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Note on the use of reciprocity of chiral recognition in designing liquid chromatographic chiral stationary phases

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Abstract

A new high-performance liquid chromatographic chiral stationary phase (CSP) was prepared from (*S*)-*N*-(3,5-dimethylbenzoyl)leucine *N*-phenyl *N*-allyl amide. The new CSP was applied for the resolution of *N*-(3,5-dinitrobenzoyl)-α-amino amides and esters and the chromatographic resolution results were compared with those on another CSP derived from (*S*)-*N*-(3,5-dimethoxylbenzoyl)leucine *N*-phenyl *N*-allyl amide. The new CSP was found to exert greater enantioselectivity than the other one. These results are contrary to what was expected from the reciprocity of chiral recognition. From these results it was concluded that the reciprocity of chiral recognition should be used with some degree of care in developing effective CSPs or in predicting chromatographic resolution behaviors.

Keywords: Chiral stationary phases, LC; Chiral recognition; Enantiomer separation

1. Introduction

Liquid chromatographic separation of enantiomers on high-performance liquid chromatography (HPLC) chiral stationary phases (CSPs) has been known as the most accurate and convenient means in determining the enantiomeric composition of chiral compounds. Therefore, significant efforts have been devoted to the development of effective CSPs for the liquid chromatographic resolution of enantiomers and various CSPs derived from optically active natural or synthetic chiral compounds are now available [1–3]. In developing effective CSPs, the success depends on the selection of effective chiral selectors. In most cases, the processes of selecting effective chiral selectors have been done on the basis of the trial-and-error method. However, Pirkle and co-workers have successfully employed the conception of reciprocity of chiral recognition in designing chiral selectors rationally [4–6]. The reciprocity of chiral recognition is simple in that if a CSP derived from (+)-A can distinguish between (+)-B and (−)-B, then a CSP derived from (+)-B may distinguish (+)-A from (−)-A. Thus, the enantiomer from a racemate resolvable best on a CSP can be a potential candidate for incorporation into a reciprocal CSP intended to resolve the racemate related to the original CSP. For example, *N*-(3,5-dinitrobenzoyl)-α-amino amides, which are resolvable on a CSP based on 9-anthryl fluoro carbinol [7], have been successfully incorporated into reciprocal CSPs for the resolution of racemic aryl fluoro alcohols [4,5]. The first generated reciprocal CSPs based on *N*-(3,5-dinitrobenzoyl)-α-amino amides were also very effective for the resolution of racemic compounds such

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as *N*-acylated α-arylalkylamines [8] and *N*-aryl-α-amino esters or amides [9]. Consequently, the second generated reciprocal CSPs based on an *N*-acylated α-arylalkylamine [10,11] and an *N*-aryl-α-amino ester [12,13] have been developed and successfully utilized in resolving *N*-(3,5-dinitrobenzoyl)-α-amino amides and other related racemic compounds.

Very recently, by modifying the original first generated reciprocal CSP (CSP **1**), we developed a very effective CSP (CSP **2**) based on (*S*)-leucine (see Fig. 1 for the structures of CSPs). CSP **2** was more effective than CSP **1** for the resolution of derivatives of α-amino amides [14,15] and for the resolution of derivatives of 2-hydroxycarboxylic acids [16]. Especially *N*-(3,5-dimethoxybonzoly)leucine *N*-phenyl *N*-allyl amide **3** was resolved very well on CSP **2**. Consequently one of the two enantiomers of compound **3** was selected as a best candidate for the chiral selector of a new reciprocal CSP (CSP **4**). A new reciprocal CSP (CSP **4**) developed based on the reciprocity conception of chiral recognition was excellent in resolving various *N*-(3,5-dinitrobenzoyl)-α-amino amides and esters [17].

In this study, based on *N*-(3,5-dimethylbenzoyl)leucine *N*-phenyl *N*-allyl amide **5**, we prepared another new CSP (CSP **6**). In the previous study, *N*-(3,5-dimethylbenzoyl)leucine *N*-phenyl *N*-allyl amide **5**, chiral selector of CSP **6**, was reported to be resolved worse than *N*-(3,5-dimethoxybonzoly)leucine *N*-phenyl *N*-allyl amide **3**, chiral selector of CSP **4** [17]. Consequently, it is expected that CSP **6** might be not so effective as CSP **4** in resolving *N*-(3,5-dinitrobenzoyl)-α-amino amides and esters because of the reciprocity of chiral recognition. However, on the contrary, CSP **6** was more effective than CSP **4**. We herein report the details for the resolution of *N*-(3,5-dinitrobenzoyl)-α-amino amides and esters on CSP **4** and CSP **6** and discuss the use of reciprocity of chiral recognition in developing new CSPs or in predicting chromatographic resolution results.

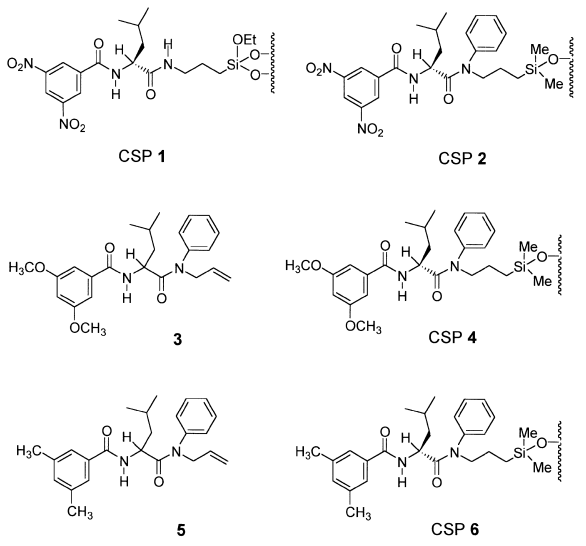


Fig. 1. Structures of CSPs and compounds used in this study.

2. Experimental

Chromatography was performed with a HPLC system consisting of a Waters Model 510 pump, a Rheodyne Model 7125 injector with a 20-μl sample loop, a Youngin Model 710 absorbance detector with a 254-nm UV filter and a Youngin D520B computing integrator. All chromatographic experiments were carried out at a flow-rate of 2 ml/min at room temperature. Column void volume was measured by injecting 1,3,5-tri-*tert*.-butylbenzene. Analytes and chiral column packed with CSP **4** used in this study were available from the previous study [17].

CSP **6** was prepared via the method reported previously for the preparation of CSP **4** [17] by using 3,5-dimethylbenzoyl chloride instead of 3,5-dimethoxybenzoyl chloride as a benzoylating agent. Based on the elemental analysis of CSP **6** (C, 6.30%; H, 0.86%, N, 0.53%), the loading of chiral selector on 5 μm Rexchrom silica gel (Regis, Morton Grove, IL, USA) was calculated to be 0.19 mmol (based on N) or 0.20 mmol (based on C) per gram of stationary phase. The loading level of chiral selector on silica gel in CSP **6** was found to be quite similar to that in CSP **4** (0.16 mmol based on N or 0.19 mmol based on C) [17]. CSP **6** thus prepared was packed into a 250 mm×4.6 mm I.D. stainless steel HPLC column using conventional slurry packing method with an Alltech slurry packer. The residual silanol group was protected by eluting a solution of hexamethyldisilazane (2 ml) dissolved in methylene chloride (50 ml) through the column. Then the column packed with CSP **6** was washed before use

by eluting 100 ml of methylene chloride through the column.

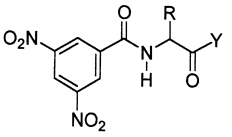
3. Results and discussion

CSP **6** was applied for the resolution of *N*-(3,5-dinitrobenzoyl)-α-amino amides and esters **7**. The results are summarized and compared with those on CSP **4** in Table 1. As shown in Table 1, both CSP **4** and CSP **6** were excellent in resolving *N*-(3,5-dinitrobenzoyl)-α-amino amides and esters **7**. In general, *N*-(3,5-dinitrobenzoyl)-α-amino *N*,*N*-diethyl amides were resolved better than the corresponding *N*-(3,5-dinitrobenzoyl)-α-amino *N*-propyl amides or *N*-(3,5-dinitrobenzoyl)-α-amino ethyl esters. The rationalization for these results on CSP **4** has been proposed previously [17]. The exactly same rationalization can be applied to the chromatographic behaviors for the resolution of *N*-(3,5-dinitrobenzoyl)-α-amino amides and esters **7** on CSP **6**.

One interesting observation to note is that CSP **6** is more effective than CSP **4** for the resolution of *N*-(3,5-dinitrobenzoyl)-α-amino amides and esters **7**. As shown in Table 1, the enantioselectivity of CSP **6** denoted by the separation factors, α, is always greater than that of CSP **4**. These results are exactly the opposite to what we expected from the reciprocity of chiral recognition.

Previously, it was found that *N*-(3,5-dimethoxy-

Table 1
Resolution of *N*-(3,5-dinitrobenzoyl)-α-amino amides and esters **7** on CSP **4** and CSP **6** with a mobile phase of 20% isopropanol in hexane[a]



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Analyte	R	Y	CSP **4**			CSP **6**		
			k_1'[b]	k_2'[c]	α[d]	k_1'[b]	k_2'[c]	α[d]
7a	CH_3 (alanine)	$NHCH_2CH_2CH_3$	(1.86)	(25.71)	(13.82)	1.21	18.60	15.37
7b		$N(CH_2CH_3)_2$	(2.06)	(37.07)	(17.99)	1.20	28.82	24.02
7c		OCH_2CH_3	(3.98)	(15.06)	(3.78)	2.64	12.94	4.90
7d	$CH(CH_3)_2$ (valine)	$NHCH_2CH_2CH_3$	(1.12)	(11.15)	(9.96)	0.84	10.76	12.81
7e		$N(CH_2CH_3)_2$	1.25	12.14	9.71	0.80	11.31	14.14
7f		OCH_2CH_3	(2.66)	(10.34)	(3.89)	2.65	12.89	4.86
7g	$CH_2CH(CH_3)_2$ (leucine)	$NHCH_2CH_2CH_3$	(1.07)	(14.55)	(13.60)	0.79	11.96	15.14
7h		$N(CH_2CH_3)_2$	(1.12)	(22.10)	(19.73)	0.72	15.10	20.97
7i		OCH_2CH_3	(2.26)	(11.22)	(4.92)	1.82	9.40	5.16
7j	C_6H_5 (phenylglycine)	$NHCH_2CH_2CH_3$	(1.97)	(15.56)	(7.90)	1.48	13.26	8.96
7k		$N(CH_2CH_3)_2$	(1.80)	(17.94)	(9.97)	1.13	14.48	12.81
7l		OCH_2CH_3	(3.56)	(10.22)	(2.87)	3.11	10.08	3.24
7m	$CH_2C_6H_5$ (phenylalanine)	$NHCH_2CH_2CH_3$	(1.81)	(29.22)	(16.14)	1.29	27.02	20.95
7n		$N(CH_2CH_3)_2$	1.65	25.39	15.39	1.11	22.97	20.69
7o		OCH_2CH_3	(3.48)	(15.96)	(4.59)	3.15	15.81	5.02
7p	$CH_2(C_6H_5OH)$ (tyrosine)	$NHCH_2CH_2CH_3$	(3.07)	(34.73)	(11.31)	3.73	76.76	20.58
7q		$N(CH_2CH_3)_2$	3.32	36.38	10.96	3.05	65.92	21.61
7r		OCH_2CH_3	(6.49)	(25.85)	(3.98)	9.07	50.08	5.52
7s	$CH(OH)CH_3$ (threonine)	$NHCH_2CH_2CH_3$	(1.72)	(13.39)	(7.79)	1.97	19.75	10.03
7t		$N(CH_2CH_3)_2$	2.71	20.78	7.66	2.47	19.49	7.90
7u		OCH_2CH_3	(2.72)	(12.02)	4.42	2.32	10.47	4.51

[a] See the Experimental section for the chromatographic conditions. The data in parentheses were quoted from Ref. [17]. In every case, the (*S*)-enantiomer was eluted second.
[b] Retention factor of the first eluted enantiomer.
[c] Retention factor of the second eluted enantiomer.
[d] Separation factor.

benzoyl)leucine *N*-phenyl *N*-allyl amide **3** was resolved better ($k_1'=1.69$, $k_2'=25.98$, $\alpha=15.37$) than *N*-(3,5-dimethylbenzoyl)leucine *N*-phenyl *N*-allyl amide **5** ($k_1'=0.79$, $k_2'=8.63$, $\alpha=10.92$) on CSP **2** [17]. Based on the reciprocity of chiral recognition, we expected that CSP **4** prepared from *N*-(3,5-dimethoxybenzoyl)leucine *N*-phenyl *N*-allyl amide **3** might show greater enantioselectivity for the resolution of *N*-(3,5-dinitrobenzoyl)-α-amino acid derivatives than CSP **6** prepared from *N*-(3,5-dimethylbenzoyl)leucine *N*-phenyl *N*-allyl amide **5** does.

Table 1 shows that the two retention factors (k_1' and k_2') on CSP **6** are smaller than those on CSP **4** except for the resolution of the derivatives of tyrosine and threonine and the separation factors (α) are always greater on CSP **6** than on CSP **4**. Representative chromatograms for the resolution of *N*-(3,5-dinitrobenzoyl)leucine *N*,*N*-diethylamide on CSP **4** and CSP **6** are compared in Fig. 2. Fig. 2 clearly demonstrates that the two enantiomers of *N*-(3,5-dinitrobenzoyl)leucine *N*,*N*-diethylamide are eluted faster on CSP **6** than on CSP **4**. However, the separation factor (α) is measured to be greater on CSP **6** than on CSP **4**. From these results, the greater enantioselectivity of CSP **6** is expected to be originated from the relatively more highly reduced retention time of the first eluted enantiomer compared to that of the second eluted enantiomer. However, in the cases for the resolution of tyrosine or threonine derivatives, the second eluted enantiomer is retained even longer on CSP **6** than on CSP **4** and consequently the enantioselectivity was enhanced quite much. Chromatograms for the resolution of *N*-(3,5-dinitrobenzoyl)tyrosine *N*,*N*-diethylamide on CSP **4** and CSP **6** are also illustrated in Fig. 3. As shown in Fig. 3, the second enantiomer is retained quite longer on CSP **6** than on CSP **4**. Tyrosine and threonine derivatives contain an additional hydroxy group. This additional hydroxy group might be responsible for the enhanced retention of the second eluted enantiomer on CSP **6**. However, at the present time, rationalization for these peculiar chromatographic resolution behaviors needs further study.

Resolution of *N*-(3,5-dinitrobenzoyl)-α-amino amides and esters **7** on CSP **4** and CSP **6** was also performed with a mobile phase of 50% THF in hexane. The chromatographic resolution results are summarized in Table 2. As shown in Table 2, resolutions are even greater with a mobile phase of 50% THF in hexane than with a mobile phase of 20% isopropanol in hexane. This time, the retention factors of the second eluted enantiomers are generally greater on CSP **6** than on CSP **4** while the retention factors of the first eluted enantiomers are generally smaller on CSP **6** than on CSP **4**. The represent chromatograms for the resolution of *N*-(3,5-dinitrobenzoyl)leucine *N*,*N*-diethylamide and for the resolution of *N*-(3,5-dinitrobenzoyl)tyrosine *N*,*N*-diethylamide are illustrated in Fig. 4 and Fig. 5. As shown in Fig. 4 and Fig. 5, the second eluted

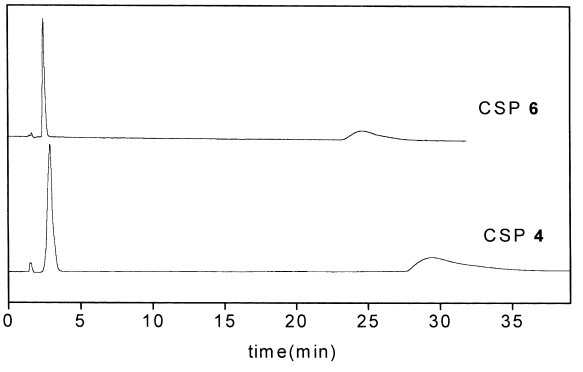


Fig. 2. Comparison of the chromatograms for the resolution of *N*-(3,5-dinitrobenzoyl)leucine *N*,*N*-diethylamide **7h** on CSP **4** and CSP **6** with a mobile phase of 20% isopropanol in hexane. The chromatographic conditions are given in the Experimental section.

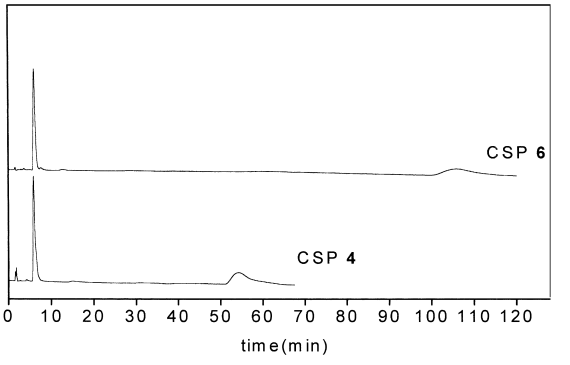
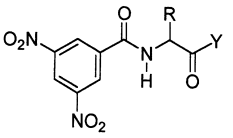


Fig. 3. Comparison of the chromatograms for the resolution of *N*-(3,5-dinitrobenzoyl)tyrosine *N*,*N*-diethylamide **7q** on CSP **4** and CSP **6** with a mobile phase of 20% isopropanol in hexane. The chromatographic conditions are given in the Experimental section.

Table 2
Resolution of *N*-(3,5-dinitrobenzoyl)-α-amino amides and esters **7** on CSP **4** and CSP **6** with a mobile phase of 50% THF in hexane[a]



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Analyte	R	Y	CSP **4**			CSP **6**		
			k_1'[b]	k_2'[c]	α[d]	k_1'[b]	k_2'[c]	α[d]
7a	CH_3 (alanine)	$NHCH_2CH_2CH_3$	0.81	16.74	20.67	0.74	20.00	27.03
7b		$N(CH_2CH_3)_2$	0.52	16.00	30.77	0.30	16.03	53.03
7c		OCH_2CH_3	0.32	1.36	4.25	0.30	1.56	5.20
7d	$CH(CH_3)_2$ (valine)	$NHCH_2CH_2CH_3$	0.44	6.52	14.82	0.44	10.67	24.24
7e		$N(CH_2CH_3)_2$	0.30	4.22	14.01	0.22	6.52	29.64
7f		OCH_2CH_3	0.24	0.81	3.38	0.15	0.97	6.47
7g	$CH_2CH(CH_3)_2$ (leucine)	$NHCH_2CH_2CH_3$	0.44	7.85	17.84	0.37	10.15	27.42
7h		$N(CH_2CH_3)_2$	0.30	8.81	29.37	0.22	9.70	44.09
7i		OCH_2CH_3	0.24	0.88	3.67	0.15	0.97	6.47
7j	C_6H_5 (phenylglycine)	$NHCH_2CH_2CH_3$	0.44	3.63	8.25	0.37	4.44	12.00
7k		$N(CH_2CH_3)_2$	0.22	2.81	12.77	0.15	2.81	18.73
7l		OCH_2CH_3	0.24	0.56	2.33	0.15	0.52	3.47
7m	$CH_2C_6H_5$ (phenylalanine)	$NHCH_2CH_2CH_3$	0.81	16.03	19.79	0.56	15.00	26.79
7n		$N(CH_2CH_3)_2$	0.50	11.86	23.72	0.38	14.12	37.16
7o		OCH_2CH_3	0.33	1.35	4.09	0.32	1.57	4.91
7p	$CH_2(C_6H_5OH)$ (tyrosine)	$NHCH_2CH_2CH_3$	1.19	24.08	20.24	1.19	35.56	29.88
7q		$N(CH_2CH_3)_2$	0.97	23.19	23.91	0.81	35.04	43.21
7r		OCH_2CH_3	0.64	2.73	4.27	0.67	3.56	5.32
7s	$CH(OH)CH_3$ (threonine)	$NHCH_2CH_2CH_3$	1.01	15.35	15.20	0.85	14.15	16.65
7t		$N(CH_2CH_3)_2$	0.66	7.78	11.79	0.60	8.16	13.60
7u		OCH_2CH_3	0.53	2.12	4.00	0.53	2.31	4.36

[a] See the Experimental section for the chromatographic conditions. In every case, the (*S*)-enantiomer was eluted second.
[b] Retention factor of the first eluted enantiomer.
[c] Retention factor of the second eluted enantiomer.
[d] Separation factor.

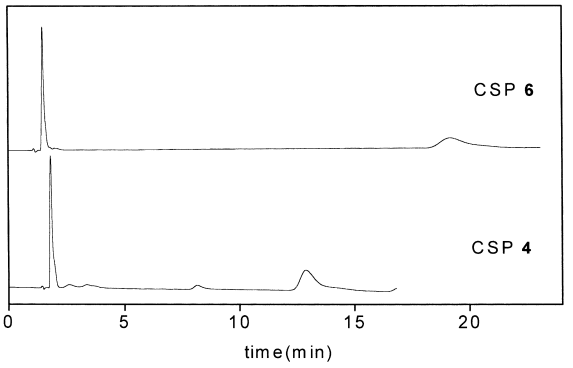

Fig. 4. Comparison of the chromatograms for the resolution of *N*-(3,5-dinitrobenzoyl)leucine *N*,*N*-diethylamide **7h** on CSP **4** and CSP **6** with a mobile phase of 50% THF in hexane. The chromatographic conditions are given in the Experimental section.

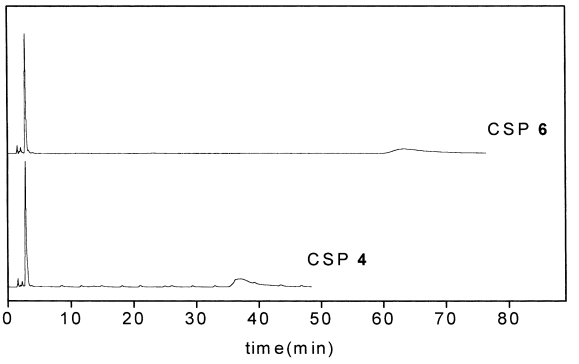

Fig. 5. Comparison of the chromatograms for the resolution of *N*-(3,5-dinitrobenzoyl)tyrosine *N*,*N*-diethylamide **7q** on CSP **4** and CSP **6** with a mobile phase of 50% THF in hexane. The chromatographic conditions are given in the Experimental section.

enantiomers are retained longer on CSP **6** than on CSP **4** while the first eluted enantiomers are eluted faster on CSP **6** than on CSP **4**. Consequently, the enantioselectivity of CSP **6** is much greater than that of CSP **4**.

These results prompted us to reconsider the resolution of *N*-(3,5-dimethoxybenzoyl)leucine *N*-phenyl *N*-allyl amide **3** and *N*-(3,5-dimethylbenzoyl)leucine *N*-phenyl *N*-allyl amide **5** on CSP **2** this time with a mobile phase of 50% THF in hexane. With a mobile phase of 50% THF in hexane, we found that *N*-(3,5-dimethoxybenzoyl)leucine *N*-phenyl *N*-allyl amide **3** is still resolved better ($k_1'=0.53$, $k_2'=12.69$, $\alpha=23.94$) than *N*-(3,5-dimethylbenzoyl)leucine *N*-phenyl *N*-allyl amide **5** ($k_1'=0.43$, $k_2'=9.07$, $\alpha=21.09$) on CSP **2**. In addition, both enantiomers of *N*-(3,5-dimethoxybenzoyl)leucine *N*-phenyl *N*-allyl amide **3** are still retained longer on CSP **2** than those of *N*-(3,5-dimethylbenzoyl)leucine *N*-phenyl *N*-allyl amide **5**. Consequently, CSP **4** was also expected, based on the reciprocity of chiral recognition, to show greater enantioselectivity and longer retention of the two enantiomers than CSP **6** for the resolution of *N*-(3,5-dinitrobenzoyl)-α-amino acid derivatives with a mobile phase of 50% THF in hexane. However, as shown in Table 2, the chromatographic resolution results are also opposite to those expectations.

According to the chiral recognition mechanism proposed for the resolution of *N*-(3,5-dinitrobenzoyl)-α-amino amides on CSP **4** [17], the π–π donor–acceptor interaction between the 3,5-dimethoxyphenyl group of the CSP and the *N*-(3,5-dinitrobenzoyl) group of analytes does play an important role in the chiral recognition. Based on this chiral recognition mechanism, it is expected that CSP **4** should retain the enantiomers longer than CSP **6** because the 3,5-dimethoxyphenyl group of CSP **4** is more π-basic than the 3,5-dimethylphenyl group of CSP **6**. This expectation was fulfilled with a mobile phase of 20% isopropanol in hexane, but not with a mobile phase of 50% THF in hexane. Consequently, chromatographic resolution behaviors for the resolution of *N*-(3,5-dinitrobenzoyl)-α-amino amides and esters **7** on CSP **4** and CSP **6** seem to be dependent on the fact whether the mobile phase is protic or aprotic. However, at the present time, it is not clear why the second eluted enantiomers are retained longer on CSP **6** than on CSP **4** when the mobile phase is aprotic.

The chromatographic resolution data shown in Tables 1 and 2 demonstrate that CSP **6** always shows the greater enantioselectivity than CSP **4** does for the resolution of *N*-(3,5-dinitrobenzoyl)-α-amino amides and esters **7**. These results are different from what we expected from the reciprocity of chiral recognition. Both CSP **4** and CSP **6** were prepared by simply connecting selected chiral moiety to the support through the amide alkyl chain, the functional groups required for the chiral recognition being remained intact. Consequently, it is hard to understand why the chromatographic resolution results on CSPs **4** and **6** are contrary to what we expected from the reciprocity conception of chiral recognition. The only difference between CSP **4** and CSP **6** is the 3,5-dimethoxy and the 3,5-dimethyl group on the benzoyl ring. The two methoxy groups of the benzoyl ring of CSP **4** have been already demonstrated to enhance the π-basicity of the benzoyl ring more significantly that the two methyl groups [15]. However, some steric interruption of the two methyl groups may be smaller than that of the two dimethoxy groups. These steric factors might be responsible for the unexpected chromatographic resolution behaviors of CSP **4** and CSP **6**. In addition, the two oxygen atoms of 3,5-dimethoxy group of the benzoyl ring of CSP **4** are expected to be involved in the nonstereoselective hydrogen bondings with analytes or protic solvent in the mobile phase. These nonstereselective hydrogen bondings might be also responsible for the unexpected chromatographic resolution behaviors. However, at the present time, why CSP **4** and CSP **6** show different chromatographic resolution behaviors from those expected from the reciprocity conception of chiral recognition is not clear.

Reciprocity conception of chiral recognition was originally applied to the reciprocal resolution of racemic acids or racemic amines by optically active amines or optically active acids. However, it has been pointed out that reciprocal systems are not mirror images of one another and consequently the success of one of reciprocal resolutions does not absolutely exclude the failure of the other [18]. In addition, the manner in which the selector is immobilized on solid support can influence the ener-

getics of the separation process and consequently may result in nonreciprocal behavior [6]. Simultaneous interaction of the analyte with more than one strand of bonded phase may also result in nonreciprocal behavior [6]. While this risk does exist, reciprocity of chiral recognition has been successfully utilized in developing effective CSPs. In the case of CSP **4** and CSP **6**, the manner in which the selector is immobilized on silica is exactly equivalent. In addition, the mode of analyte interaction with the strand of bonded phase might be equivalent. Consequently, nonreciprocal behaviors were not expected in the use of CSP **4** and CSP **6**. However, the chromatographic resolution behaviors on CSPs **4** and **6** were opposite to what we expected from the reciprocity of chiral recognition. Consequently, it should be noted that the use of the chromatographic separability of enantiomers on a given CSP as a gauge to judge how well a CSP derived from one of those enantiomers work in a reciprocal fashion does not always successful. In addition, the mobile phase composition should be noted to be important factor influencing the chromatographic resolution behaviors.

In summary, in this study, we compared the resolution of *N*-(3,5-dinitrobenzoyl)-α-amino amides and esters on two reciprocal CSPs **4** and **6**. Based on the reciprocity of chiral recognition, we expected that CSP **4** exerts greater enantioselectivity than CSP **6** does. However, on the contrary, CSP **6** shows greater enantioselectivity than CSP **4** does for the resolution of *N*-(3,5-dinitrobenzoyl)-α-amino amides and esters. From these results, it was concluded that the use of reciprocity of chiral recognition in developing effective CSPs or in predicting chromatographic resolution behaviors should take some degree of care.

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