Liquid Chromatographic Resolution of *N*-(3,5-Dinitrobenzoyl)-α-amino Acids on a New Chiral Stationary Phase: the First Liquid Chromatographic Utilization of a Double-Ureide Pocket for the Recognition of Chiral Carboxylate Anions†

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Received May 30, 2007

An HPLC chiral stationary phase (CSP) which has only two ureide functional groups was prepared starting from (1*S*,2*S*)-1,2-diaminocyclohexane. The CSP was successful in the resolution of various *N*-(3,5-dinitrobenzoyl)-α-amino acids, the separation (α) and the resolution factors (R_S) being within the range of 1.11-1.35 and 2.19-5.17, respectively with the use of 20% 2-propanol in hexane containing 0.1% trifluoroacetic acid as a mobile phase. However, ethyl esters of *N*-(3,5-dinitrobenzoyl)-α-amino acids were not resolved or resolved with only marginal separation and resolution factors on the CSP under the identical mobile phase condition. From these results, the complexation of the carboxylate anions of analytes inside the double-ureide pocket of the CSP was expected to play some important role for the chiral recognition. In contrast, *N*-(3,5-dinitrobenzoyl)-α-amino acid *N*-propylamides were resolved on the CSP with reasonable separation and resolution factors. Enantioselective hydrogen bonding interactions between analytes and the CSP were presumed to be responsible for these resolutions.

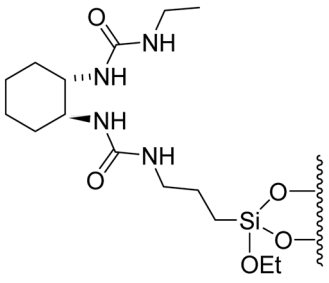
Key Words : Chiral stationary phase, Chiral carboxylate anion, Liquid chromatography, *N*-(3,5-Dinitrobenzoyl)-α-amino acids

Introduction

Liquid chromatographic separation of enantiomers on chiral stationary phases (CSPs) have been known as the most accurate and economic means for the exact determination of enantiomeric composition of chiral compounds.[1] The successful utilization of liquid chromatographic separation of enantiomers depends on the availability of effective CSPs. Consequently, various efforts have been devoted to the development of effective CSPs. Actually various CSPs based on natural chiral molecules,[2] macrocyclic antibiotics,[3] chiral crown ethers[4] and other synthetic optically active chiral molecules[5] have been developed and successfully utilized in liquid chromatographic separation of enantiomers.

As continuous efforts to develop effective CSPs in our laboratory, we directed our attention to the utilization of optically active *trans*-1,2-diaminocyclohexane as a chiral selector. Optically active *trans*-1,2-diaminocyclohexane is commercially available as (1*R*,2*R*)- or (1*S*,2*S*)-form. Consequently, optically active *trans*-1,2-diaminocyclohexane has been utilized as a chiral selector for various purposes. For example, optically active *trans*-1,2-diaminocyclohexane has been utilized for the preparation of chiral catalysts[6] and chiral macrocycles for molecular sensing.[7] In addition, *trans*-1,2-diaminocyclohexane has also been utilized as a chiral selector of liquid chromatographic Pirkle-type CSPs after derivatization with 3,5-dinitrobenzoyl chloride [8] or as a chiral selector of CSPs based on polymeric diacryloyl derivative of *trans*-1,2-diaminocyclohexane.[9] However, di-ureide derivatives of *trans*-1,2-diaminocyclohexane have not been utilized as chiral selectors of CSPs to the best of our knowledge.

Compounds containing two ureide functional groups have been successfully utilized as chemosensors for anions.[10] The double-ureide pocket provided by the compounds containing two ureide functional groups can be a complexation site for anions. In this study, we wish to prepare a new CSP (CSP **1**) containing two ureide groups starting from *trans*-1,2-diaminocyclohexane. The double-ureide pocket provided by the chiral selector of the CSP is expected to be useful for the recognition of the two enantiomers of chiral carboxylate anionic compounds.



CSP **1**

Experimental

General. ^{1}H NMR spectrum was recorded with a Varian Mercury 300 spectrometer. Chemical shifts were reported in parts per million (ppm) relative to tetramethylsilane as an

† This paper is dedicated to Professor Sang Cheol Shim for his distinguished achievements in chemistry.

internal standard. IR spectrum was measured with a Jasco FT/IR-300E. Optical rotation was taken on a Rudolph Research Analytical AUTOPOL IV Polarimeter (Flanders, NJ, USA).

Chromatography was performed with an HPLC system consisting of a Waters model 510 HPLC Pump, a Rheodyne model 7725i injector with a 20 μL sample loop, a Waters 2487 Absorbance Detector and a YoungLin Autochro Data Module (Software: YoungLin Autochro-WIN 2.0 plus). The temperature of the chiral column was maintained at 20 °C by using a Julabo F30 Ultratemp 2000 cooling circulator.

Racemic and optically active analytes were available from previous studies or prepared according to the procedure reported in the previous studies.[11] Each of racemic and optically active samples was dissolved in tetrahydrofuran (usually 1.0 mg/mL) and then used for the resolution on CSP **1**. The usual injection volume was 1.0 μL.

Preparation of CSP 1. CSP **1** was prepared starting from (1*S*,2*S*)-(+)-diaminocyclohexane (available from Aldrich) as following (Scheme 1):

***N*-Ethylaminocarbonyl-(1*S*,2*S*)-diaminocyclohexane, 2.** *N*-Ethylaminocarbonyl-(1*S*,2*S*)-diaminocyclohexane, **2**, was prepared simply by treating (1*S*,2*S*)-1,2-diaminocyclohexane with ethyl isocyanate in methylene chloride. The detailed procedure for the preparation of compound **2** was reported previously.[12]

***N*-(3-Triethoxysilylpropylamino)carbonyl-*N*′-ethylaminocarbonyl-(1*S*,2*S*)-diaminocyclohexane, 3.** Compound **2** (0.93 g, 5.0 mmol) and triethylamine (1.0 mL, 7.2 mmol) was dissolved in methylene chloride (20 mL). The solution was stirred for 30 min at room temperature. And then, 3-(triethoxysilyl)propyl isocyanate (1.24 g, 5.0 mmol) was added to the solution and the whole mixture was stirred for 12 hr at room temperature. Solvent and excess triethylamine were removed by rotary evaporator and the residue was purified by silica gel flash column chromatography (tetrahydrofuran/chloroform = 1/1, v/v) to afford compound **3** as a colorless liquid material (1.84 g, 85%). $[\alpha]_D^{21.4}$ −23.0 (0.27, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.58 (t, 2H), 1.18 (t, 9H), 1.26 (t, 3H), 1.48-1.60 (m, 2H), 1.68-1.76 (m, 2H), 1.78-1.84 (m, 2H), 1.96-2.02 (m, 2H), 2.24-2.32 (m, 2H), 2.88-3.16 (m, 2H), 3.29-3.39 (m, 1H), 3.48-3.56 (m, 1H), 3.68-3.72 (m, 2H), 3.78 (q, 6H), 4.02 (br s, 1H), 4.88 (br s, 1H), 5.49 (br s, 1H), 7.12 (br s, 1H). IR (KBr) 3335, 2981, 2886, 1698, 1650, 1557 cm^{-1}.

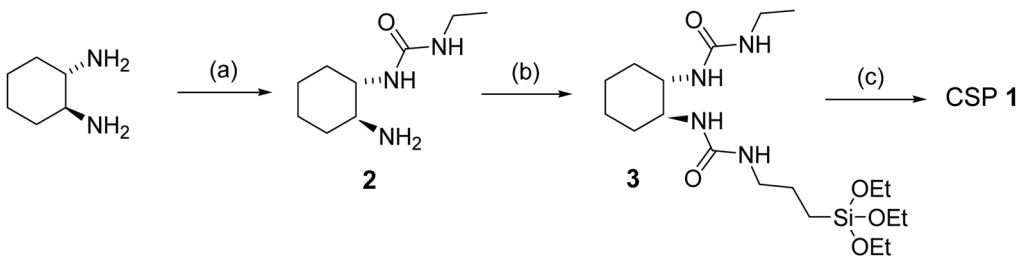
Preparation of CSP 1 and column packing. A 250 mL flask equipped with a Dean-Stark trap, a condenser and a magnetic stirring bar was charged with silica gel (3.5 g, 5 μm, 100 Å Regis Rexchrom Silica) and toluene (100 mL). The mixture was heated to reflux until the complete azeotropic removal of water. To the heterogeneous solution was added compound **3** (0.9 g, 2.1 mmol) dissolved in 10 mL of toluene. The whole mixture was heated to reflux for 72 hr and then cooled to room temperature. The modified silica gel was collected through filtration and then washed successively with toluene, methanol, acetone, ethyl acetate, methylene chloride, hexane and diethyl ether. Finally, the modified silica gel was dried under high vacuum. Elemental analysis of the modified silica gel (Found: C, 3.85%; H, 0.52%; N, 1.23%) showed a loading of 0.21 mmol of selector (based on C) or 0.22 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 **1** was designed to have two ureide functional groups, at least one ureide group being flexible. The two ureide functional groups can form a kind of pocket, the four acidic N-H hydrogens being directed inside the pocket. In this instance, anions can form complex inside the pocket through the hydrogen bonding interactions between the four N-H hydrogens and anions. In the case of chiral anions, the two enantiomers are expected to be recognized during the process of complexation inside the double urea pocket of the CSP because of the chiral environment provided by the 1,2-disubstituted cyclohexane ring. The simple model for the complexation of chiral carboxylate anions inside the double urea pocket of CSP **1** are presented in Figure 1.

α-Amino acids or *N*-substituted α-amino acids are typical chiral anions because they are present as their dissociate forms (carboxylates) in solution under usual condition. Various α-amino acids or *N*-substituted α-amino acids were tested for their resolution on CSP **1**. Fortunately, we found that *N*-benzoyl- or *N*-(substituted benzoyl)-α-amino acids were resolvable on CSP **1** when alcohol-hexane mixture containing a small amount of acetic or trifluoroacetic acid was used as a mobile phase.

To find out the optimal mobile phase condition for the resolution of *N*-(substituted benzoyl)-α-amino acids on CSP



Scheme 1. (a) Ethyl isocyanate, triethylamine, CH_2CH_2, room temperature. (c) 3-(triethoxysilyl)propyl isocyanate, triethylamine, CH_2Cl_2, 50 °C. (c) silica gel (5 μm), toluene, reflux, Dean-Stark trap.

Table 1. Resolution of *N*-(3,5-dinitrobenzoyl)valine on CSP **1** with the variation of the type and the content of alcohol and acid in hexane[a]

	Mobile phase	k_1	k_2	α	R_S
a	10% 2-PrOH in Hexane + 0.1% CH_3COOH	5.45	6.21	1.14	1.39
b	10% 2-PrOH in Hexane + 0.1% CF_3COOH	4.04	4.73	1.17	3.19
c	10% Ethanol in Hexane + 0.1% CF_3COOH	3.57	3.86	1.08	1.63
d	5% 2-PrOH in Hexane + 0.1% CF_3COOH	9.33	11.10	1.19	3.91
e	20% 2-PrOH in Hexane + 0.1% CF_3COOH	1.63	1.87	1.15	2.13
f	10% 2-PrOH in Hexane + 0.5% CF_3COOH	2.87	3.21	1.12	2.00

[a]Flow rate: 0.5 mL/min. Detection: 254 nm UV. Temperature: 20 °C. k_1: Retention factor of the first eluted enantiomer. k_2: Retention factor of the second eluted enantiomer. α: Separation factor. R_S: Resolution factor

1, *N*-(3,5-dinitrobenzoyl)valine was resolved on CSP **1** with the variation of the type and the content of alcohol and acid in hexane. The chromatographic resolution results are summarized in Table 1. 2-Propanol in hexane has been widely utilized as a mobile phase in normal phase liquid chromatography.[1,5c] Consequently, as a first attempt, we tried to use 10% 2-propanol in hexane as a mobile phase for the resolution of *N*-(3,5-dinitrobenzoyl)valine on CSP **1**. However, the retention times of the two enantiomers were too long and consequently a small amount of acetic acid (0.1%) was added to the mobile phase. With the use of 10% 2-propanol in hexane containing 0.1% acetic acid, *N*-(3,5-dinitrobenzoyl)valine was resolved. As shown in Table 1 (entry a), the separation factor (α) was not so high, but clean base-line resolution was observed. When trifluoroacetic acid was used instead of acetic acid in the mobile phase, the separation factor (α) for the resolution of *N*-(3,5-dinitrobenzoyl) valine on CSP **1** improved slightly from 1.14 to 1.17, but the resolution factor (R_S) improved quite much from 1.39 to 3.19 (entry b, Table 1). Use of ethanol instead of 2-propanol was found to diminish both the separation (α) and the resolution factor (R_S) (compare entries b and c, Table 1). When the content of 2-propanol in hexane was decreased from 10 to 5%, both the separation and the resolution factors improved (compare entries b and d, Table 1). In addition, the retention factors also improved, but too much. Completion of the resolution took more than 40 min when 5% 2-propanol in hexane containing 0.1% trifluoroacetic acid was used as a mobile phase as shown in Figure 2. In contrast, when the content of 2-propanol in hexane was increased from 10 to 20%, the retention factors diminished quite much and the separation and the resolution factor also diminished (compare entries b and e, Table 1). When the content of trifluoroacetic acid was increased from 0.1 to 0.5%, all of the retention, the separation and the resolution factor diminished (compare entries b and f, Table 1).

Based on the chromatographic behaviors summarized in Table 1, the optimal mobile phase condition for the resolution of *N*-benzoyl- or *N*-(substituted benzoyl)-α-amino acids on CSP **1** is concluded to be 10% 2-propanol in hexane containing 0.1% trifluoroacetic acid. Using 10% 2-propanol in hexane containing 0.1% trifluoroacetic acid as a mobile phase, various *N*-benzoyl- and *N*-(substituted benzoyl)-α-amino acids are resolved on CSP **1** and the results are summarized in Table 2. Resolution of *N*-(3,5-dinitrobenzoyl)-α-amino acids are resolved quite well (see entries a-h, Table 2). Even though the separation factors are not so large (within the range of 1.11-1.35), the resolution factors are quite large (within the range of 2.19-5.17) and clean base-line resolution is observed in each case for the resolution of *N*-(3,5-dinitrobenzoyl)-α-amino acids. These resolution results are quite surprising in that the CSP contains only simple two ureide functional groups. When the number of nitro groups on the benzoyl ring was changed from two to one and to none, both the separation and the resolution factors were diminished quite much (see entries i-l and m-p, Table 2). From these results, it is expected that the nitro groups on the benzoyl ring play some role for the chiral recognition. By adding nitro groups on the benzoyl ring, the

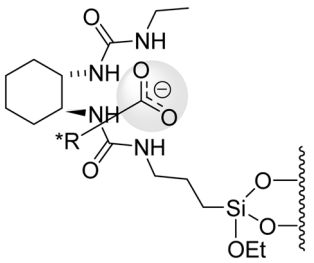


Figure 1. Schematic presentation for the complexation of a chiral carboxylate anion inside the double-ureide pocket of CSP **1**.

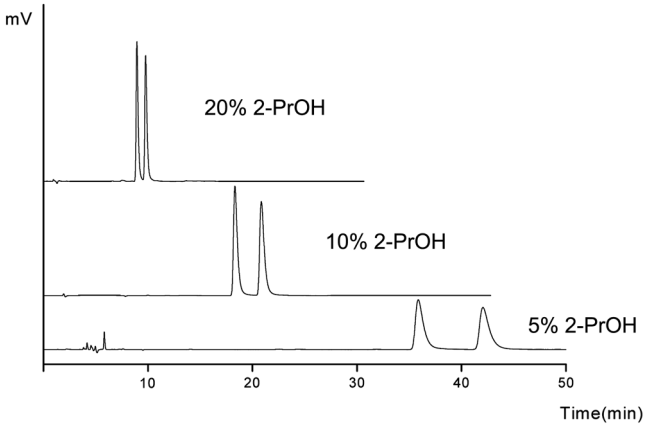
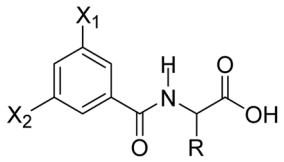


Figure 2. Comparison of the chromatograms for the resolution of *N*-(3,5-dinitrobenzoyl)valine on CSP **1** with the use of 5, 10 or 20% 2-propanol in hexane containing 0.1% trifluoroacetic acid as a mobile phase. Flow rate: 0.5 mL/min. Detection: 254 nm UV. Temperature: 20 °C.

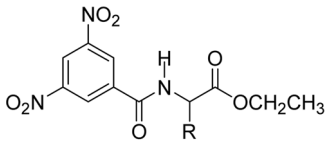
Table 2. Resolution of *N*-(substituted benzoyl)-α-amino acids on CSP **1**[a]



	R	X_1	X_2	k_1	k_2	α	R_S
a	CH_3	NO_2	NO_2	6.22 (L)	7.22 (D)	1.16	2.55
b	$(CH_3)_2CH$	NO_2	NO_2	4.04 (L)	4.73 (D)	1.17	3.19
c	$(CH_3)_2CHCH_2$	NO_2	NO_2	3.75 (L)	4.31 (D)	1.15	2.75
d	C_6H_5	NO_2	NO_2	6.04 (L)	7.19 (D)	1.19	3.40
e	$C_6H_5CH_2$	NO_2	NO_2	4.83 (L)	5.36 (D)	1.11	2.32
f	$HO(CH_3)CH$	NO_2	NO_2	10.83 (L)	14.62 (D)	1.35	5.17
g	$HOCH_2$	NO_2	NO_2	12.00 (L)	13.92 (D)	1.16	2.60
h	$(4\text{-}HOC_6H_4)CH_2$	NO_2	NO_2	19.55 (L)	22.09 (D)	1.13	2.19
i	CH_3	NO_2	H	7.61	8.45	1.11	2.24
j	$(CH_3)_2CH$	NO_2	H	4.56	4.97	1.09	1.68
k	$(CH_3)_2CHCH_2$	NO_2	H	4.71	5.18	1.10	2.07
l	C_6H_5	NO_2	H	7.13	7.99	1.12	2.32
m	CH_3	H	H	4.25	4.72	1.11	2.05
n	$(CH_3)_2CH$	H	H	2.52	2.65	1.05	0.87
o	$(CH_3)_2CHCH_2$	H	H	3.06	3.27	1.07	1.39
p	C_6H_5	H	H	4.49	4.85	1.08	1.69

[a]Mobile phase: 10% 2-propanol in hexane + 0.1% CF_3COOH. Flow rate: 0.5 mL/min. Detection: 254 nm UV. Temperature: 20 °C. k_1: Retention factor of the first eluted enantiomer (the absolute configuration of the first eluted enantiomer is presented in the parenthesis). k_2: Retention factor of the second eluted enantiomer (the absolute configuration of the second eluted enantiomer is presented in the parenthesis). α: Separation factor. R_S: Resolution factor.

Table 3. Resolution of *N*-(3,5-dinitrobenzoyl)-α-amino acid ethyl esters on CSP **1**[a]



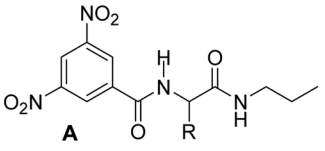
R	k_1	k_2	α	R_S
CH_3	2.34	2.34	1.00	–
$(CH_3)_2CH$	1.41	1.49	1.06	0.77
$(CH_3)_2CHCH_2$	1.28	1.33	1.04	0.58
C_6H_5	2.48	2.58	1.04	0.71
$C_6H_5CH_2$	1.78	1.83	1.03	0.41
Proline	3.00	3.00	1.00	–
Tryptophan	6.92	6.92	1.00	–
Lysine	0.50	0.50	1.00	–

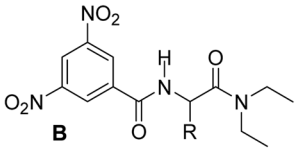
[a]Mobile phase: 10% 2-propanol in hexane + 0.1% CF_3COOH. Flow rate: 0.5 mL/min. Detection: 254 nm UV. Temperature: 20 °C. k_1: Retention factor of the first eluted enantiomer. k_2: Retention factor of the second eluted enantiomer. α: Separation factor. R_S: Resolution factor.

free carboxylic acid group of analytes seems to be more easily deprotonated and consequently complexation shown in Figure 1 seems to become more significant.

N-(3,5-Dinitrobenzoyl)-α-amino acid ethyl esters were also resolved on CSP **1** as summarized in Table 3. The separation and the resolution factors for the resolution of *N*-(3,5-dinitrobenzoyl)-α-amino acid ethyl esters on CSP **1** are diminished quite much compared to those for the resolution of corresponding *N*-(3,5-dinitrobenzoyl)-α-amino acids. Converting the carboxylic acid group of *N*-(3,5-dinitrobenzoyl)-α-amino acids to ethyl ester group seems to diminish the separation and the resolution factors quite much. The pH value of the mobile phase was measured to be 7.8. Under this condition, the carboxylic acid groups of *N*-(substituted benzoyl)-α-amino acids are expected to be dissociated to carboxylates. In this instance, complexation of carboxylate anions of analytes inside the double-ureide pocket of the CSP shown in Figure 1 seems to play some important role for the chiral recognition.

Table 4. Resolution of *N*-(3,5-dinitrobenzoyl)-α-amino acid *N*-propylamides (A) and *N*-(3,5-dinitrobenzoyl)-α-amino acid *N,N*-diethylamides (B) on CSP **1**[a]





R	A			B		
	k_1	α	R_S	k_1	α	R_S
CH_3	1.66	1.20	2.52	1.76	1.12	1.60
$(CH_3)_2CH$	0.79	1.23	2.39	0.85	1.15	1.51
$(CH_3)_2CHCH_2$	0.77	1.15	1.75	0.79	1.09	0.90
C_6H_5	1.46	1.23	2.97	1.20	1.10	1.38
$C_6H_5CH_2$	1.03	1.16	1.84	1.00	1.08	0.88
$(4\text{-}HOC_6H_4)CH_2$	5.59	1.21	3.50	4.98	1.09	2.00
Proline	5.49	1.00	–	5.78	1.00	–
Tryptophan	5.38	1.00	–	5.21	1.00	–
Lysine	3.06	1.00	–	1.89	1.00	–

[a]Mobile phase: 10% 2-propanol in hexane + 0.1% CF_3COOH. Flow rate: 0.5 mL/min. Detection: 254 nm UV. Temperature: 20 °C. k_1: Retention factor of the first eluted enantiomer. α: Separation factor. R_S: Resolution factor.

In contrast, resolution of *N*-(3,5-dinitrobenzoyl)-α-amino acid *N*-propylamides and *N*-(3,5-dinitrobenzoyl)-α-amino acid *N,N*-diethylamides on CSP **1** summarized in Table 4 is relatively good even though the analytes do not contain carboxylic acid group. Consequently, it is expected that the chiral recognition mechanism for the resolution of *N*-(3,5-dinitrobenzoyl)-α-amino acid *N*-propylamides and *N*-(3,5-dinitrobenzoyl)-α-amino acid *N,N*-diethylamides is different from that for the resolution of *N*-(3,5-dinitrobenzoyl)-α-amino acids. In the resolution of *N*-(3,5-dinitrobenzoyl)-α-amino acid *N*-propylamides and *N*-(3,5-dinitrobenzoyl)-α-amino acid *N,N*-diethylamides, enantioselective hydrogen bonding interactions between the analytes and the CSP might be responsible for the chiral recognition. In addition, *N*-(3,5-dinitrobenzoyl)-α-amino acid *N*-propylamides are resolved better than *N*-(3,5-dinitrobenzoyl)-α-amino acid *N,N*-diethylamides. Consequently, the N-H hydrogen of *N*-propylamide group of *N*-(3,5-dinitrobenzoyl)-α-amino acid *N*-propylamides seems to play a certain role for the chiral recognition even though the exact role is not clear yet.

In summary, CSP **1** was quite successful for the resolution of *N*-(3,5-dinitrobenzoyl)-α-amino acids even though the CSP contains only simple two ureide functional groups. Optimum mobile phase condition was found to be 10% 2-propanol in hexane containing 0.l% trifluoroacetic acid. Under the mobile phase condition, *N*-(3,5-dinitrobenzoyl)-α-amino acids are expected to be dissociated and the resulting carboxylates can form complex inside the double-ureide pocket of the CSP. The complexation of the carboxylates of analytes inside the double-ureide pocket of the CSP seems to be an important factor for the chiral recognition based on the fact that *N*-(3,5-dinitrobenzoyl)-α-amino acid ethyl esters are not resolved or resolved very poorly. CSP **1** was also useful for the resolution of *N*-(3,5-dinitrobenzoyl)-α-amino acid *N*-propylamides, but in this case enantioselective hydrogen bonding interactions between analytes and the CSP might be the important factor for the chiral recognition. However, the details for the chiral recognition mechanism should be elucidated by the further study.

Acknowledgements. This work has been supported by the grant from KOSEF (NRL program: M1-0318-00-0005) and by grants-in-aid for the National Core Research Center Program from MOST/KOSEF (No. R15-2006-022-03001-0).

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