Preparation and Application of a New HPLC Chiral Stationary Phase Derived from 2-Amino-1-indanol

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Received December 13, 2000

A new chiral stationary phase (CSP) based on (1*R*,2*S*)-2-amino-1-indanol, which is expected to be conformationally rigid because of its cyclic nature, was prepared. The new CSP was applied in resolving various *N*-acyl-α-arylalkylamines. The chromatographic resolution results on the new CSP were compared with those on the other CSP based on (1*S*,2*R*)-norephedrine, which is believed to be conformationally flexible. Comparison of the chromatographic resolution results on the two CSPs demonstrated that conformationally flexible analytes are resolved better on the conformationally rigid CSP while conformationally rigid analytes are resolved better on the conformationally flexible CSP. From these results it was concluded that conformational rigidity or flexibility of CSPs is the important factor for the chiral recognition.

Keywords : Chiral stationary phase, Enantiomer separation, Liquid chromatography, 2-Amino-1-indanol.

Introduction

Chiral liquid chromatography has been known as the preferred method for the determination of enantiomeric purity of optically active compounds.[1] The successful use of the techniques related to chiral liquid chromatography depends on the availability of appropriate chiral stationary phases (CSPs). Consequently, various types of CSPs based on helical polymers,[2] proteins,[3] cellulose derivatives,[4] cyclodextrins,[5] chiral crown ethers,[6] macrocyclic antibiotics[7] and other low molecular weight chiral molecules[8] have been introduced.

Previously, we were interested in the use of (1*S*,2*R*)-norephedrine, **1**, as a chiral selector for chiral liquid chromatography and developed (1*S*,2*R*)-*N*-(3,5-dinitrobenzoyl)-norephedrine bonded to silica gel (CSP **2**).[9] CSP **2** was quite successful in separating the two enantiomers of *N*-acyl-α-arylalkylamines. (1*S*,2*R*)-Norephedrine is known to be conformationally flexible because of the low energy barrier for the rotation about the bond between the carbons bearing the hydroxy and the amino group.[10] Consequently, CSP **2** deriv-

ed from (1*S*,2*R*)-norephedrine is also expected to retain a certain degree of conformational flexibility.[9]

The chiral recognition by a CSP has been known to require a minimum of three simultaneous interactions between a CSP and at least one of the two enantiomers.[11] In this instance, it can be easily imagined that a conformationally rigid CSP that retains three interaction sites in a distinct geometric array can best discriminate between enantiomers, one of which has three complimentary interaction sites at the proper positions. However, in general, the three complimentary interaction sites of most analytes are not properly arranged and analyte conformation should be altered to conform to the shape of the CSP. In consequence, a rigid CSP might show greater enantioselectivity for conformationally flexible analytes than a flexible CSP. In turn, a flexible CSP can easily change its conformation to interact with conformationally rigid analytes and, in consequence, a flexible CSP might show greater enantioselectivity for conformationally rigid analytes than a rigid CSP.[9b]

As a conformationally rigid version of CSP **2**, in this study, we wish to report the preparation of a new CSP from 2-amino1-indanol **3**, which is just the cyclic form of norephedrine, and its application. 2-Amino-1-indanol is conformationally fixed because the rotation about the bond between the carbons bearing the hydroxy and the amino group is impossible. Consequently, CSP **4** derived from 2-amino-1-indanol, **3**, is expected to be conformationally rigid. Therefore, comparison of the chromatographic resolution behaviors on CSP **4** with those on CSP **2** may provide insights into the role of the conformational rigidity or flexibility of CSPs in the enantioselectivity.

Experimental Section

General. ¹H NMR spectra were obtained with a Varian Gemini 200 or 300 spectrometer. Chemical shifts were reported in parts per million (ppm) relative to tetramethyl-
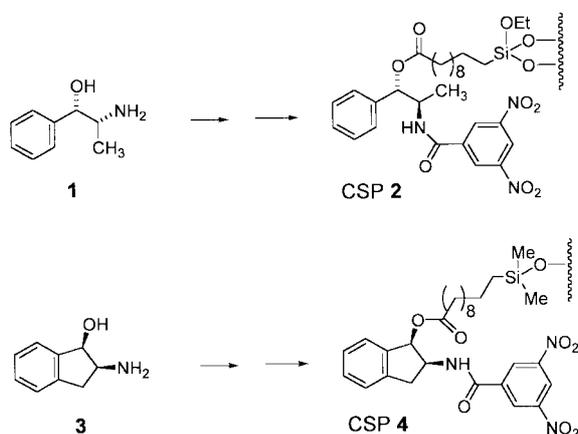
Figure 1. Structural relationship between CSP **2** and CSP **4**.
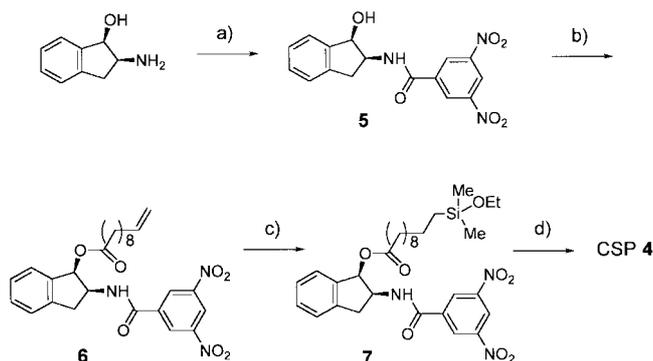
Scheme 1. (a) 3,5-Dinitrobenzoyl chloride, triethylamine, methylene chloride, 0 °C. (b) Undecenoyl chloride, triethylamine, methylene chloride, 0 °C. (c) (1) Dimethylchlorosilane, $H_2PtCl_6 \cdot 6H_2O$, methylene chloride, reflux. (2) Ethanol-triethylamine (1 : 1, v/v), methylene chloride, room temperature. (d) Silica gel (5 mm), Dean-Stark trap, toluene, reflux.

silane as an internal standard. IR spectra were measured on a Mattson Polaris FT-IR spectrometer. Melting points were taken on an Electrothermal Capillary Melting Point Apparatus and reported without correction. Elemental analysis was performed at the Organic Chemistry Research Center, Sogang University, Seoul, Korea.

Chromatography was performed with an HPLC system consisting of a Waters Model 510 pump, a Rheodyne 7125 injector with a 20 μL sample loop, a Youngin 710 absorbance detector with a 254 nm UV filter and a Youngin D520B computing integrator. All chromatographic data were collected using 20% isopropyl alcohol in hexane as a mobile phase with a flow rate of 2.0 mL/min at room temperature. The column void volumes were determined by injecting 1,3,5-tri-*tert*-butylbenzene. Analytes used in this study were available from previous studies.[9]

Preparation of CSP 4. CSP **4** was prepared starting from (*S*)-phenylalanine as shown in Scheme 1. All reactions were carried out under an argon atmosphere.

***N*-(3,5-Dinitrobenzoyl)-2-amino-1-indanol 5**. 2-Amino-1-indanol **3** (1.52 g, 10.2 mmol), which was prepared *via* the known procedure starting from (*S*)-phenylalanine,[12] and triethylamine (3.5 mL, 25.5 mmol) were dissolved in 50 mL of CH_2Cl_2. To the stirred solution was slowly added a solution of 3,5-dinitrobenzoyl chloride (2.4 g, 11.1 mmol) in 20 mL of CH_2Cl_2 at 0 °C. The whole mixture was stirred for 30 min at room temperature and then washed with 50 mL of 0.5 N HCl solution, 0.5 N NaOH solution and brine. The organic layer was dried over anhydrous $MgSO_4$ and then evaporated to dryness. The residue was purified by flash column chromatography on silica gel (chloroform/acetone: 8/2) to afford 2.52 g (72% yield) of *N*-(3,5-dinitrobenzoyl)-2-amino-1-indanol **3** as a colorless crystalline solid. mp 205-207 °C. ^{1}H NMR (Acetone-d_6), δ 3.12-3.28 (m, 2H), 4.61 (d, 1H), 4.78-4.86 (m, 1H), 5.17-5.22 (m, 1H), 7.20-7.43 (m, 5H), 8.50 (d, 1H), 9.05-9.11 (m, 3H). IR (KBr), cm^{-1} 3556, 3404, 3327, 1672.

***N*-(3,5-Dinitrobenzoyl)-*O*-undecenoyl-2-amino-1-indanol 6**. *N*-(3,5-Dinitrobenzoyl)-2-amino-1-indanol **5** (2.3 g, 6.7

mmol) and triethylamine (2.0 mL, 14.5 mmol) were dissolved in 20 mL of methylene chloride. To the stirred solution was slowly added undecenoyl chloride (1.6 mL, 7.5 mmol) at 0 °C. The whole mixture was stirred for 30 min at room temperature and then washed with 50 mL of 0.5 N HCl solution, 0.5 N NaOH solution and brine. The organic solution was dried over anhydrous $MgSO_4$ and then evaporated to dryness. The residue was purified by flash column chromatography on silica gel (ethyl acetate/chloroform: 1/10) to afford 2.97 g (87% yield) of desired product **6** as a colorless crystalline solid. Optical purity of the product was 72% ee by HPLC analysis on a CSP available from previous study.[13] Resolution of the enantiomerically enriched product on a CSP based on (*S*)-naproxen by medium pressure liquid chromatography afforded enantiomerically pure (1*R*,2*S*)-**6**. The detailed procedure for the resolution of the enantiomerically enriched product by medium pressure liquid chromatography was reported previously.[14] mp 134-135 °C. ^{1}H NMR (CDCl$_3$), δ 1.21 (broad s, 10 H), 1.50-1.70 (m, 2H), 1.95-2.03 (m, 2H), 2.36 (t, 2H), 3.11 (dd, 1H), 3.46 (dd, 1H), 4.92-5.13 (m, 3H), 5.69-5.86 (m, 1H), 6.24 (d, 1H), 6.81 (d, 1H), 7.26-7.54 (m, 4H), 8.95 (d, 2H), 9.19 (t, 1H). IR (KBr), cm^{-1} 3414, 3097, 2926, 1707, 1666.

***N*-(3,5-Dinitrobenzoyl)-*O*-(11-ethoxydimethylsilylundecanoyl)-2-amino-1-indanol 7**. *N*-(3,5-Dinitrobenzoyl)-*O*-undecenoyl-2-amino-1-indanol **6** (2.9 g, 5.7 mmol) was dissolved in 25 mL of methylene chloride. To the stirred solution was added 20 mL of chlorodimethylsilane and $H_2PtCl_6 \cdot 6H_2O$ (15 mg dissolved in 2 mL of tetrahydrofuran). The whole mixture was heated to reflux for 2 hrs and then methylene chloride and excess chlorodimethylsilane were removed by simple distillation. The residue was dissolved in 20 mL of methylene chloride and then 10 mL of triethylamine-absolute ethanol (1 : 1, v/v) was added slowly with stirring. The mixture was stirred at room temperature for 1 hr and then concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate, 5/ 1) to afford compound **7** (2.62 g, 75% yield) as a yellow solid. Optical purity was greater than 99% by HPLC analysis on a CSP available from previous study.[13] mp 111-113 °C. ^{1}H NMR (CDCl$_3$), δ 0.08 (s, 6H), 0.57 (m,2H), 1.08-1.26 (m, 17H), 1.56-1.63 (m, 2H), 2.34 (t, 2H), 3.11 (dd, 1H), 3.43 (dd, 1H), 3.65 (q, 2H), 5.04-5.11 (m, 1H), 6.23 (d, 1H), 6.94 (d, 1H), 7.23-7.52 (m, 4H), 8.95 (d, 2H), 9.17 (t, 1H). IR (NaCl in CDCl$_3$), cm^{-1} 3441, 3344, 1736, 1674, 1547.

Preparation of CSP 4 and HPLC column packing. A 250 mL flask equipped with a Dean-Stark trap, a condenser and a magnetic stirring bar was charged with Rexchrom silica gel (4.5 g, 5 μm available from Regis Chemical Co.) and toluene (100 mL). The mixture was heated to reflux until the complete azeotropic removal of water. To the heterogeneous solution was added compound **7** (1.8 g, 2.9 mmol) dissolved in 10 mL of toluene. The whole mixture was heated to reflux for 5 days and then cooled to room temperature. The modified silica gel was collected by filtering and then washed successively with toluene, methanol, acetone, diethyl ether and hexane. Finally, the modified silica gel was dried under

Table 1. Separation of the two enantiomers of *N*-acyl-α-arylalkylamines **8** on CSP **2** and **4**[a]

$$\underset{\underset{\text{Ar}}{\overset{|}{\diagdown}}\overset{\text{R}}{\diagup}}{\text{NH}}-\overset{\overset{\text{O}}{\|}}{\text{C}}-(\text{CH}_2)\text{n-H} \qquad \textbf{8}$$

	Ar	Analyte **8**		CSP **2**				CSP **4**			
		R	n	k_1' [b]	k_2' [c]	α [d]	Conf. [e]	k_1' [b]	k_2' [c]	α [d]	Conf. [e]
8a	phenyl	CH$_3$	1	5.55	6.19	1.12	S	1.67	1.67	1.00	
b			2	3.73	4.05	1.09	S	1.68	1.81	1.08	R
c			3	3.52	3.84	1.09	S	1.46	1.60	1.10	R
d			6	2.13	2.13	1.00		1.25	1.37	1.10	R
e			11	1.71	1.71	1.00		0.98	1.10	1.12	R
f	1-Naphthyl	CH$_3$	1	10.99	12.27	1.12	S	2.95	3.56	1.21	R
g			2	8.53	9.17	1.08	S	2.98	3.52	1.18	R
h			3	6.72	7.25	1.08	S	2.59	3.03	1.17	R
i			6	5.33	5.33	1.00		2.54	3.02	1.19	R
j			11	4.05	4.05	1.00		2.01	2.31	1.15	R
k	1-Naphthyl	CH(CH$_3$)$_2$	1	8.11	11.63	1.43		2.47	4.13	1.67	
l			2	7.36	9.28	1.26		2.61	3.52	1.35	
m			3	5.97	7.68	1.29		2.37	3.21	1.35	
n			6	5.01	6.29	1.26		2.22	3.17	1.43	
o	1-(6,7-Dimethylnaphthyl)	CH$_3$	1	12.59	18.35	1.46		3.67	6.39	1.74	
p			2	10.56	15.36	1.45		3.60	6.35	1.76	
q			3	8.43	12.05	1.43		3.16	5.36	1.70	
r			6	6.83	9.71	1.42		3.00	5.20	1.74	
s			11	5.12	7.04	1.38		2.41	4.04	1.64	
8t	1-(6,7-Dimethylnaphthyl)	CH(CH$_3$)$_2$	1	6.72	20.16	3.00		2.55	7.05	2.77	
u			2	6.19	17.77	2.87		2.53	6.50	2.57	
v			3	4.91	15.22	3.10		2.24	5.77	2.58	
w			6	4.05	12.49	3.08		2.11	5.81	2.75	
x			11	3.09	9.27	3.00		1.80	4.91	2.73	

[a]See the Experimental part for the chromatographic conditions. [b]Retention factor for the first eluted enantiomer. [c]Retention factor for the second eluted enantiomer. [d]Separation factor. [e]Absolute configuration of the second eluted enantiomer. For blanks, elution orders have not been established.

high vacuum. Elemental analysis of the modified silica gel (Found: C, 4.63%; H, 0.65%; N, 0.46%) showed a loading of 0.13 mmol of selector (based on C) or 0.11 mmol of selector (based on N) per gram of stationary phase. The modified silica gel was slurried in methanol and packed into a 250 mm × 4.6 mm I.D. stainless-steel HPLC column using a conventional slurry packing method with an Alltech slurry packer.

Results and Discussion

CSP **4** was prepared *via* the procedure shown in Scheme 1. One thing to note is that optical purity of (1*R*,2*S*)-2-amino-1-indanol, **3**, which was prepared starting from (*S*)-phenyl-alanine *via* the reported procedure,[12] was only 72% ee by HPLC analysis as its *N*-(3,5-dinitrobenzoyl) and *O*-acetyl derivative on a CSP available from our previous study.[13] The low optical purity of compound **3** was found to occur during the cyclization of *N*-protected (*S*)-phenylalanine. Enantio-merically impure **3** was used for the next reaction without any further effort to improve its optical purity. Instead, enantiomerically impure *N*-(3,5-dinitrobenzoyl)-*O*-undecenoyl-

2-amino-1-indanol **6** was resolved on a CSP derived from (*S*)-naproxen.[14]

CSP **4** prepared as shown in Scheme 1 was applied in resolving various *N*-acyl-α-arylalkylamines **8**. The chromatographic resolution results for the resolution of *N*-acyl-α-arylalkylamines **8** on CSP **4** are summarized in Table 1 and compared with those on CSP **2**. Elution orders shown in Table 1 were determined by injecting configurationally known samples. The reversed elution orders observed on CSP **2** and CSP **4** were originated from the opposite stereochemistry of the two CSPs.

As shown in Table 1, resolution of *N*-acyl-α-phenylethyl-amines (**8a-8e**) was not so good on both CSP **2** and CSP **4**. When the α-aryl group of the analyte was changed from phenyl to 1-naphthyl or 6,7-dimethyl-1-naphthyl, however, the enantioselectivity (α) improved quite much. These results demonstrate that the π-π interaction between the aryl group of the analyte and the 3,5-dinitrobenzoyl group of CSPs is the important factor for the chiral recognition. As shown in Table 1, the enantioselectivity (α) on CSP **4** is generally greater than that on CSP **2** except for the resolution of *N*-acyl-α-(6,7-dimethyl-1-naphthyl)isobutylamines (**8t-x**). In

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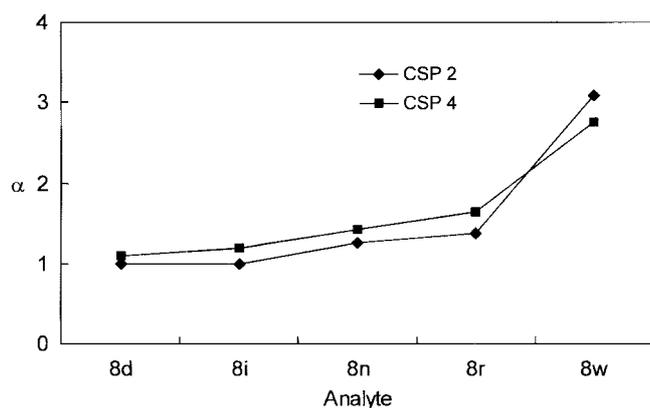
Figure 2. The trends of the separation factors (α) for the resolution of *N*-heptanoyl-a-arylalkylamines (**8d**: aryl = phenyl, alkyl = methyl. **8i**: aryl = 1-naphthyl, alkyl = methyl. **8n**: aryl = 1-naphthyl, alkyl = isopropyl. **8r**: aryl = 1-(6,7-dimethylnaphthyl), alkyl = methyl. **8w**: aryl = 1-(6,7-dimethylnaphthyl), alkyl = isopropyl) on CSP **2** and CSP **4**. See the footnote to Table 1 for the chromatographic conditions.

resolving *N*-acyl-α-(6,7-dimethyl-1-naphthyl)isobutylamines (**8t-x**), CSP **2** shows greater enantioselectivity than CSP **4** does. These trends for the resolution of *N*-heptanoyl-α-arylalkylamines on CSP **2** and CSP **4** are graphically illustrated in Figure 2.

In the introduction section, we discussed the importance of the conformational rigidity or flexibility of a CSP for the chiral recognition. Based on the discussion, it is understandable that conformationally rigid CSP **4** shows greater enantioselectivity (α) for the two enantiomers of *N*-acyl-α-arylalkylamines (**8a-s**), which retain a certain degree of conformational flexibility, than conformationally flexible CSP **2** does. However, in the resolution of *N*-acyl-α-(6,7-dimethyl-1-naphthyl)isobutylamines (**8t-x**), which is believed to retain considerable conformational rigidity engendered by the *peri*-hydrogen of the naphthalene ring and by the sterically bulky isopropyl group at the chiral center, CSP **2** is superior to CSP **4**. These results demonstrate that a rigid CSP shows greater enantioselectivity for conformationally flexible analytes than a flexible CSP, and *vice versa*. One thing to note is that conformational rigidity or flexibility of analytes alone is not responsible for the chiral recognition. For example, *N*-acyl-α-(1-naphthyl)isobutylamines (**8k-n**) seem to retain the same degree of conformational rigidity as *N*-acyl-α-(6,7-dimethyl-1-naphthyl)isobutylamines (**8t-w**) because of the same *peri*-hydrogen and the same sterically bulky isobutyl group at the chiral center. However, *N*-acyl-α-(1-naphthyl)isobutylamines (**8k-n**) are resolved better on CSP **4** than on CSP **2**. From these results, we can assume that the conformational rigidity of analytes alone is not responsible for the good chiral recognition on a conformationally flexible CSP. In addition to the conformational rigidity, it seems that an analyte should contain a strong π-basic aryl functional group to be resolved better on a conformationally flexible π-acidic CSP than on a conformationally rigid π-acidic CSP. Without the strongly π-basic aryl functional group, it might be very difficult for an analyte, which has a steric bulky group controlling its con-

formation, to approach the CSP.

In summary, in this study, we prepared a new CSP (CSP **4**) based on (1*R*,2*S*)-2-amino-1-indanol for the liquid chromatographic separation of enantiomers. The new CSP was expected to contain a certain degree of conformational rigidity because of its cyclic nature. The new CSP was applied in resolving various *N*-acyl-α-arylalkylamines. The chromatographic resolution results on the new CSP were compared with those on an old CSP (CSP **2**) based on (1*S*,2*R*)-norephedrine, which is believed to be conformationally flexible. Comparison of the chromatographic resolution results on CSP **2** and CSP **4** demonstrated that conformationally flexible analytes are resolved better on conformationally rigid CSP **4** while conformationally rigid analytes are resolved better on conformationally flexible CSP **2**. From these results we can conclude that conformational rigidity or flexibility of CSPs might be the important factor for the chiral recognition.

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