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Enantioseparation of *N*-(1-Arylethyl)amides and α-[*N*-(3,5-Dinitrobenzoyl)]amino Esters by Column Chromatography. Chiral Recognition Using a Hydrogen Bond Acceptor Centered in a Pseudo-C_2 Symmetric Environment. 2

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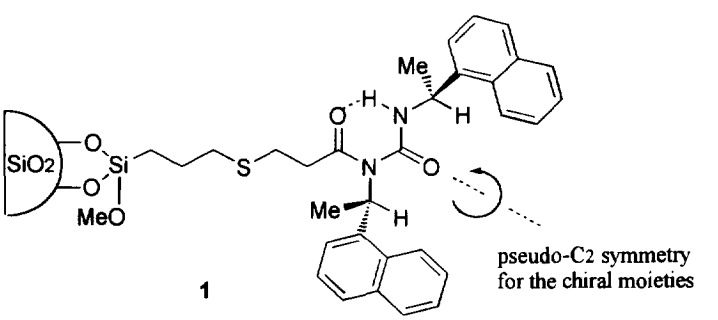
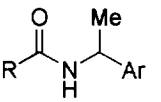
Abstract: Enantioseparation of *N*-(1-arylethyl)amides and α-[*N*-(3,5-dinitrobenzoyl)]amino esters was achieved by column chromatography on silica gel modified with a chiral acylurea which has two (*S*)-1-(1-naphthyl)ethyl moieties in a pseudo-C_2 symmetric position around an axis of the urea-carbonyl. Copyright © 1996 Elsevier Science Ltd

In our previous paper we reported enantioseparation of *N*-(1-arylethyl)amides by column chromatography on silica gel modified with *N*, *N*'-bis[(*S*)-1-phenylethyl]urea.[1] In the chiral stationary phase (CSP) the intramolecular hydrogen bonding between the NH and the acyl-carbonyl arranges the two (*S*)-1-phenylethyl moieties in the pseudo-C_2 symmetric position around an axis of the urea-carbonyl,[2] which creates the suitable geometry for chiral recognition of amides. In order to improve the separation, we designed a new CSP **1** which has a hydrogen bond acceptor between two large conjugated π-systems (naphthalene). Not only were larger α values obtained in the separation of *N*-(1-arylethyl)amides, but CSP **1** could be utilized for the practical determination of the enantiomeric excess of α-amino esters using their dinitrobenzoyl derivatives.[3] Similar to the previous work, (*S*)-enantiomers are the second eluted ones. The mechanism for the separation is postulated.



1

The CSP **1** was prepared from *N*-propenoyl-*N*,*N*'-bis[(*S*)-1-(1-naphthyl)ethyl]urea **2**[4] by Pirkle's method.[5] The HPLC was performed on CSP **1** packed column (4.6 x 500) eluting with hexane-ethyl acetate (4 : 1). Racemic amides were separated clearly to give individual peaks for the enantiomers on HPLC. The k_1 and α values were shown in Table1 and Table 2. The CSP **1** showed substrate dependent separability. In enantio-



3a-l

Table 1. Enantioseparation of N-(1-arylethyl)amide **3a-l**. [a]

No.	amide	Ar	R	k_1 [b]	α
1	**3a**	Ph	H	15.72(-)	1.00
2	**3b**		Me	8.88(R)	1.06
3	**3c**		Ph	4.17(R)	1.13
4	**3d**	1-naph	H	16.98(-)	1.00
5	**3e**		Me	18.60(R)	1.08
6	**3f**		Ph	4.64(R)	1.20
7	**3g**		2-naph	5.47(R)	1.27
8	**3h**		t-Bu	1.72(R)	1.20
9	**3i**		4-methoxyphenyl	8.50(R)	1.23
10	**3j**		4-nitrophenyl	8.58(R)	1.95
11	**3k**		3,5-dinitrophenyl	11.98(R)	3.76
12	**3l**		pentafluorophenyl	0.97(R)	1.18

[a] Column: 4.6 x 500 mm; eluant: haxane-ethyl acetate, 4:1, 3 ml/min; detector: 254 nm.
[b] Reference 7.

separations of *N*-(1-arylethyl)amides **3a-l**, the larger substituents (**3b**, **3e** (R = Me), **3c**, **3f** (R = Ph)) gave the larger value and *N*-(1-arylethyl)amides **3a** and **3d** (R = H) could not be resolved (Table 1). Separation of *N*-[1-(1-naphthyl)ethyl]amides **3e**, **3f** gave larger k_1 and α values than that of *N*-(1-phenylethyl)amides **3b**, **3c**. In the separation of **3h** which has a bulky substituent (R = tBu), small k_1 was observed. In order to investigate the electronic effect of the amide-benzoyl moiety, the following substituted benzoylamides, 4-methoxybenzoylamide, 4-nitrobenzoylamide, 3,5-dinitrobenzoylamide and pentafluorobenzoylamide (**3i**, **3j**, **3k** and **3l**) were examined. The α value of **3i** (R = 4-

methoxyphenyl) is almost the same as that of **3f** (R = Ph). On the other hand, **3j** (R = 4-nitrophenyl) showed the larger value (α = 1.95). The largest α value was observed for **3k** (α = 3.76) in this series. The CSP **1** showed better separation than the previously reported CSP possessing *N*,*N*'-bis[(*S*)-1-phenylethyl]acylurea moieties which showed smaller α values of 1.40 and 1.94 for **3j** and **3k**, respectively.[1] These results indicate that π-π interaction between 4-nitro- or 3,5-dinitrobenzoyl (π-acceptor) and naphthyl (π-donor) of **1** should be the most effective interaction for the enantioseparation.[3,6] However, separation of **3l** gave a small value (α = 1.18) and k_1 is the smallest in this series, because of the electrostatic repulsion between the fluorides of the analyte and π-electron of the naphthyl group in **1**. For the determination of the absolute configuration, (*S*)-enantiomers **3b**, **3c**, **3e** and **3f-l** were prepared by acylation of commercially available (*S*)-1-phenylethylamine and (*S*)-1-(1-naphthyl)ethylamine. In all cases the (*R*)-enantiomers eluted faster than the (*S*)-enantiomers.

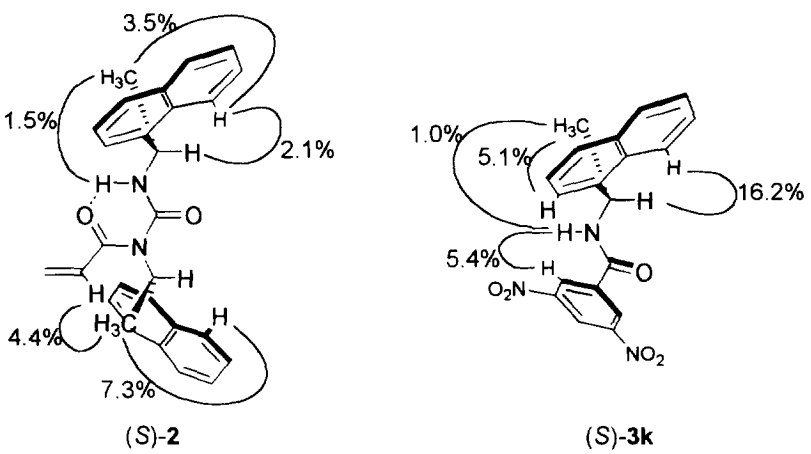


Fig 1. NOE spectra of (*S*)-**2** and (*S*)-**3k**

To estimate the conformation of CSP **1**, NOE spectrum of (*S*)-**2** was measured (Fig 1). Direction of α-hydrogens of both the naphthylethyl groups is parallel to the urea carbonyl. The *peri*-hydrogens of the naphthyls are positioned between the α-hydrogen and the α-methyl group. From this NOE experiment, it was confirmed that the two (*S*)-1-(1-naphthyl)ethyls are located in the C_2 symmetric geometry. Further, from NOE spectrum of the analyte (*S*)-**3k** which showed the largest α value in this study, it was found that the naphthylethyl group has the same configuration as that of (*S*)-**2**.

From the above results, we postulate the following mechanism involving the pseudo-C_2 symmetric geometry of **1** for this enantioseparation. During the separation, (*S*)-enantiomers have the acidic amide-hydrogen bonding with the electron rich urea-carbonyl oxygen of **1** and the amide-benzoyl group interacts with the π-electrons of the naphthyl of **1** (**A** or **B**) in Fig. 2. Due to the above two interactions, the stereogenic center of the amide approaches one of the naphthylethyl moieties in the CSP from the

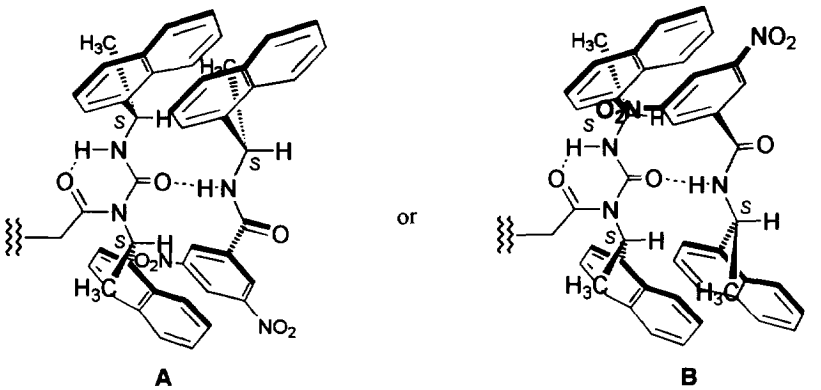
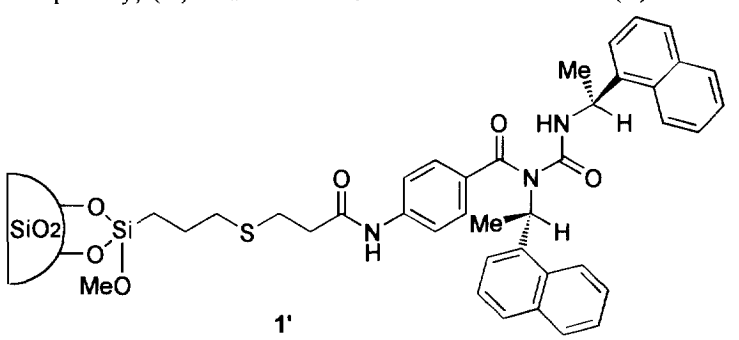


Fig 2. Complexation of (*S*)-**3k** with **1**

least hindered side. In either complexes (**A**, **B**) (*S*)-enantiomers have the third interaction, π-π interaction between the two naphthylethyl moieties of the analyte and **1**. However, (*R*)-enantiomers can not have the third one due to the steric repulsion in the complex. Consequently, (*R*)-enantiomers eluted faster than the (*S*)-enantiomers.



To investigate the importance of C_2 symmetry in **1**, enantioseparation by CSP **1'** was performed. *N*-[4-(acryloylamino)benzoyl]-*N,N'*-bis[(*S*)-1-(1-naphthyl)ethyl]urea **2'**

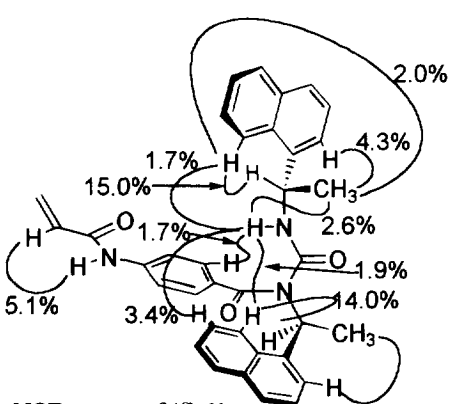
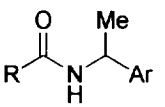


Fig 3. NOE spectra of (*S*)-**2'**

was prepared from 4-(acrylamino)benzoic acid and *N,N'*-bis[(*S*)-1-(1-naphthyl)ethyl]-

carbodiimide by the usual procedure. From NOE experiments the conformation of **2'** was estimated (Fig 3). Steric repulsion between the benzoyl and the urea moiety makes the structure twisted. Due to this, it is difficult to create intramolecular hydrogen bonding between N-H hydrogen and the hetero atoms. The C_2 symmetric geometry of the chiral urea group in **2** was changed to the unsymmetric geometry (**2'**) by induction of -NH-C_6H_4-CO-. Enantioseparation of **3a-l** with **1'** was attempted under the same conditions as that with **1**. Benzoylamides **3a-c** (Ar = Ph) could not be separated. In the separation of naphthoylamides **3g**, **3j** and **3k** all the α values decreased. The π-π interaction between the analytes and the CSP might become weaker by unsymmetrization of the CSP geometry.



3a-l

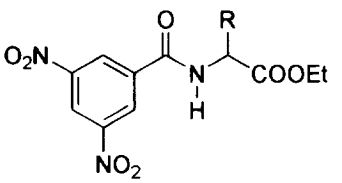
Table 2. Enantioseparation of N-(1-arylethyl)amide **3a-l** by CSP **1'**.[a]

No.	amide	Ar	R	k_1[b]	α
1	**3a**	Ph	H	7.50(-)	1.00
2	**3b**		Me	7.25(-)	1.00
3	**3c**		Ph	4.00(-)	1.00
4	**3d**	1-naph	H	9.67(R)	1.08
5	**3e**		Me	3.14(R)	1.14
6	**3f**		Ph	4.83(R)	1.21
7	**3g**		2-naph	4.71(R)	1.18
8	**3h**		t-Bu	3.57(R)	1.20
9	**3i**		4-methoxyphenyl	8.33(R)	1.20
10	**3j**		4-nitrophenyl	4.43(R)	1.65
11	**3k**		3,5-dinitrophenyl	9.00(R)	2.53
12	**3l**		pentafluorophenyl	3.29(R)	1.17

[a] Column: 4.6 x 500 mm; eluant: haxane-ethyl acetate, 4:1, 3 ml/min; detector: 254 nm.
[b] Reference 7.

In order to establish a practical method for the determination of enantiomeric excesses of α-amino esters, separations of *N*-(3,5-dinitrobenzoyl)amino esters **4a-f** were investigated (Table 3). The *N*-benzoylamino esters were prepared by

ethyl-esterification of the α-amino acid followed by condensation with 3,5-dinitrobenzoyl-chloride. The amino esters **4a** and **4b** which have phenyl groups at their α- and β-positions, gave small α values (α = 1.17 and 1.59). On the contrary, the analytes **4c-f** which have no phenyl group, showed large α values (α = 2.20-2.64). The



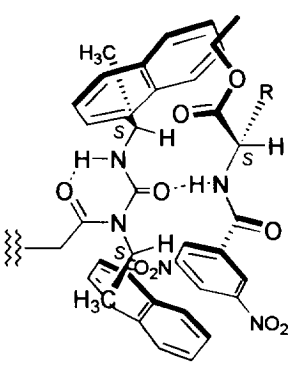
4a-f

Table 3. Enantioseparation of N-(1-arylethyl)amide **4a-f** by CSP **1**.[a]

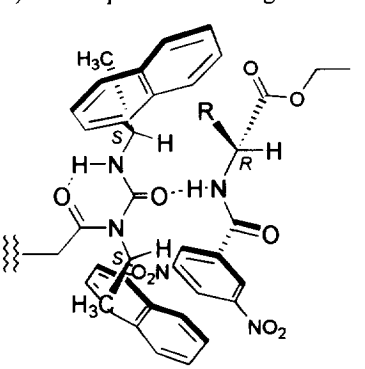
No.	amide	R	k_1[b]	α
1	**4a**	Ph	13.49	1.17
2	**4b**	CH_2Ph	8.83	1.59
3	**4c**	Me	6.39	2.20
4	**4d**	CH_2CH_2COOEt	8.18	2.23
5	**4e**	$CH_2CH_2SCH_3$	8.99	2.53
6	**4f**	iPr	2.96	2.64

[a] Column: 4.6 x 500 mm; eluant: haxane-ethyl acetate, 4:1, 3 ml/min; detector: 254 nm. [b] Reference 7.

enantiomers separated on HPLC were identified by comparison with authentic samples. The two complexes of **1** with (*S*)-**4** (**C**) and (*R*)-**4** (**D**) are depicted in Fig. 4. In the



C (**1** + (*S*)-**4**)
strong interaction



D (**1**+ (*R*)-**4**)
weak interaction

Fig 4. Complexation of (*S*)-**4** (**C**) and (*R*)-**4** (**D**) with **1**

complex **C** the ester-carbonyl of (*S*)-**4** has π-π interaction with the naphthyl of **1**. On

the other hand in **D**, R of (*R*)-**4** interacts with the naphthyl in the case of R = Ph (**4a**) and R = CH_2Ph (**4b**). Though (*R*)-enantiomers of **4c-f** do not have the third interaction with **1**, (*R*)-enantiomers of **4a** and **4b** interact with **1** using the third weak π-π interaction. This makes the α values of **4a** and **4b** smaller than that of **4c-f**.

From this study, we could indicate that this easily understandable model has the advantage of realizing the molecular recognition in enantioseparations by column chromatography.

Experimental

Preparation of Chiral Stationary Phase 1. A suspended solution of silica gel (10.6 g, Wakogel LC-5H) and (3-mercaptopropyl)trimethoxysilane (10.6 g, 54.0 mmol) in benzene (25 ml) and pyridine (25 ml) in 200 ml flask was refluxed for 24 h. After cooling, the suspended solution was filtered with suction. The fine powder was washed with acetone, diethylether and pentane, and dried in vacuo to give a thiol (12.0 g).

A solution of triethylamine (0.909 g, 9.00 mmol) in toluene (20 ml) was added to the thiol (4.00 g) in 200 ml-flask and the suspended solution was refluxed for 14 h. After cooling, a solution of acrylylurea **2** (2.67 g, 6.32 mmol)[2] in toluene (20 ml) was added to the resulting solution dropwise and the solution was refluxed for 48 h. After cooling, the suspended solution was filtered with suction. The powder was washed with methanol, acetone, diethylether and pentane, and dried in vacuo to give the CSP **1** (4.48 g). The powdery **1** was suspended in carbon tetrachloride and the packing in an HPLC column (4.6 x 500) was carried out under a pressure of 150 kg/cm^2. Then the column was washed with ethyl acetate and hexane.

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5. CSP **1** was synthesized from **2** and a thiol which was prepared from (3-mercapto-propyl)trimethoxysilane and silica gel (5μ, Wakogel LC-H5). Pirkle, W. H.; House, D. W. *J. Org. Chem.* **1979**, *44*, 1957.
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7. The absolute configuration of enantiomers was determined by comparison with k_1 of the authentic samples.

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