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Enantioseparation of racemic *N*-acylarylalkylamines on various amino alcohol derived π-acidic chiral stationary phases

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Abstract

Five π-acidic chiral stationary phases (CSPs), **CSP 4**, **CSP 5**, **CSP 6**, **CSP 7** and **CSP 8**, were prepared by connecting the *N*-(3,5-dimethylbenzoyl) derivative of (*R*)-alaninol, (*S*)-leucinol, (1*S*,2*R*)-ephedrine and (*S*)-*tert*-leucinol and the *O*-(3,5-dinitrobenzoyl) derivative of (*R*)-phenylglycinol to silica gel through a carbamate or urea linkage. The CSPs were applied to the resolution of various racemic *N*-acyl-1-naphthylaminoalkanes by chiral HPLC, and the chromatographic resolution results were compared with those of previously reported CSPs (**CSP 2**, **CSP 3**), which are derived from *N*-(3,5-dinitrobenzoyl)-(1*S*,2*R*)-norephedrine and *N*-(3,5-dinitrobenzoyl-(*R*)-phenylglycinol. Based on a comparison of the resolution results for each CSP, the role of each functional group on the five chiral selectors is explained.

Keywords: Enantiomer separation; Chiral stationary phases, LC; Acylarylalkylamines; Amines; Alkylamines

1. Introduction

Over the past three decades, there has been intense interest in liquid chromatographic enantioseparation due to the versatility of chiral stationary phases (CSPs) and its effective application for both small- and large-scale separations [1–4]. Significant efforts have been devoted to the development of effective CSPs, and various CSPs derived from optically active natural and synthetic chiral compounds are now available [5,6]. The success of developing effective CSPs depends on the selection of an effective chiral selector. Pirkle and co-workers first employed the concept of reciprocity of chiral recognition in designing effective chiral selectors [7,8]. The reciprocity of chiral recognition states that if a CSP derived from an optically pure compound A can discriminate each isomer of compound B, then a CSP derived from an optically pure B may discriminate each enantiomer of compound A. Pirkle et al. developed an α-arylalkylamine-derived CSP (**CSP 1**) and resolved racemic (1*S*,2*R*)-norephedrine-*N*-3,5-dinitrobenzamide [9,10]. Hyun and Kim developed **CSP 2** from optically pure (1*S*,2*R*)-norephedrine using the concept of reciprocity of chiral recognition and resolved various racemic *N*-acyl-1-arylalkylamines [11,12]. Hyun et al. also resolved racemic *N*-acyl-1-arylalkylamines on a commercially

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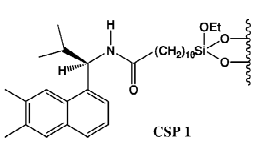
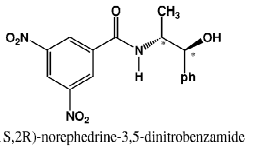
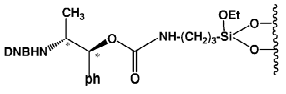
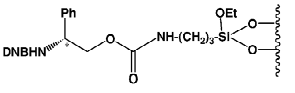
available 3,5-dinitrobenzoyl leucine derived CSP and a 3,5-dinitrobenzoyl phenylglycine derived CSP and proposed the chiral recognition model and elucidated the model with chromatographic resolution data [13].





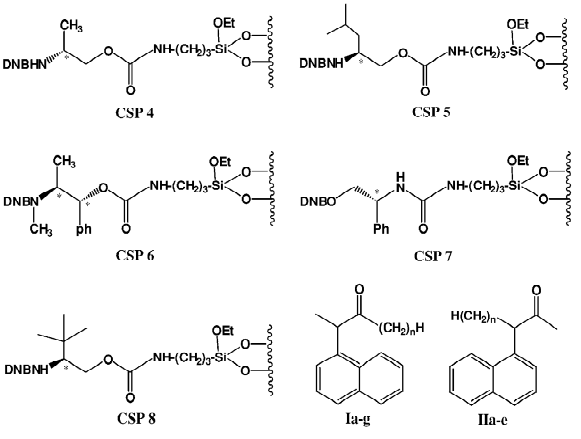




Recently, a 3,5-dinitrobenzoyl phenylglycinol derived CSP (**CSP 3**) was prepared to check the role of the first chiral center containing a phenyl group in **CSP 2** for the enantioseparation of *N*-acyl-1-arylaminoalkanes. It was elucidated that the first chiral center of **CSP 2** does not play an important role in chiral separation [14]. However, it was difficult to clearly explain the role of the first chiral center in **CSP 2** because the substituents that connect to the second chiral center of **CSP 2** and **CSP 3** are not the same.

In this study, we prepared **CSP 4**, which substitutes a phenyl group for a methyl group in **CSP 3**, and applied the CSP to the resolution of racemic *N*-acyl-1-arylalkylamines by chiral HPLC. We also prepared **CSP 5**[1], **CSP 6**, **CSP 7** and **CSP 8** and applied them to compare the chiral separation results with those of **CSP 2**, **CSP 3** and **CSP 4**. **CSP 5** has a similar structure to **CSP 4**, but a bulkier isobutyl group is connected to the chiral carbon instead of the methyl group on **CSP 4**. Thus, **CSP 5** should exhibit a similar resolution pattern and more improved resolution than **CSP 4,** but a slightly different resolution pattern from **CSP 3**, in which a phenyl group is bonded to its chiral carbon. **CSP 6** was prepared from optically pure ephedrine. The hydrogen of the π-acidic 3,5-dinitrobenzamide in **CSP 2** was changed to a methyl group to check the role of the amide proton in chiral discrimination. **CSP 7** was prepared from (*R*)-phenylglycinol 3,5-dinitrobenzoyl ester, which has a similar intermediate to **CSP 3** (phenylglycinol 3,5-dinitrobenzoyl amide). The π-acidic 3,5-dinitrobenzoyl (3,5-DNB) group of **CSP 7** is distant from the chiral carbon, but that of **CSP 3** is directly connected to the chiral carbon. Thus, we can check the importance of the π-acidic 3,5-dinitrobenzoyl (3,5-DNB) group in this chiral discrimination through a comparison of the enantioseparation results for **CSP 3** and **CSP 7**. Finally, **CSP 8** was prepared from (*S*)-*tert*-leucinol to compare the chiral discrimination ability with **CSP 5** for the resolution of racemic *N*-acyl-1-arylalkylamines.

CSP 4, **CSP 5**, **CSP 6**, **CSP 7** and **CSP 8**, together with the previously reported **CSP 2** and **CSP 3**, were synthesized by a synthetic procedure similar to that previously described [14]. The enantioseparation results for racemic *N*-acyl-1-naphthylalkylamines (**Ia**–**g**, **IIa**–**e**) on these CSPs were then compared.



2. Experimental

2.1. General methods

^{1}H NMR spectra were recorded on a Varian Unity Inova 300WB spectrometer (300 Mz). IR spectra were measured with a Mattson Galaxy 7020 Polaris FT-IR spectrometer. Melting points were estimated on a capillary melting point apparatus. Elemental analysis data were obtained with a Carlo Erba EA 1108 elemental analyzer.

[1]A report of the application of **CSP 5** to the resolution of racemic *N*-acyl-1-arylalkylamines compared with a π-acidic sulfonamide-containing CSP has been submitted for publication.

All reagent used in this study were from Aldrich. Test racemic materials were prepared according to the procedure described previously [15]. Solvents for HPLC analysis were of Merck HPLC grade. All reactions were performed under a nitrogen atmosphere.

2.2. Preparation of **CSPs 2–6** and **CSP 8**

2.2.1. N-3,5-Dinitrobenzoyl amino alcohol (**2a–6a, 8a**)

N-3,5-Dinitrobenzoyl amino alcohols (**2a**–**6a**, **8a**) were prepared from optically pure amino alcohols with 3,5-dinitrobenzoylchloride using a published procedure [12,14]. To a stirred solution of 3,5-dinitrobenzoylchloride (10 mmol) and triethylamine (11 mmol) in 40 mL of methylene chloride was slowly added a solution of each optically pure amino alcohol (10 mmol) in 10 ml of methylene chloride at 0 °C. The reaction mixture was stirred at room temperature under nitrogen for 2 h and then washed successively with 1 *M* HCl, saturated $NaHCO_3$, and water. After drying over anhydrous $MgSO_4$, the solvent was removed. Flash column chromatography on silica gel (mixed eluent of hexane and ethyl acetate) afforded a yellowish white solid product.

2a, **3a**: the same spectroscopic results as for previously prepared compounds [12,14].

4a: m.p.: 178–180 °C, yield 74.0%. ^{1}H NMR (C^2HCl_3) δ: 1.13–1.14 (d, 3H), 4.48–4.52 (m, 1H), 4.76–4.77 (d, 1H), 5.01 (s, 1H), 7.25–7.48 (m, 5H), 8.41–8.43 (d, 1H), 9.13–9.15 (t, 1H), 9.26–9.27 (d, 2H); IR (KBr) cm^{-1}: 3533, 3371, 3096, 2972, 1666, 1631, 1650, 717.

5a: m.p.: 132–134 °C, yield 61.1%, ^{1}H NMR (C^2HCl_3) δ: 0.98–1.01 (d, 6H), 1.49–1.73 (m, 3H), 3.71–3.76 (m, 1H), 3.84–3.89 (m, 1H), 4.36–4.39 (m, 1H), 6.69–6.71 (d, 1H), 8.97–8.99 (d, 2H), 9.16–9.17 (t, 1H); IR (KBr) cm^{-1}: 3395, 3271, 3090, 2960, 1647, 1541, 1467.

6a: m.p.: 62–64 °C, yield 85.2%, ^{1}H NMR [C^2HCl_3, dimethyl sulfoxide (DMSO)] δ: 1.26–1.27 (d, 3H), 2.77–3.08 (d, 3H), 4.96–4.98 (d, 1H), 7.07–7.09 (d, 1H), 7.42–7.46 (m, 5H), 7.85 (s, 1H), 8.18–8.19 (d, 1H), 8.98–9.02 (d, 1H); IR (KBr) cm^{-1}: 3408, 2984, 1628, 1545, 1344.

8a: yield 82.1%, ^{1}H NMR (C^2HCl_3, DMSO) δ: 1.04 (s, 9H), 2.36 (s, 6H), 3.66–3.70 (q, 1H), 3.94–4.07 (m, 2H), 7.15 (s, 1H), 7.37 (s, 2H); IR (KBr) cm^{-1}: 3353, 2970, 1637, 1599, 1540.

2.2.2. (R)-N-(3,5-Dinitrobenzoyl)amino alcohol (triethoxysilyl)propylcarbamate (**2b–6b, 8b**)

A solution of 3-(triethoxysilyl)propylisocyanate (3.0 mmol), amino alcohol-*N*-3,5-dinitrobenzamide (**2a**–**6a**, **8a**) (2.9 mmol), and triethylamine (3.0 mmol) in 40 mL of benzene was stirred under reflux for 72 h. After cooling, the mixture was evaporated under reduced pressure. Flash column chromatography on silica gel (mixed eluent of methylene chloride, ethyl acetate, and hexane) afforded a white solid.

2b, **3b**: the same spectroscopic results as for previously prepared compounds [12,14].

4b: m.p.: 89–91 °C, yield 64.7%. ^{1}H NMR (C^2HCl_3) δ: 0.60–0.65 (t, 2H), 1.18–1.33 (m, 12H), 1.57–1.69 (m, 2H), 3.22–3.30 (q, 6H), 4.15–4.19 (m, 1H), 4.29–4.34 (m, 2H), 5.30 (t, 1H), 7.97 (d, 1H); IR (KBr) cm^{-1}: 3340, 3094, 2976, 1693, 1643, 1543.

5b: m.p.: 128.5–131.5 °C, yield 45.7%. ^{1}H NMR (C^2HCl_3) δ: 0.58–0.63 (t, 2H), 0.99–1.01 (d, 6H), 1.18–1.27 (m, 9H), 1.55–1.66 (m, 4H), 3.18–3.23 (m, 2H), 3.76–3.83 (q, 6H), 5.22 (t, 1H), 7.44–7.47 (d, 1H), 9.01 (d, 2H), 9.15–9.16 (t, 1H); IR (KBr) cm^{-1}: 3333, 3283, 3105, 2974, 1691, 1649, 1545.

6b: yield 24.7%. ^{1}H NMR (C^2HCl_3) δ: 0.38–0.59 (m, 2H), 0.98–1.23 (m, 12H), 1.43–1.54 (m, 4H), 2.75, 3.09 (s, 3H), 3.46–3.53 (q, 6H), 5.12–5.14 (d, 1H), 7.03–7.06 (d, 1H), 7.38–7.45 (m, 5H), 7.77–7.78 (d, 1H), 8.06–8.07 (d, 1H), 8.98–8.99 (t, 1H); IR (KBr) cm^{-1}: 3342, 2976, 1714, 1641, 1545, 1344, 1080.

8b: yield 40.2%. ^{1}H NMR (C^2HCl_3) δ: 0.55 (t, 2H), 1.01 (s, 9H), 1.17–1.21 (t, 9H), 2.36 (s, 6H), 3.0–3.15 (m, 2H), 3.74–3.80 (m, 6H), 4.12 (t, 1H), 4.30 (d, 2H), 7.09 (t, 1H), 7.37 (d, 2H); IR (KBr) cm^{-1}: 3440, 2923, 1730, 1631, 1456, 1382, 1105.

2.2.3. CSPs

To a 100 mL round bottom flask were added 3.70 g of 5 μm silica gel and 50 mL toluene. Water was removed from the resulting slurry azeotropically using a Dean-Stark trap. After the complete removal of water, the silyl compound (**2b**–**6b**, **8b**) (2.0

mmol) in 20 mL of toluene was added to the slurry and the whole mixture was heated to reflux for 80 h under magnetic stirring. The modified silica gel was washed with benzene, methanol, acetone, ethyl acetate, methylene chloride, and hexane and dried. **CSP 2**, anal. found C, 4.70; N, 0.96; calculated 0.18 mmol/g (based on C), 0.17 mmol/g (based on N). **CSP 3**, anal. found C, 3.79; N, 0.78; calculated 0.15 mmol/g (based on C), 0.14 mmol/g (based on N). **CSP 4**, microanal. found C, 6.10; N, 1.74%; calculated 0.32 mmol/g (based on C), 0.31 mmol/g (based on N). **CSP 5**, microanal. found C, 6.91; N, 1.74%; calculated 0.30 mmol/g (based on C), 0.27 mmol/g (based on N). **CSP 6**, microanal. found C, 2.77; N, 0.56%; calculated 0.09 mmol/g (based on C), 0.10 mmol/g (based on N). **CSP 8**, microanal. found C, 9.20; N, 2.30%; calculated 0.43 mmol/g (based on C), 0.41 mmol/g (based on N). The modified silica gel was packed into a 250×4.6 mm I.D stainless steel column using conventional methods.

2.3. Preparation of *CSP 7*

2.3.1. (R)-Phenylglycinol-N-(triethoxysilyl)propylcarbamate (*7a*)

A solution of 3-(triethoxysilyl)propylisocyanate (3.0 mmol), (*R*)-phenylglycinol (2.9 mmol), and triethylamine (3.0 mmol) in 40 mL of benzene was stirred under reflux for 72 h. After cooling, the mixture was evaporated under reduced pressure. Flash column chromatography on silica gel (mixed eluent of methylene chloride, ethyl acetate, and hexane) afforded a yellowish white solid. Yield 26%. ^{1}H NMR (C^2HCl_3) δ: 8.81–8.85 (d, 1H), 7.51–7.59 (m, 5H), 4.10–4.94 (t, 2H), 1.17–1.27 (m, 9H), 0.86–0.88 (d, 1H); IR (KBr) cm^{-1}: 3929, 2976, 1691, 1629, 1550, 1390, 1080, 777.

2.3.2. O-3,5-Dinitrobenzoyl-(R)-phenylglycinol-N-(triethoxysilyl)propylcarbamate (*7b*)

To a stirred solution of 3,5-dinitrobenzoylchloride (10 mmol) and triethylamine(11 mmol) in 40 mL of methylene chloride was slowly added a solution of **7a** (10 mmol) in 10 mL of methylene chloride at 0 °C. The reaction mixture was stirred at room temperature under nitrogen for 2 h and then washed successively with 1 *M* HCl, saturated $NaHCO_3$, and water. After drying over anhydrous $MgSO_4$, the solvent was removed. Flash column chromatography on silica gel (mixed eluent of hexane and ethyl acetate) afforded a yellow solid product. Yield 28%. ^{1}H NMR (C^2HCl_3) δ: 9.23–9.24 (t, 1H), 9.17 (d, 2H), 7.34–7.52 (m, 5H), 4.49–4.55 (q, 2H), 3.79–3.82 (m, 6H), 3.69–3.75 (q, 2H), 1.31–1.49 (m, 9H), 1.22–1.26 (q, 4H), 0.85–0.88 (t, 2H); IR (KBr) cm^{-1}: 3092, 2926, 1730, 1628, 1545, 1464, 1278, 1080.

2.3.3. CSP 7

To a 100 mL round bottom flask were added 3.70 g of 5 μm silica gel and 50 mL toluene. Water was removed from the resulting slurry azeotropically using a Dean-Stark trap. After the complete removal of water, the silyl compound **7b** (2.0 mmol) in 20 mL of toluene was added to the slurry and the whole mixture was heated to reflux for 80 h under magnetic stirring. The modified silica gel was washed with benzene, methanol, acetone, ethyl acetate, methylene chloride, and hexane and dried. Microanal. found C, 1.98; N, 0.25%; calculated 0.076 mmol/g (based on C), 0.045 mmol/g (based on N). The modified silica gel was packed into a 250×4.6 mm I.D. stainless steel column using conventional methods.

2.4. Chromatography

An HPLC system consisting of a Beckmann (San Ramon, CA, USA) Model 110B pump, a Rheodyne (Cotati, CA, USA) Model 7125 injector with a 20 μL sample loop, a Young In (Seoul, South Korea) Model 710 absorbance detector with a 254 nm UV filter and a Young In D520B integrator was used for HPLC analysis. All chromatographic data were obtained using 2-propanol–hexane (20:80) as mobile phase at a flow-rate of 1.5 mL/min. The column void volume was checked by injecting 1,3,5-tri-*tert*-butylbenzene [16], a presumed unretained solute obtained from Aldrich.

3. Result and discussion

Our preparation of **CSPs 2–8** is summarized in Fig. 1. The synthetic procedure involved only three

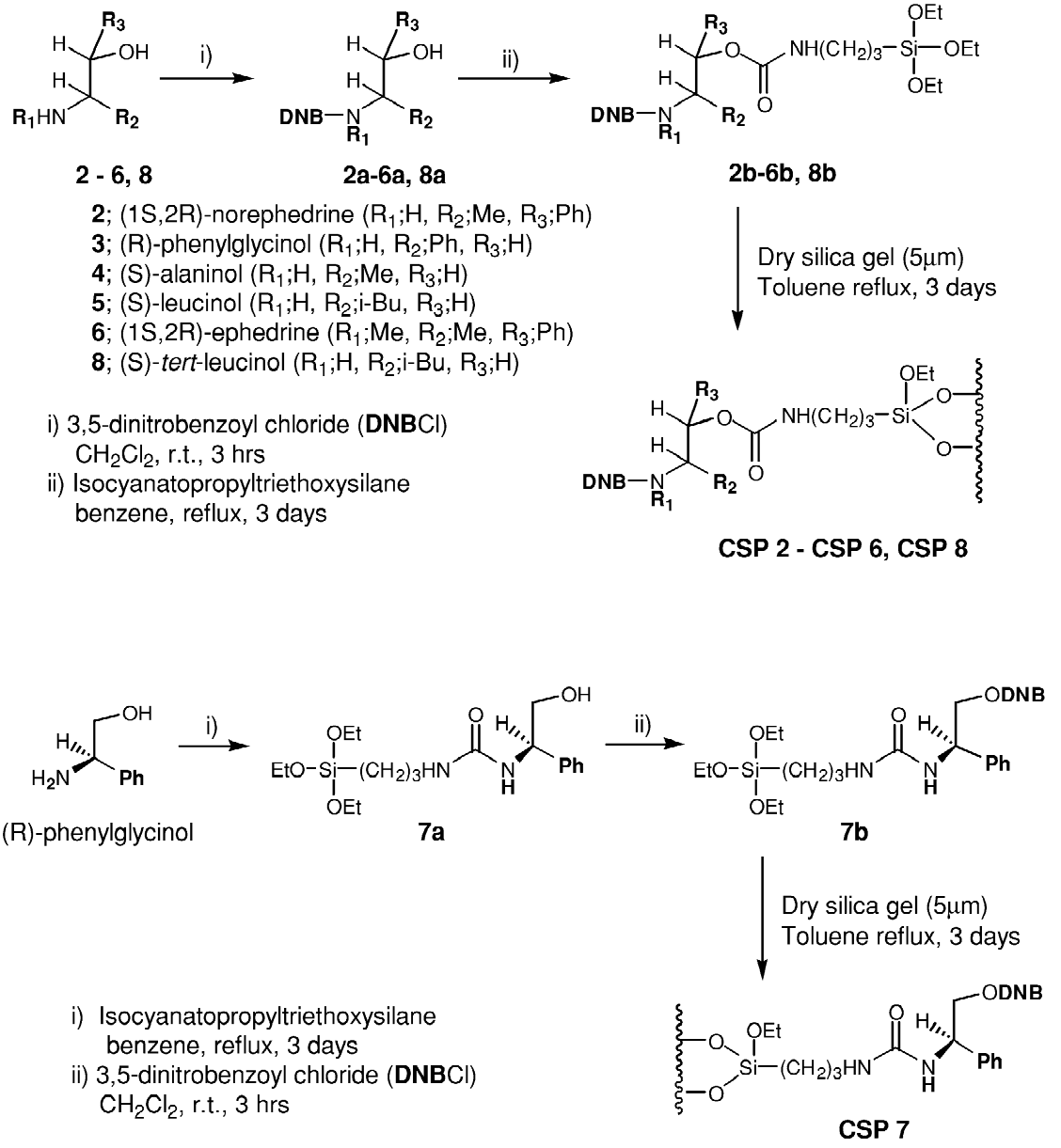


Fig. 1. Preparation of **CSPs 2–8**.

steps: amidation, silylation and bonding to silica gel. The synthetic procedure order was changed for **CSP 7**, i.e. silylation was performed first.

Each step was quite simple, but only low yields were obtained at each step of the synthesis for **CSP 6** and **CSP 7**.

An example of the resolution of *N*-acetyl-1-naphthylaminohexadecane (**IIe**) on **CSPs 2–8** with 20% 2-propanol in hexane as mobile phase is shown in Fig. 2. The two enantiomers of *N*-acetyl-1-naphthylaminohexadecane were clearly separated on **CSPs 2–5** and **CSP 8**, but not on **CSP 6** and **CSP 7**.

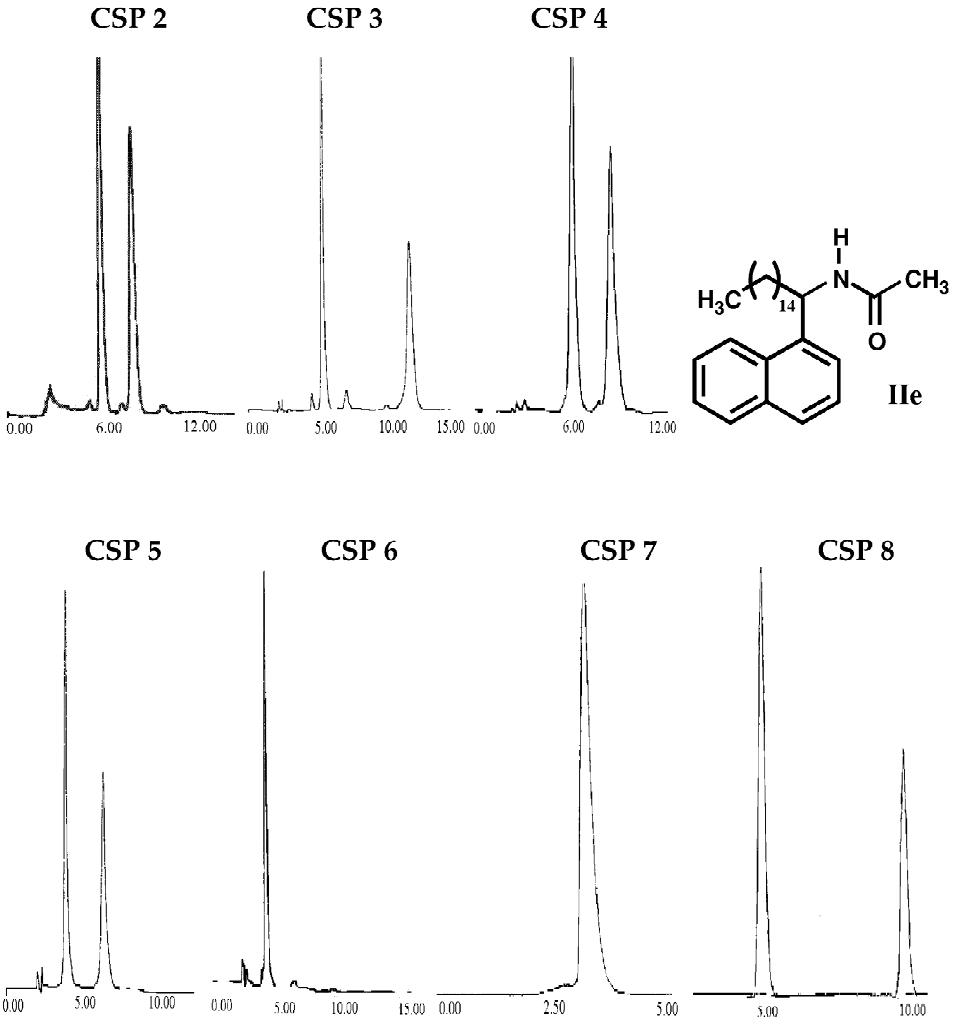


Fig. 2. Chromatographic separation of racemic *N*-acetyl-1-naphthylaminohexadecane (**IIe**) on **CSPs 2–8** (see footnote ''a'' to Table 1 for chromatographic conditions).

Chromatographic resolution data for racemic *N*-acyl-1-naphthylaminoethanes (**Ia–g**) on **CSPs 2–8** are summarized in Table 1.

As shown in Table 1, all retention factors (k_1) of the first-eluted isomer of **Ia–g** on all CSPs decrease continuously as the *N*-acyl chain of **Ia–g** increases in length. Moreover, racemic **Ia–g** were not separated on **CSP 6**. Because of the steric hindrance between the analytes and chiral selector on the CSPs, all retention factors of **Ia–g** on all CSPs decrease continuously as the *N*-acyl chain of **Ia–g** increases in length. **CSP 6** was prepared from optically pure ephedrine. The hydrogen of the π-acidic 3,5-dinitrobenzamide of **CSP 2** was changed to a methyl group to check the role of the amide proton in this chiral discrimination. From the chiral separation results for racemic **Ia–g** on **CSP 2** and **CSP 6**, it is clear that the role of the amide (3,5-dinitrobenzamide) hydrogen of **CSP 2** is very important for chiral discrimination. It is generally accepted that the amide hydrogen interacts with chiral analytes through hydrogen bonding [7].

There are some consistencies in the elution order of **Ia–g** on the CSPs. The absolute configuration of

Table 1
Resolution of *N*-acyl-1-naphthylaminoethanes on **CSPs 2–8**

Analyte	*n*	1*S*,2*R*-**CSP 2**		(*R*)-**CSP 3**		(*R*)-**CSP 4**		(*S*)-**CSP 5**		1*S*,2*R*-**CSP 6**		(*R*)-**CSP 7**		(*S*)-**CSP 8**	
		α[a]	k_1[b]	α	k_1	α	k_1	α	k_1	α	k_1	α	k_1	α	k_1
Ia	1	1.05	5.05[d]	1.63	5.72[c]	1.00	7.10	1.10	5.17[d]	1.00	2.29	1.00	4.57	1.00	23.74
Ib	2	1.08	3.57[d]	1.44	5.40[c]	1.00	5.71	1.10	3.29[c]	1.00	1.49	1.14	2.79	1.36[c]	15.7[c]
Ic	4	1.06	2.38[d]	1.29	3.41[c]	1.11	3.24[d]	1.26	2.18[c]	1.00	0.92	1.00	1.70	1.60	9.13[c]
Id	7	1.00	1.89	1.13	2.78	1.18	2.49	1.44	1.60	1.00	0.74	1.00	1.32	1.92	8.47
Ie	9	1.00	1.70	1.06	2.51	1.22	2.22	1.51	1.39	1.00	0.66	1.00	1.10	2.24	6.01
If	11	1.00	1.56	1.00	2.41	1.24	1.96	1.56	1.27	1.00	0.61	1.00	1.01	2.24	5.61
Ig	13	1.00	1.44	1.00	2.27	1.26	1.84	1.62	1.21	1.00	0.58	1.00	0.36	2.25	3.66

[a] Mobile phase 20% 2-propanol in hexane; flow-rate 1.5 mL/min; detection UV 254 nm. Separation factor: $\alpha = k_2/k_1$; dead time (t_0) was checked by 1,3,5-tri-*tert*-butylbenzene (TTBB).
[b] Retention factor: $k = (t_R - t_0)/t_0$.
[c] Absolute configuration of the first eluted enantiomer was ''*R*''.
[d] Absolute configuration of the first eluted enantiomer was ''*S*''.

the first eluted isomer of the two enantiomers of **Ia**–**d** on (1*S*,2*R*)-**CSP 2** is ''*S*'', that on (*R*)-**CSP 3** is ''*R*'' and that on (*R*)-**CSP 4** is ''*S*''. The absolute configuration of the first eluted isomer of **Ia** on (*S*)-**CSP 5** is ''*S*'', but that of **Ib**–**d** on (*S*)-**CSP 5** and (*S*)-**CSP 8** is ''*R*''. As a result, **CSP 2**, **CSP 4**, **CSP 5** and **CSP 8** show the same elution patterns, but different elution patterns are found for **CSP 3**. Based on the classical chiral recognition model proposed by Pirkle et al. [15]. **CSP 3**, **CSP 4**, **CSP 5** and **CSP 8** are expected to show the same elution patterns. However, Hyun et al. recently found opposite results for the resolution of the same analytes, **Ia**–**g**, on two commercially available π-acidic 3,5-dinitrobenzoyl (3,5-DNB) phenylglycine- and 3,5-DNB leucine-derived chiral columns. They explained the reason for this using the face-to-edge π–π interaction model [13]. According to this new interaction model, there are three point interactions between the chiral selector of the CSPs and the analytes. A face-to-face π–π interaction between the π-acidic 3,5-dinitrobenzoyl group on the CSPs and the π-basic naphthyl group on the analytes occurs first. In addition, hydrogen bonding between the carbonyl oxygen of the analyte and the amide hydrogen of the CSPs occurs as an attractive interaction. Additionally, steric hindrance between the acyl or alkyl group of the analytes and the connecting tether of the CSP occurs. However, because of the additional face-to-edge π–π interaction between the phenyl group of the CSP and the naphthyl group of the analytes that occurs for **CSP 3**, the elution patterns for **CSP 3** are different from the others. Thus, the (*R*)-isomers of **Ia**–**g** on (*R*)-**CSP 3** and the (*R*)-isomers of **Ib**–**g** on (*S*)-**CSP 5** elute first, while the (*S*)-isomer of **Ic**–**g** elutes first on (*R*)-**CSP 4**. However, at this time, we do not understand the reason for the inverse elution order of **Ia** on (*S*)-**CSP 5**.

It was also found that the separation factors (α) for the resolution of **Ia**–**g** on **CSP 4** and **CSP 5** increase continuously as the *N*-acyl chain of **Ia**–**g** increases in length, but the separations on **CSP 3** become worse as the *N*-acyl chain of **Ia**–**g** increases in length. These results show the same resolution patterns as Hyun et al. [13], who used the same analytes and a similar chiral selector as in this study. According to the interaction model proposed by Hyun et al., the *N*-acyl alkyl chain of the (*S*)-analytes is oriented along the direction of the connecting tether of **CSP 3** and eventually intercalates between the adjacent strands of the CSP. The stability of the interaction between the second-eluted (*S*)-analytes and **CSP 3** decreases as the *N*-acyl chain increases in length. The chiral discrimination between the first-eluted (*R*)-isomer and the second-eluted (*S*)-isomer then decreases continuously. Furthermore, the separation factor decreases continuously as the *N*-acyl alkyl chain of the analyte increases in length. In the case of **CSP 5**, however, as the *N*-acyl alkyl chain of the analyte increases in length, intercalation of the *N*-acyl alkyl chain of the (*R*)-enantiomer between adjacent strands of the bonded phase becomes more difficult and the retention of the (*R*)-analytes de-

creases more rapidly than that of the (*S*)-analytes. Thus, the stability of the interaction between the first-eluted (*R*)-analytes and **CSP 5** decreases as the *N*-acyl chain increases in length and the separation improves continuously.

CSP 7 was prepared from (*R*)-phenylglycinol 3,5-dinitrobenzoyl ester, which has a similar intermediate to **CSP 3** (phenylglycinol 3,5-dinitrobenzoyl amide), to check the importance of the π-acidic 3,5-dinitrobenzoyl (3,5-DNB) group for this chiral discrimination. The π-acidic group of **CSP 7** is distant from the chiral carbon, but that of **CSP 3** is directly connected to the chiral carbon. Based on a comparison on the enantioseparation results for racemic **Ia**–**g** on **CSP 3** and **CSP 7**, those on **CSP 7** are poor, as shown in Table 1. As a result, it is concluded that chiral discrimination is strongly affected by the binding position of the π-acidic group in these types of CSPs.

Because (*R*)-**CSP 4**, (*S*)-**CSP 5** and (*S*)-**CSP 8** have different alkyl groups (methyl, iso-butyl and *tert*-butyl) and no phenyl groups on their chiral carbons, the same elution patterns, but different selectivities, were expected. From a comparison of the chiral separation results for **Ia**–**g** on **CSP 4**, **CSP 5** and **CSP 8** (Table 1), it was found that the best results were for **CSP 8**. Thus, optically pure *tert*-leucine or *tert*-leucinol can be used as an excellent starting material for the synthesis of a chiral selector or chiral catalyst rather than the generally used leucine or leucinol.

In the case of (1*S*,2*R*)-**CSP 2**, as explained previously [14], the second (*R*)-chiral center, which is connected directly to the 3,5-dinitrobenzamide nitrogen, plays a more important role in this chiral recognition than the first chiral center. This is clearly seen by a comparison of the resolution data for **Ia**–**g** on two CSPs, **CSP 2** and **CSP 4**, which show similar elution patterns.

The chromatographic selectivity factors shown in Table 1 are illustrated graphically in Fig. 3. The changes in the enantioselectivities of racemic *N*-acyl-1-naphthylaminoethanes (**Ia**–**g**) on **CSPs 2**–**8** can clearly be seen.

Chromatographic resolution data for racemic *N*-acetyl-1-naphthylaminoalkanes (**IIa**–**e**) on **CSPs 2**–**8** are summarized in Table 2, and the selectivity factors (α) shown in Table 2 are illustrated graphically in Fig. 4.

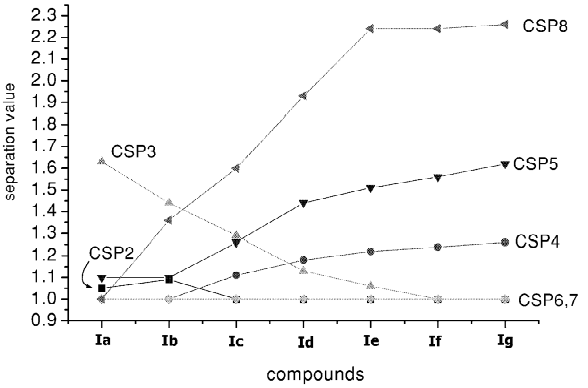


Fig. 3. Enantioselectivity trends of *N*-acyl-1-naphthylaminoethanes (**Ia**–**g**) on **CSPs 2**–**8**.

As shown in Table 2, all retention factors (k_1) of the first-eluted isomer of **IIa**–**e** on all CSPs decrease continuously as the alkyl chain of **IIa**–**e** increases in length. In addition, racemic **IIa**–**e** were not separated on **CSP 6**. Because of steric hindrance between the analytes and chiral selector of the CSPs, all retention factors of **IIa**–**e** on all CSPs decrease continuously as the alkyl chain of **IIa**–**e** increases in length. **CSP 6** was prepared from optically pure ephedrine. From the chiral separation results for racemic **IIa**–**e** on **CSP 2** and **CSP 6**, we confirmed the role of the amide (3,5-dinitrobenzamide) hydrogen of **CSP 2** as being very important for chiral discrimination.

There is consistency in the elution order. The absolute configuration of the first-eluted isomer of the two enantiomers of **IIa**–**e** on all CSPs is the same as the absolute configuration of the chiral stationary phase. That is, the ''*S*'' isomer is eluted first on (*S*)-CSPs while the ''*R*'' isomer is eluted first on (*R*)-CSPs. In the case of (1*S*,2*R*)-**CSP 2**, the absolute configuration of the first-eluted isomer of **IIa**–**e** is ''*R*''. As explained previously, the second chiral center is important for this chiral discrimination. This result is also very similar to the previous results of Hyun et al. [13], who used the same analytes, **IIa**–**e**, but different chiral selectors, π-acidic 3,5-dinitrobenzoyl (3,5-DNB) phenylglycine- and 3,5-DNB leucine-derived chiral selectors.

As shown in Table 2 and Fig. 4, the separation factors (α) for the resolution of **IIa**–**e** on **CSPs 2**–**5** and **CSP 8** increase continuously as the alkyl chain of **IIa**–**e** increases in length. According to the interaction model between the same analytes and the

Table 2
Resolution of *N*-acetyl-1-naphthylaminoalkanes on **CSPs 2–8**

Analyte	*n*	1*S*,2*R*-**CSP 2**		(*R*)-**CSP 3**		(*R*)-**CSP 4**		(*S*)-**CSP 5**		1*S*,2*R*-**CSP 6**		(*R*)-**CSP 7**		(*S*)-**CSP 8**	
		α	k_1	α	k_1	α	k_1	α	k_1	α	k_1	α	k_1	α	k_1
IIa	3	1.46	2.59	1.90	3.93	1.37	3.61	1.58	2.90	1.00	1.47	1.13	3.32	1.54	9.88
IIb	5	1.52	2.01	2.26	2.96	1.53	2.72	1.94	2.08	1.00	1.15	1.00	2.57	2.01	7.10
IIc	9	1.53	1.58	2.63	2.16	1.68	2.00	2.25	1.51	1.00	0.93	1.00	2.06	2.33	4.75
IId	13	1.54	1.37	2.80	1.83	1.71	1.67	2.36	1.29	1.00	0.79	1.00	1.79	2.54	3.75
IIe	15	1.56	1.26[a]	2.85	1.70[a]	1.72	1.53[a]	2.37	0.89[b]	1.00	0.79	1.00	1.59	2.62	3.34[b]

[a] Absolute configuration of the first-eluted enantiomer was ''*R*''.
[b] Absolute configuration of the first-eluted enantiomer was ''*S*''.

corresponding amino acid (phenylglycine and leucine)-derived CSPs proposed by Hyun et al., intercalation of the *N*-acyl alkyl chain of the analytes on these CSPs does not influence the enantioseparation any further. In addition, the alkyl group at the chiral center of the analytes is thought to influence the enantioselectivity. The alkyl group of the less-retained (*R*)-analyte is directed alongside the connecting tether of **CSP 3** and presumably intercalates between the adjacent strands of the CSP. In this instance, the stability of the interaction between the less-retained (*R*)-analytes and **CSP 3** decreases as the *N*-acyl chain increases in length and the chiral discrimination between the first-eluted (*R*)-isomer and the second-eluted (*S*)-isomers increases continuously. On the other hand, in the case of **CSP 5**, the alkyl group at the chiral center of the (*S*)-enantiomer of analytes **IIa**–**e** is oriented along the direction of the connecting tether of **CSP 5** and presumably intercalates between the connecting tether. In this event, lengthening the alkyl chain of the analyte diminishes the retention of the (*S*)-enantiomer on **CSP 5** more significantly than that of the (*R*)-enantiomer. Consequently, it increases the separation factor continuously, with the (*R*)-isomer being retained longer. The resolution pattern of racemic **IIa**–**e** on **CSP 4** and **CSP 8** is the same as that on **CSP 5**.

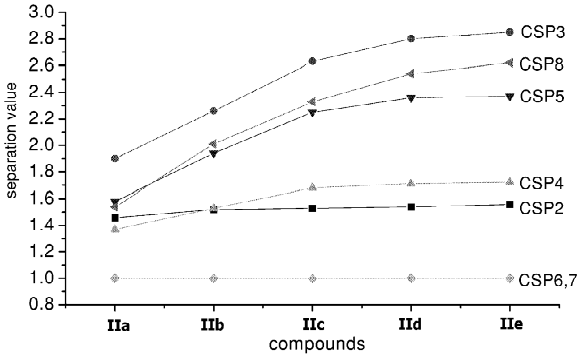


Fig. 4. Enantioselectivity trends for *N*-acetyl-1-naphthylaminoalkanes (**IIa**–**e**) on **CSPs 2–8**.

In a comparison of the enantioseparation results for racemic **IIa**–**e** on **CSP 3** and **CSP 7**, the chiral separation on **CSP 7** is so poor (as shown in Tables 1 and 2) that the π-acidic group of these CSPs must play an important role in chiral discrimination. However, it is interesting that racemic mixtures of **Ib** and **IIa** are resolved on **CSP 7**. The chiral separation results for **IIa**–**e** on **CSP 4**, **CSP 5** and **CSP 8** are shown in Table 2. The resolution patterns are similar to those for **Ia**–**g**, as previously explained.

4. Conclusion

Because of the steric hindrance between the analytes and chiral selector of the CSPs, all retention factors for **Ia**–**g** and **IIa**–**e** on all CSPs decrease continuously as the *N*-acyl or alkyl chain of **Ia**–**g** or **IIa**–**e** increases in length. From the chiral separation results for racemic **Ia**–**g** and **IIa**–**e** on **CSP 2** (prepared from norephedrine) and **CSP 6** (prepared from ephedrine), it is clear that the role of the amide (3,5-dinitrobenzamide) hydrogen of **CSP 2** is very important for this chiral discrimination. There are consistencies in the elution order for racemic **Ia**–**g** and **IIa**–**e** on all CSPs except for **CSP 3**. The ''*R*'' isomers of **Ia**–**g** and the ''*S*'' isomers of **IIa**–**e** are eluted first on (*S*)-CSPs, while the ''*R*'' isomers of **Ia**–**g** and **IIa**–**e** are eluted first on **CSP 3**. The reason for this can be explained by the additional face-to-edge π–π interaction between the phenyl group of **CSP 3** and the naphthyl group of the analytes. In a

comparison of the enantioseparation results for racemic **Ia**–**g** and **IIa**–**e** on **CSP 3** and **CSP 7**, chiral separation on **CSP 7** is so poor that the π-acidic group of these kinds of CSPs must play an important role in the chiral discrimination. From a comparison of the chiral separation results for **Ia**–**g** and **IIa**–**e** on **CSP 4** (prepared from alaninol), **CSP 5** (prepared from leucinol) and **CSP 8** (prepared from *tert*-leucinol), it was found that the best results were for **CSP 8**. Thus, optically pure *tert*-leucine or *tert*-leucinol can be used as an excellent starting material for the synthesis of a chiral selector or chiral catalyst rather than the generally used leucine or leucinol.

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