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Note

High-performance liquid chromatographic separation of enantiomers on axially chiral binaphthalene dicarboxylic acid–chiral phenylethylamine bonded to silica gel

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A variety of chiral stationary phases(CSPs) derived from amino acids and amines have been developed for the direct separation of enantiomers by high-performance liquid chromatography (HPLC)[1,2]. Recently, chiral stationary phases involving two stereogenic centres have been reported to be more effective for the chromatographic separation of the various types of enantiomers[3–7].

In a previous paper, we described the preparation of several axially chiral binaphthalene-derived phases and their effectiveness for the separation of a wide range of enantiomers[8]. Thus, in this paper, we describe the preparation and effectiveness of novel chiral stationary phases involving two different stereogenic centres, axially chiral 1,1′-binaphthalene-2,2′-dicarboxylic acid coupled with chiral 1-phenylethylamine.

EXPERIMENTAL

Materials

1,1′-Binaphthalene-2,2′-dicarboxylic acid (compound **1**)[9,10] and 11-aminoundecyl silanized silica gel (spherical 5-μm particles, amino group 0.66 mmol/g) (compound **2**)[11] were prepared according to the reported procedures.

Preparation of (*aS*, 1*S*)-(−)- and (*aR*, 1*S*)-(+)-2-(N-1-phenylethylcarbamoyl)-1,1′-binaphthalene-2-carboxylic acid (**3**-*a*SS and **3**-*a*RS) was accomplished according to Fig. 1. Compound **1** was treated with dicyclohexylcarbodiimide (DCC), followed by (1*S*)-(−)-1-phenylethylamine to yield diastereomeric mixture **3**, which was recrystallized from acetonitrile to afford **3**-*a*SS–acetonitrile (1:1 inclusion complex)(m.p. 190.5°C; $[\alpha]_D^{20} = -123.3°$, $c = 1.038$, $CHCl_3$. Found: C, 79.27; H, 5.67; N, 5.29%. Calc. for $C_{30}H_{23}NO_3 \cdot C_2H_3N$, C, 78.99; H, 5.39; N, 5.76%). The filtered acetonitrile solution was evaporated and the residue was recrystallized from ethanol

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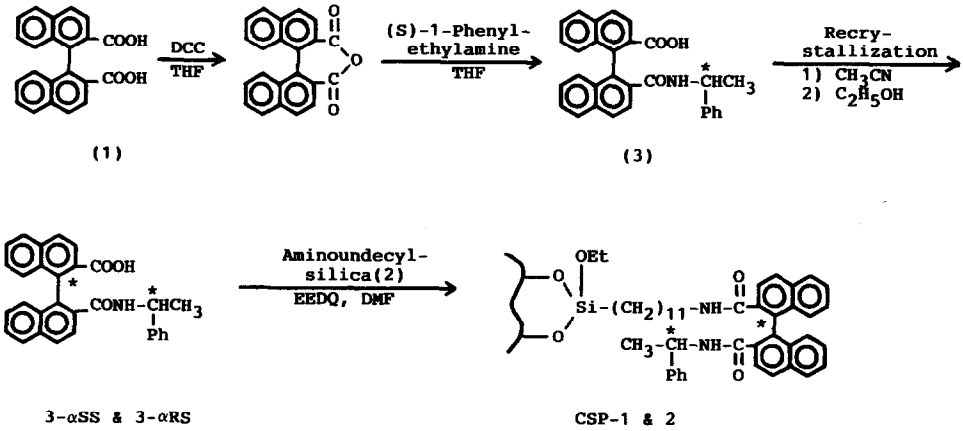

Fig. 1. Preparation of CSP 1 and 2. THF = tetrahydrofuran; Et = ethyl; Ph = phenyl.

to afford 3-*a*RS–ethanol (1:1 inclusion complex)(m.p. 260.0–261.0°C; $[\alpha]_D^{20}$ = 183.2°, c = 1.01, $CHCl_3$. Found: C, 78.25; H, 6.09; N, 2.91%. Calc. for $C_{30}H_{23}NO_3 \cdot C_2H_6O$, C, 78.19; H, 5.95; N, 2.85%). Total yields of 3-*a*SS and 3-*a*RS starting from compound **1** were 86 and 81% respectively. The optical purities of 3-*a*SS and 3-*a*RS were determined to be 100% by HPLC as their methyl esters. The configuration of the binaphthalene carboxylic acid moiety in each diastereomer **3** was determined by hydrolysis of the amides to the corresponding acids. The experimental details will be described elsewhere[12].

Preparation of stationary phases

CSP1. To a solution of 3.30 g of compound **2** in 60 ml of dry dimethylformamide (DMF) were added 3.00 g of compound 3-*a*SS and 3.30 g of N-ethoxycarbonyl-2-ethoxy-1,3-dihydroquinone (EEDQ). The slurry was irradiated under a nitrogen atmosphere in the water-bath of an ultrasound laboratory cleaner (35 W, 41 kHz) which was maintained at 70°C. After 8 h of irradiation, the modified silica gel was collected and washed exhaustively with DMF, methanol, acetone and diethyl ether and then dried under reduced pressure to afford CSP 1 (Found: C, 15.05; H, 2.20; N, 1.02%. Calc. for. 3-*a*SS: 0.18 mmol/g based on % C).

CSP 2. Phase CSP 2 was prepared similarly using compound 3-*a*RS instead of 3-*a*SS (Found: C, 14.88; H, 2.18; N, 1.02%. Calc. for 3-*a*RS: 0.18 mmol/g based on % C).

Liquid chromatography

The experiments were carried out using a Shimadzu LC-5A or a JASCO Trirotor III high-performance liquid chromatograph equipped with a Shimadzu SPD-6A or a JASCO UVIDEC-100-III ultraviolet detector (254 nm). Stainless-steel columns (250 mm × 4.6 mm I.D.) were slurry packed using conventional techniques.

Various derivatized compounds for use as solutes were prepared by employing reagent-grade chemicals.

TABLE I

SEPARATION OF THE ENANTIOMERS OF AMINO ACID, AMINE AND ALCOHOL DERIVATIVES ON CHIRAL STATIONARY PHASES

Mobile phases: 2-propanol–*n*-hexane, 10:90 (A); 20:80 (B). Flow-rate: 1 ml/min. k' = Capacity factor for the initially eluted enantiomer. The configuration of the more strongly retained enantiomer is indicated in parentheses. The separation coefficient of the enantiomers, α, is the ratio of the capacity factors of the enantiomers. 3,5-DNB = 3,5-Dinitrobenzoyl; 3,5-DNPC = 3,5-dinitrophenylcarbamate.

Racemate	*CSP 1*			*CSP 2*		
	Mobile phase	k'	α	*Mobile phase*	k'	α
N-3,5-DNB-alanine butyl ester	A	6.39	1.14(*S*)	A	5.26	1.27(*S*)
N-3,5-DNB-valine butyl ester	A	3.42	1.08(*S*)	A	2.91	1.24(*S*)
N-3,5-DNB-leucine butyl ester	A	3.88	1.05(*R*)	A	3.23	1.13(*S*)
N-3,5-DNB-phenylglycine butyl ester	A	4.64	1.24(*R*)	A	4.30	1.13(*R*)
N-3,5-DNB-phenylalanine butyl ester	A	6.12	1.09(*R*)	A	5.94	1.42(*S*)
N-3,5-DNB-1-phenylethylamine	B	6.20	1.40(*S*)	B	7.22	1.40(*S*)
N-3,5-DNB-1-(1-naphthyl)ethylamine	B	7.00	2.12	B	9.93	1.84
1-Phenylethanol 3,5-DNPC	A	9.25	1.09(*R*)	A	11.03	1.26(*S*)
1-Phenylpropanol 3,5-DNPC	A	8.08	1.11	A	9.72	1.29
1-Phenylbutanol 3,5-DNPC	A	7.37	1.11	A	8.94	1.27

RESULTS AND DISCUSSION

The preparation of the diastereomers **3**-*a*SS and **3**-*a*RS was easily accomplished according to Fig. 1, starting from racemic compound **1** and (1*S*)-1-phenylethylamine, whereby the troublesome optical resolution of compound **1**[9,13] was excluded.

Chromatographic results for the derivatives of amino acids, amines and alcohols are summarized in Table I. Both CSPs have the same configuration in the amine moiety, but different configurations in the binaphthalene unit. Better separation was achieved on CSP 2 than on CSP 1 except for phenylglycine and naphthylethylamine, which shows that both chiral sites of CSP 2, *aR*-binaphthalene and *S*-phenylethyl-

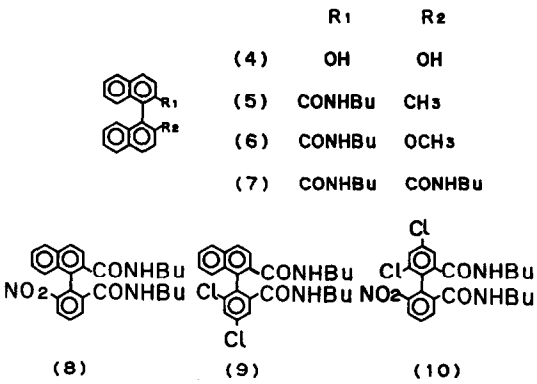

Fig. 2. Structures of biaryls. Bu = Butyl.

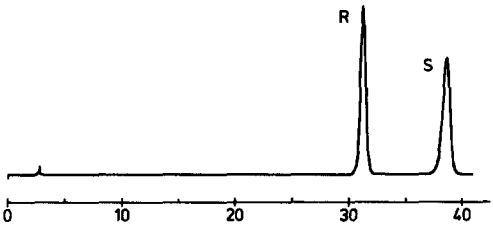

Fig. 3. Chromatographic separation of enantiomers of 1-phenylethanol 3,5-dinitrophenylcarbamate on CSP 2. Chromatographic conditions as in Tabel I. Elution time in min.

amine, cooperate with each other in separating enantiomers. In the case of CSP 1, the chiral recognition ability of the inverted configuration of the binaphthalene site may be opposite to that of the *S*-phenylethylamine site and the separation factors were reduced or the elution order was reversed for leucine, phenylalanine and 1-phenylethanol.

Axially disymmetric biaryls (Fig. 2) are separated as shown in Fig. 3 and Table II. Better separation was also achieved on CSP 2 than on CSP 1. The configuration of the more strongly retained enantiomers is inverted between CSP 1 and 2, which suggests the major site for chiral recognition is the binanpthalene moiety and the contribution of *S*-phenylethylamine moiety is small for the enantiomer separation of biaryls.

TABLE II

SEPARATION OF THE ENANTIOMERS OF BIARYLS ON CHIRAL STATIONARY PHASES

Chromatographic conditions, α and k' as in Table I. Mobile phases: 2-propanol–*n*-hexane, 10:90 (A), 20:80 (B), 5:95 (C).

Racemate	*CSP 1*			*CSP 2*		
	Mobile phase	k'	α	*Mobile phase*	k'	α
4	B	7.36	1.09(*R*)	B	6.76	1.09(*S*)
5	C	1.81	1.00	C	1.80	1.06
6	C	4.16	1.12(*R*)	C	4.19	1.13(*S*)
7	B	3.61	1.30(*R*)	B	3.71	1.50(*S*)
8	A	6.50	1.13(*R*)	A	6.50	1.22(*S*)
9	A	6.43	1.23	A	6.07	1.32
10	A	6.64	1.11(*R*)	A	5.45	1.17(*S*)

We consider that these novel phases are potentially very useful for the separation of a wide range of enantiomers as they have two stereogenic centres of different types in the same molecule.

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