-propylamide was found to be widely applicable in the resolution of 1,1′-bi-2-naphthol and 3,3′-diaryl-1,1′-bi-2-naphthols. Interestingly, the elution order for the resolution of 1,1′-bi-2-naphthol was opposite to those for the resolution of 3,3′-diaryl-1,1′-bi-2-naphthols. In order to rationalize the reversed elution orders, we proposed two different chiral recognition mechanisms. One chiral recognition mechanism for the resolution of 1,1′-bi-2-naphthol utilizes the naphthyl system of the analyte for the face-to-face $\pi-\pi$ interaction, while the other mechanism for the resolution of 3,3′-diaryl-1,1′-bi-2-naphthols utilizes the aryl group at the 3- or 3′-position of the naphthyl system of the analyte.

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