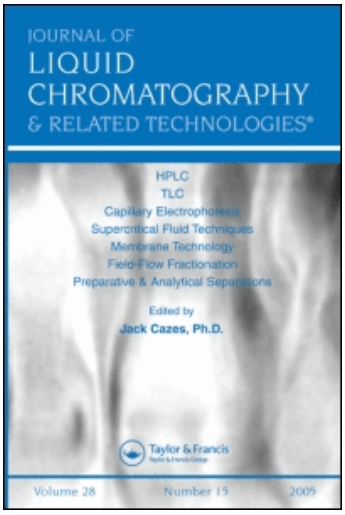

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Enantiomer Separation by HPLC with Some Urea Derivatives of L-Valine as Novel Chiral Stationary Phases

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ENANTIOMER SEPARATION BY HPLC WITH SOME UREA DERIVATIVES OF L-VALINE AS NOVEL CHIRAL STATIONARY PHASES

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ABSTRACT

Two novel chiral stationary phases derived from (R)- and (S)-1-(α-naphthyl)ethylamine with (S)-valine chemically bonded to γ-aminopropyl silanized silica, which contain two asymmetric carbon atoms attached to two nitrogen atoms of the urea group, have been prepared.

These phases showed excellent enantioselectivity for derivatives of amino acid, amine, carboxylic acid and alcohol enantiomers. Some alcohol and ester enantiomers were well resolved directly without any prederivatization upon these phases.

INTRODUCTION

Recently we[1)2)] found that some urea derivatives such as N-(tert-butylaminocarbonyl)-L-valyl-aminopropyl silica gel I , (R)-1-(α-naphthyl)ethylaminocarbonyl-aminopropyl silica gel II , which contain an asymmetric carbon atom attached to the nitrogen atom of the urea group, are efficient for the enantiomer separation by high-performance liquid chromatography. This fact shows the bonding of urea nitrogen to the asymmetric carbon atom is the active site for diastereomeric

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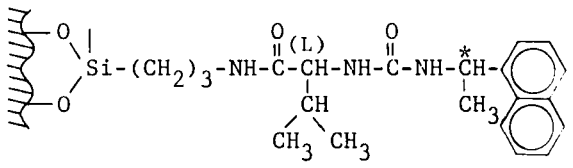
hydrogen bond association in the enantiomer separation by high-performance liquid chromatography.

On the other hand, we[3-5] showed that a second chiral constituent in amide stationary phases can influence efficiently the chiral recognition in liquid chromatography as well as gas chromatography.

In this paper we report the high-performance liquid chromatographic properties of two novel chiral stationary phases III and IV derived from (S)- and (R)-1-(α-naphthyl)ethylamine with L-valine chemically bonded to γ-aminopropyl silanized silica, which contain two asymmetric carbon atoms attached to two nitrogen atoms of the urea group.



* III : (S) , IV : (R)

EXPERIMENTAL

Preparation of chiral stationary phase

Phase III : To a solution of 3.7g of L-valine in 17ml of 2N sodium hydroxide, 8.9g of (S)-1-(α-naphthyl)ethylisocyanate and 5ml of tetrahydrofuran were added, and this mixture was stirred at room temperature for 6h. The reaction mixture was washed with ethylacetate and acidified with 6N hydrochloric acid. The white crystalline material was extracted with ethylacetate. The solvent was removed under reduced pressure to afford crude N-(S)-1-(α-naphthyl)ethylaminocarbonyl-L-valine. This crystalline material was recrystallized from ethylacetate-hexane mixture (m.p.(decomposed) 176-177°C). Analysis : calculated for $C_{18}H_{22}N_2O_3$, C 68.77, H 7.05, N 8.91% ; found, C 68.69, H 7.28, N 8.79%. To a solution of 1.6g of N-(S)-1-(α-naphthyl)ethylaminocarbonyl-L-valine in 35ml of tetrahydrofuran and dioxane mixture, 2.5g of LiChrosorb-NH_2 (5μm) (E. Merck, Darmstadt, G.F.R.) and 1.36g of N-ethoxycarbonyl-2-ethoxy-1,2-

dihydroquinoline were added with stirring at 0°C for 1h, then the mixture was stirred at room temperature overnight. Modified silica III was collected by centrifugation and washed exhaustively with tetrahydrofuran, methanol, chloroform and diethylether, and dried under reduced pressure. It contained about 0.45mmol of N-(S)-1-(α-naphthyl)ethylaminocarbonyl-L-valine per gram of support (based on C and N).

Phase IV : (R)-1-(α-naphthyl)ethylaminocarbonyl-L-valine was synthesized as for (S)-1-(α-naphthyl)ethylaminocarbonyl-L-valine but using (R)-1-(α-naphthyl)ethylisocyanate instead of (S)-1-(α-naphthyl)-ethylisocyanate. This compound was colourless crystalline(m.p.(decomposed) 189-190°C). Analysis : calculated for $C_{18}H_{22}N_2O_3$, C 68.77, H 7.05, N 8.91%, found C 68.47, H 7.22, N 8.87%. Phase IV was prepared as for phase III but using N-(R)-1-(α-naphthyl)ethylaminocarbonyl-L-valine instead of N-(S)-1-(α-naphthyl)ethylaminocarbonyl-L-valine, and this modified silica contained 0.45 mmol of N-(R)-1-(α-naphthyl)ethylaminocarbonyl-L-valine per gram of support (based on C and N).

Liquid chromatography

The experiments were carried out with a Shimadzu LC-5A high-performance liquid chromatograph equipped with a UVD-2 ultraviolet detector. Steel columns (250 x 4 mm I.D.) were slurry packed with III and IV using a conventional technique.

RESULTS AND DISCUSSION

The chromatographic results are summarized in TABLE I. Two novel phases III and IV are efficient for the separation of amino acid ester enantiomers as both N-acetyl and N-3,5-dinitrobenzoyl derivatives. These results indicate that the second chiral constituent improves the enantioselectivity of phase I and II both of which contain only one asymmetric center, because phase II has little

TABLE I HPLC SEPARATION OF ENANTIOMERS UPON CHIRAL STATIONARY PHASES

The separation factor of the enantiomers, α, is the ratio of their capacity factors, k_1' is the capacity factor for the initially eluted enantiomer. Mobile phases : A = n-hexane - isopropanol (93 : 7) ; B = n-hexane - isopropanol (39 : 1) ; C = n-hexane -dichloromethane - ethanol (15 : 4 : 1) ; D = n-hexane - dichloromethane - ethanol (50 : 10 : 1) ; E = n-hexane - dichloromethane - ethanol (100 : 20 : 1) ; F = n-hexane - dichloromethane (500 : 1). Flow rates of 1 ml/min were typically used.

Compound	Phase III			Phase IV		
	α	k_1'	Mobile phase	α	k_1'	Mobile phase
Amino acids						
Alanine[a)]	1.15	3.87	A	1.15	4.87	A
Valine[a)]	1.28	1.80	A	1.32	2.18	A
Leucine[a)]	1.30	1.65	A	1.52	1.95	A
Alanine[b)]	1.86	1.49	C	1.73	2.13	C
Valine[b)]	1.77	0.77	C	1.91	1.20	C
Leucine[b)]	1.44	0.79	C	1.29	1.66	C
Amines[c)]						
1-Phenylethylamine	1.98	1.54	C	2.31	2.44	C
1-(α-Naphthyl)ethylamine	3.94	1.37	C	3.83	2.53	C
2-Octylamine	1.20	2.74	D	1.25	5.00	D
Carboxylic acids[d)]						
2-Phenylpropionic acid	2.89	2.56	C	2.32	3.05	C
2-(4-Chlorophenyl)isovaleric acid	2.02	2.10	C	2.50	2.48	C
2-Bromo-3,3-dimethylbutyric acid	2.16	1.78	C	2.00	2.41	C
Alcohols[e)]						
1-Phenylethanol	1.54	1.43	C	1.29	1.61	C
1-(α-Naphthyl)ethanol	1.44	1.70	C	1.34	1.88	C
2-Octylalcohol	1.14	2.54	D	1.05	3.36	D
Others[f)]						
Fenpropathrin	1.22	6.00	F	1.12	5.35	F
S-3308*	1.16	3.22	E	1.20	2.90	E
S-3307**	1.11	4.23	E	1.15	3.92	E
Allethrolone	1.04	9.59	B	1.09	10.57	B
Propargyllone	1.02	15.71	B	1.07	18.62	B

a) Resolved as N-acetyl O-methylester derivatives.
b) Resolved as N-3,5-dinitrobenzoyl O-methylester derivatives.
c) Resolved as N-3,5-dinitrobenzoyl derivatives.
d) Resolved as 3,5-dinitroanilide derivatives.
e) Resolved as 3,5-dinitrophenyl urethane derivatives.
f) Resolved directly.
* 1-(2,4-Dichlorophenyl)-4,4-dimethyl-2-(1,2,4-triazol-1-yl)-1-penten-3-ol
** 1-(4-Chlorophenyl)-4,4-dimethyl-2-(1,2,4-triazol-1-yl)-1-penten-3-ol

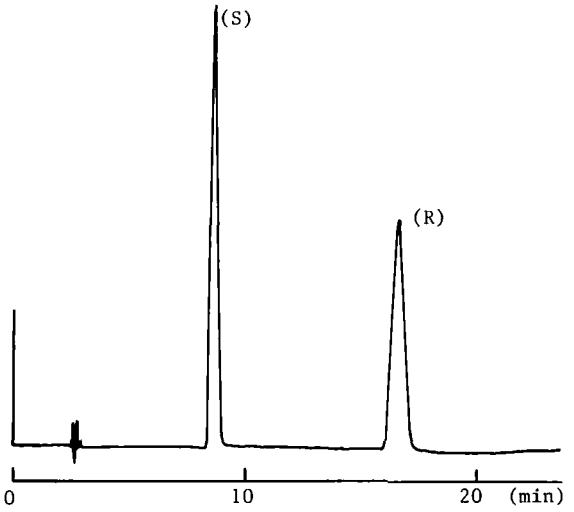


Figure 1 Chromatographic separation of the enantiomers of racemic 1-phenylethylamine as N-3,5-dinitrobenzoyl derivatives upon chiral stationary phase IV. Chromatographic conditions as in TABLE I.

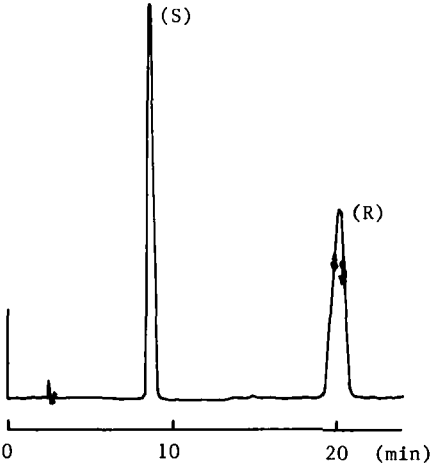


Figure 2 Chromatographic separation of the enantiomers of racemic 2-phenylpropionic acid as 3,5-dinitroanilide derivatives upon chiral stationary phase III. Chromatographic conditions as in TABLE I.

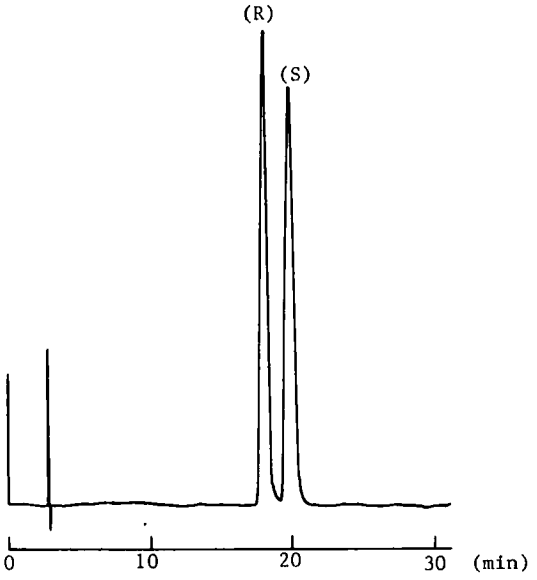


Figure 3 Chromatographic separation of the enantiomers of racemic fenpropathrin upon chiral stationary phase III. Chromatographic conditions as in TABLE I.

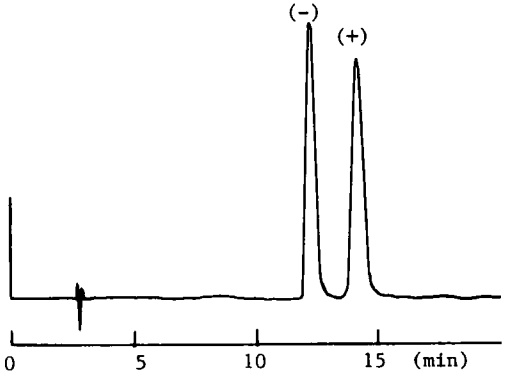


Figure 4 Chromatographic separation of the enantiomers of racemic S-3308 upon chiral stationary phase IV. Chromatographic conditions as in TABLE I.

enantioselectivity for N-acetyl derivatives, and phase I has no enantioselectivity for N-3,5-dinitrobenzoyl derivatives of amino acid esters.

Phase III and IV also showed excellent enantioselectivity for N-3,5-dinitrobenzoyl derivatives of amines, 3,5-dinitroanilide derivatives of carboxylic acids, and 3,5-dinitrophenylurethane derivatives of alcohols.[6] Typical chromatograms are shown in Figure 1 and Figure 2.

As these phases contain a chiral urea group, which has the ability to serve either as a donor or an acceptor in hydrogen bonding , a diastereomeric hydrogen bonding association may contribute to the separation of amide or urethane enantiomers. These phases also contain a chiral 1-(α-naphthyl)ethyl group, which has the ability to serve as a π-donor, so the fact that a 3,5-dinitrophenyl group is efficiently incorporated into the solutes suggests the additional contribution from a π-π donor-acceptor interaction in the separation of enantiomers. We[7] have previously reported chiral amide stationary phases, comprised of (S)-1-(α-naphthyl)ethylamine chemically bonded to γ-aminopropyl silanized silica, gave good chiral recognition for amine, carboxylic acid and alcohol derivatives. It is noticed novel urea phases III and IV show higher separation factors than these amide phases which contain one asymmetric center.

It is emphasized that some ester and alcohol enantiomers were well resolved directly without any prederivatization upon III or IV. As typical examples, chromatograms of racemic fenpropathrin and S-3308 are shown in Figure 3 and Figure 4. We consider the direct separation of various enantiomers may be possible with these novel phases.

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