Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 2, pp. 329-332, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00005-4

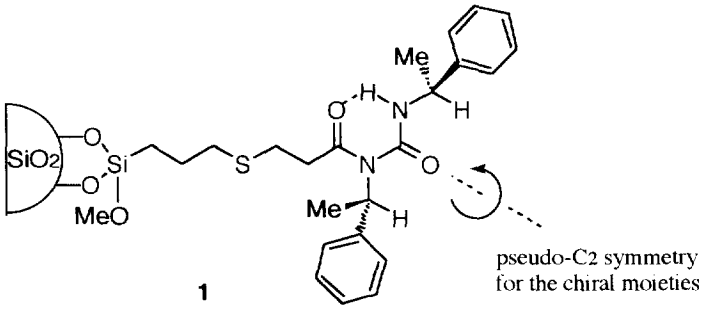
Enantioseparation of *N*-(1-Arylethyl)amides by Column Chromatography. Chiral Recognition Using a Hydrogen Bond Acceptor Centered in a pseudo-C_2 Symmetric Environment

Keiki Kishikawa,* Kotaro Otake, Shigeo Kohmoto, Makoto Yamamoto and Kazutoshi Yamada

Department of Materials Science, Faculty of Engineering, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263, Japan

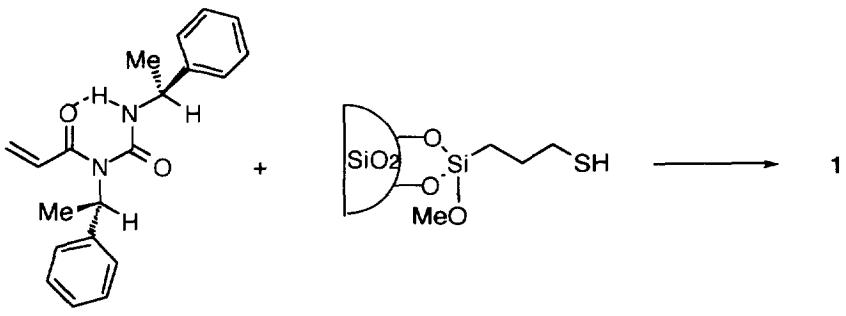
Abstract: Resolution of racemic amides was achieved by column chromatography on silica gel modified with a chiral acylurea which has two (*S*)-1-phenylethyl moieties in a pseudo-C_2 symmetric position around an axis of the urea-carbonyl.

Hydrogen bonding and π–π interactions are the most important interactions in chromatographic separation of racemic compounds.[1,2] In the complex of an analyte and a stationary phase, however, to understand the real interactions is difficult even in these days. To solve this problem, we have designed a novel chiral stationary phase (CSP) **1** which has a hydrogen bond acceptor between two conjugated π-systems. In CSP **1**, the intramolecular hydrogen bonding of 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, which is estimated from X-ray analysis of an acylurea in our preveous work.[3] High performance was observed in the enantioseparation of *N*-(1-arylethyl)amides. In all cases (*S*)-enantiomers, which have strong interaction with the CPS **1**, are the second eluted enantiomers in the column chromatography.



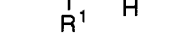
1

CPS **1** was prepared by the following method. *N*-Propenoyl-*N*,*N*'-bis[(*S*)-1-phenylethyl]urea **2**[4] was added to thiol **3**[5] to give **1**, which was packed in HPLC column (4.6 x 250 mm). The chromatography was carried out eluting with hexane-isopropanol (95 : 5).



2 **3**

Racemic alcohols, halides, ethers, esters and ketones could not be separated. However, racemic amides were separated cleanly to give separate peaks for the enantiomers on the HPLC chart. The k_1 and α values were shown in Table 1 and Table 2. Separation of 2-substituted butanamides **4a-d** shows a small α value. In particular, **4d**, which has no phenyl group at the stereogenic carbon, was not separated.



4a-d

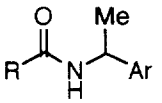
Table 1. Enantioseparation of butanamide **4a-d**.[a]

No.	amide	R^1	R^2	k_1[b]	α
1	**4a**	Ph	n-Bu	2.22	1.05
2	**4b**		i-Pr	2.50	1.05
3	**4c**		Ph	5.37	1.11
4	**4d**	Me	Ph	4.58	1.00

[a] Column: 4.6 x 250 mm; eluant: hexane-isopropanol, 95 : 5, 3 ml/min; detector: 254 nm. [b] The absolute configuration was not determined.

The *N*-(1-arylethyl)amides **5a** and **5d** which have a small R (R = H) could not be resolved. The larger substituents (**5b** (R = Me), **5c** (R = Ph)) gave the larger α values.

Separation of *N*-[1-(1-naphthyl)ethyl]amides **5e**, **5f** gave larger k_1 and α values than that of *N*-(1-phenylethyl)amides **5b**, **5c**. In the separation of **5h** small k_1 was observed. In this series, separations of 4-methoxy- and 4-nitrobenzoylamide (**5i** and **5j**) were performed to investigate the influence of the amide proton acidity: **5i** (R = 4-methoxyphenyl) gave a smaller α value than **5f** (R = Ph). On the other hand, **5j** (R = 4-nitrophenyl) showed the larger value than **5f**. Further, separation of 3,5-dinitrobenzoylamide **5k** gave the largest α value (α = 1.94) in this study. The amide proton of the analyte has hydrogen bonding with CSP **1**. (*S*)-Enantiomers of **5a-k** 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.



5a-k

Table 2. Enantioseparation of *N*-(1-arylethyl)amide **5a-k**.[a]

No.	amide	Ar	R	k_1[b]	α
1	**5a**	Ph	H	5.74(-)	1.00
2	**5b**		Me	8.62(R)	1.04
3	**5c**		Ph	3.92(R)	1.11
4	**5d**	1-naph	H	7.49(-)	1.00
5	**5e**		Me	11.22(R)	1.11
6	**5f**		Ph	10.08(R)	1.24
7	**5g**		2-naph	14.96(R)	1.24
8	**5h**		t-Bu	1.62(R)	1.24
9	**5i**		4-methoxyphenyl	20.91(R)	1.22
10	**5j**		4-nitrophenyl	18.46(R)	1.40
11	**5k**	Me	3,5-dinitrophenyl	41.67(R)	1.94

[a] Column: 4.6 x 250 mm; eluant: haxane-isopropanol, 95:5, 3 ml/min; detector: 254 nm.
[b] Reference 6.

We postulate the following mechanism for this enantioseparation. During the separation, both enantiomers have hydrogen bonding with the urea-carbonyl oxygen of the CSP. The stereogenic center of the amide approaches one of the phenylethyl moieties in the CSP because of the steric repulsion between R and another phenylethyl moiety (**A** or **B** in Fig.1). In either complexes (**A**, **B**) (*S*)-enantiomers have the stronger π–π

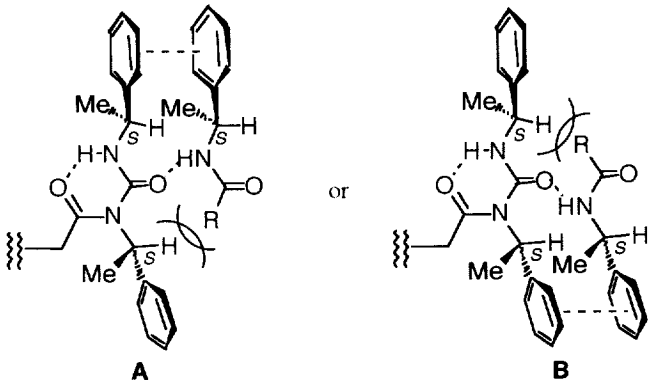


Fig 1. Comlexation of (*S*)-**5b**, **5c** with **1**

interaction with **1**. Consistent with this (*R*)-enantiomers eluted faster than the (*S*)-enantiomers. It is easy to realize the interactions in the complexation because of the pseudo-C_2 symmetry.

From this study, we are convinced that the easily understandable model can help the next advance in enantioseparation by column chromatography. Further modification of the acylurea part in the CPS is now in progress.

Acknowledgement

We are grateful to Kanto Chemical Co., Inc. for the packing of the modified silica gel in an HPLC column.

Experimental

Preparation of Chiral Stationary Phase 1. A solution of silica gel (10.0 g, Wakogel LC-5H) and (3-mercaptopropyl)trimethoxysilane (10.0 g, 50.9 mmol) in benzene and pyridine 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 thiol **3** (11.29 g).

A solution of **3** (6.48 g) and triethylamine (0.601 g, 5.94 mmol) in toluene was refluxed for 3 h and cooled to room temperature. A solution of acrylylurea **2** (3.83 g, 11.9 mmol) in toluene was added to the reaction mixture 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 thiol **1** (7.34 g). The packing of **1** in an HPLC column (4.6 x 250) was carried out by Kanto Chemical Co., Inc.

References:

1. Pirkle, W. H.; Finn, J. In *Asymmetric Synthesis; Morrison*, J. D., Ed.; Academic Press: New York, 1984; Vol. 1, pp 87-124.
2. Pirkle, W. H.; Pochapsky, T. C., *Chem. Rev.* **1989**, *89*, 347.
3. Kohmoto, S.; Kasimura, H.; Nishio, T.; Iida, I, Kishikawa, K.; Yamamoto, M.; Yamada, K., *J. Chem. Soc. Perkin 2* **1994**, 1565.
4. Kishikawa, K.; Yamamoto, M.; Kohmoto, S.; Yamada, K., *J. Org. Chem.* **1989**, *54*, 2428. Kishikawa, K.; Furusawa, A.; Kohmoto, S.; Yamamoto, M.; Yamada, K., *J. Org. Chem.* **1993**, *58*, 7296.
5. The thiol **3** was prepared from (3-mercaptopropyl)trimethoxylsilane and silica gel (5 μ, Wakogel LC-H5). Pirkle, W. H.; House, D. W., *J. Org. Chem.* **1979**, *44*, 1957.
6. The absolute configuration of enantiomers was determined by comparison with k_1 of the authentic samples.

(*Received in Japan* 16 *November* 1994; *accepted* 16 *December* 1994)