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Chiral stationary phases consisting of axially dissymmetric 2′-substituted-1,1′-binaphthyl-2-carboxylic acids bonded to silica gel for high-performance liquid chromatographic separation of enantiomers

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ABSTRACT

Seven chiral stationary phases (CSPs) were prepared by bonding axially dissymmetric 2′-substituted-1,1′-binaphthyl-2-carboxylic acids to aminoalkylsilanized silica gels through an amide linkage, and the effect of the 2′-substituents (CN, COOH, $CONH_2$, CONHEt, $CONEt_2$ and OCH_3) was investigated for the high-performance liquid chromatographic (HPLC) separation of enantiomers. Among these CSPs, that which had a 2′-carboxyl substituent showed the best performance and efficiently discriminated several enantiomeric amino acids, amines and alcohols as their 3,5-dinitrophenyl derivatives, and biaryls bearing 2,2′-polar substituents, by normal-phase HPLC. Stereoselective π-donor–acceptor interaction and dipole stacking interaction between the CSPs and the analytes seem to play a critical role in the enantioseparation.

INTRODUCTION

In the 1980s, remarkable progress was made in the direct separation of enantiomers by high-performance liquid chromatography (HPLC) on chiral stationary phases (CSPs) [1]. Various CSPs have been prepared by derivatizing a variety of chiral compounds such as amino acids [2,3], alcohols [4], amines [5], acids [6], hydroxy acids [7], phthalides [8], hydantoins [9], optically active polymeric materials such as polysaccharides [10,11] and the like [1]. Most of the chiral selectors of these CSPs have an element of C-centrochirality for differentiation of enantiomeric analytes, whereas those with other chiral elements, such as helical chirality of a helicenecarboxylic acid [12] or triarylmethyl methacrylate polymers [13], facial chirality of a paracyclophanecarboxylic acid [14], and P-centrochirality of triarylphosphine oxides [15], have also been reported. On the other hand, axially dissymmetric 1,1′-binaphthyls have been extensively utilized as efficient chiral auxiliaries in a variety of asymmetric reactions and chiral recognitions [16]. Their applications to CSPs, however, have been limited because of the difficulties in obtaining the prerequisite atropisomeric binaphthyls. Among the few examples are chiral binaphthyl crown ethers bonded [17,18] to or coated [19] on silica gel or polystyrene used for

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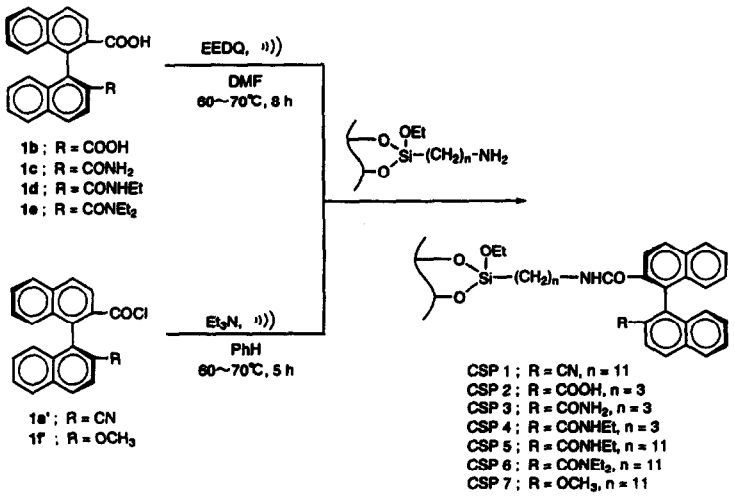


Scheme 1.

the separation of amino acids, and 1,1′-binaphthyl-2,2′-diyl hydrogenphosphate bonded to silica gel used for the resolution of racemic helicenes [20].

In a previous paper, we reported the preparation of several CSPs by using axially dissymmetric 1,1′-bi-2-naphthol and 1,1′-binaphthyl-2,2′-dicarboxylic acid (**1b**) [21]. It was shown that **1b**, rather than 1,1′-bi-2-naphthol, was promising as the chiral selector for the separation of a wide range of enantiomers, but the structures of the **1b**-derived CSPs remained ambiguous except that the starting **1b** was bonded to silica via an amide linkage using the 2-carboxylic function. In this paper, we report the preparation and performance of seven structurally well defined CSPs (CSP 1–CSP 7) which were obtained by bonding 2′-substituted-1,1′-binaphthyl-2-carboxylic acids (**1a–f**) to 3-aminopropyl- and/or 11-aminoundecylsilanized silica gel (Scheme 1). Based on the chromatographic behaviour of CSP 1–CSP 7, chiral recognition models are presented and the structures of the previously reported **1b**-based CSPs are revised.

EXPERIMENTAL

General

Liquid chromatography was performed using a Shimadzu LC-6A or a JASCO Trirotor-III apparatus 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 with the packing materials described below using conventional techniques.

IR spectra were measured on a Shimadzu IR-460 grating spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL JNM-FX 60 or Bruker AC-250T instrument with tetramethylsilane as an internal standard. Optical rotations were recorded on a Union PM-101 automatic digital polarimeter in a 1-cm cell. Melting points were measured on a Yamato MP-21 apparatus and are uncorrected. Microanalyses were carried out in the Microanalytical Laboratory of the Institute for Chemical Reaction Science, Tohoku University.

Materials

The preparation of 11-aminoundecylsilanized silica gel (Hitachi gel 3056 base; spherical 5-μm particles, microsphere diameter 80–100 Å) (found, C 7.57, H 1.69, N 0.93%; calculated, N 0.92%; 0.66 mmol/g based on N) has been described [22]. 3-Aminopropylsilanized silica gel was prepared in a similar manner to the 11-amino analogue by treatment of a silica gel (Tosoh silica gel, spherical 5-μm particles, microsphere diameter 100 Å) with 3-aminopropyltriethoxysilane in boiling toluene. Analy-

sis: found, C 8.10, H 2.07, N 1.42%; calculated, 1.01 mmol/g gel based on N. Merck silica gel $60GF_{254}$ was used for analytical and preparative TLC. Column chromatography was performed by using Nacalai Tesque silica gel 60.

Commercial materials were used as purchased unless stated otherwise. Solvents used for HPLC were distilled before use. Tetrahydrofuran (THF) was distilled from sodium diphenylketyl. Dimethylformanide (DMF) and hexamethylphosphoric triamide (HMPA) were distilled from calcium hydride under reduced pressure. Triethylamine was distilled from calcium hydride. These materials were stored under nitrogen. Water-sensitive reactions were routinely carried out in a nitrogen atmosphere.

Axially dissymmetric 2'-substituted-1,1'-binaphthyl-2-carboxylic acids

The preparation of atropisomerically pure (a*S*, 1*S*)-2'-(N-1-phenylethyl)carbamoyl-1,1'-binaphthyl-2-carboxylic acid (**2**), 2'-cyano-1,1'-binaphthyl-2-carboxylic acid chloride (**1a'**) and 1,1'-binaphthyl-2,2'-dicarboxylic acid (**1b**) [23] and (a*S*)-2'-methoxy-1,1'-binaphthyl-2-carboxylic acid chloride (**1f'**) [24] has been reported previously.

(aS)-2'-Carbamoyl-1,1'-binaphthyl-2-carboxylic acid [(aS)-1c]. By treatment with thionyl chloride, (a*S*, 1*S*)-**2** (4.02 g, 9.03 mmol) was converted into the acid chloride (a*S*)-**1a'**, which was then dissolved in ethanol (50 ml) with warming. To the solution was added a solution of KOH (5.1 g) in water (5 ml), and the mixture was heated at reflux for 11 h. After volatiles had been removed under reduced pressure, the residue was dissolved in water (100 ml) and washed with diethyl ether (2 × 30 ml) to remove non-acidic compounds. The aqueous phase was acidified with concentrated HCl and the resulting precipitate was extracted with ethyl acetate (3 × 50 ml). The combined extracts were washed with water (3 × 50 ml) and dried over $MgSO_4$. After filtration, the solvent was evaporated *in vacuo* and recrystallized from acetonitrile to give 2.44 g (79% yield) of (a*S*)-**1c** as colourless crystals, m.p. 149–150°C; $[\alpha]_D^{20} - 111°$ (*c* 1.0, acetone); ^1H NMR (C^2HCl_3), δ (ppm) 6.50 and 6.10 (2H, two s's, NH_2), 6.9–9.1 (12H, m, Ar-H); IR (KBr) (cm^{-1}), 3415, 3185, 1650, 1396, 830, 770. Analysis: found, C 77.34, H 4.62, N, 4.15%; calculated for $C_{22}H_{15}NO_3$, C 77.40, H 4.43, N 4.10%.

(aS)-2'-Ethylcarbamoyl-1,1'-binaphthyl-2-carboxylic acid [(aS)-1d]. To a stirred solution of (a*S*)-**1b** (6.06 g, 17.7 mmol) in THF (60 ml) was added a solution of 1,3-dicyclohexylcarbodiimide (DCC) (3.66 g, 17.7 mmol) in THF (40 ml) at room temperature for 1 h under a nitrogen atmosphere. The mixture was stirred for 2 h at that temperature and then heated at reflux for 4 h. After cooling to room temperature, triethylamine (2 ml) and ethylamine (1.19 g, 26.5 mmol) were added and the mixture was heated at reflux for 3 h. The mixture was allowed to cool to room temperature, precipitated N,N'-dicyclohexylurea was filtered off and the solids were rinsed with small portions of THF. The solvent was distilled out from the filtrate under reduced pressure and the residue was dissolved in chloroform (100 ml). The solution was washed with concentrated HCl (2 × 100 ml) and then with water (4 × 100 ml) and dried over $MgSO_4$. After filtration, the solvent was evaporated *in vacuo* to give 7.20 g of a mixture of unchanged (a*S*)-**1b**, (a*S*)-**1d** and 2,2'-bis(ethylcarbamoyl)-1,1'-binaphthyl.

As the separation of the mixture as such into each component was difficult, the desired (a*S*)-**1d** was purified via the methyl ester as follows. The mixture was dissolved in HMPA (50 ml) and then a 25% (w/w) aqueous solution of NaOH (5.6 ml) was added. After stirring for 1 h at room temperature methyl iodide (5.8 ml) was added to the solution and stirring was continued for another 1 h. Then 2 *M* HCl (100 ml) was added to the mixture and it was extracted with diethyl ether (3 × 50 ml). The combined organic layer was washed with 2 *M* HCl (2 × 50 ml) and then with water (2 × 50 ml) and dried over $MgSO_4$. After filtration, the solvent was evaporated *in vacuo* to give 5.7 g of the residue, which was chromatographed on a silica gel column (600 g), eluting with hexane–ethyl acetate (1:1) to give 3.3 g of the methyl ester of (a*S*)-**1d** [49% yield based on (a*S*)-**1b**]. This was then dissolved in ethanol (50 ml) with warming, and a solution of KOH (5.0 g) in water (15 ml) was added.

After the mixture had been heated at reflux for 3 h, volatiles were removed under reduced pressure. The residue was dissolved in water (200 ml) and washed with diethyl ether (2 × 30 ml) to remove non-acidic compounds. The aqueous layer was acidified with concentrated HCl and the resulting precipitate was extracted with ethyl acetate (3 × 50 ml). The combined organic layer was washed with water (3 × 50 ml) and dried over $MgSO_4$. After filtration, the solvent was removed *in vacuo* to give 2.68 g of (a*S*)-**1d** as colourless foam [41% yield based on the starting (a*S*)-**1b**], m.p. 202–203°C; $[\alpha]_D^{20} - 153°$ (*c* 1.02, acetone); ^1H NMR (C^2HCl_3), δ (ppm) 0.32 (3H, t, CH_3), 2.82 (2H, m, CH_2), 6.4–8.0 (13H, m, Ar-H and NH); IR (KBr) (cm^{-1}), 3750–2600, 3275, 2950, 1697, 1589, 1550. Analysis: found, C 78.28, H 5.03, N 3.89%; calculated for $C_{24}H_{19}NO_3$, C 78.03, H 5.18, N 3.79%.

(aS)-2'-Diethylcarbamoyl-1,1'-binaphthyl-2-carboxylic acid [(aS)-1e]. To a stirred solution of (a*S*)-**1b** (2.80 g, 8.18 mmol) in THF (30 ml) was added a solution of DCC (1.69 g, 8.18 mmol) in THF (20 ml) at room temperature for 1 h under a nitrogen atmosphere. The mixture was stirred for another 2 h at that temperature and then heated at reflux for 4 h. After cooling to room temperature, triethylamine (2 ml) and diethylamine (0.90 g, 12.3 mmol) were added to the mixture, which was then heated at reflux for 3 h. The mixture was allowed to cool to room temperature, precipitated N,N'-dicyclohexylurea was filtered off and the solids were rinsed with small portions of THF. The solvent was distilled out from the filtrate under reduced pressure and the residue was dissolved in chloroform (50 ml). The solution was washed with concentrated HCl (2 × 50 ml) and then with water (4 × 50 ml) and dried over $MgSO_4$. After filtration, the solvent was evaporated *in vacuo* and recrystallized from ethanol to give 2.27 g of (a*S*)-**1e** as colourless prisms (70% yield), m.p. 239–240°C; $[\alpha]_D^{20}$ −150° (*c* 1.02, acetone); ^1H NMR (C^2HCl_3), δ (ppm) 0.36 (3H, t, CH_3), 1.12 (3H, t, CH_3), 2.6–3.8 (4H, m, CH_2), 6.9–8.1 (12H, m, Ar-H); IR (KBr) (cm^{-1}), 3700–2500, 2950, 1715, 1565. Analysis: found, C 78.48, H 5.91, N 3.84%; calculated for $C_{26}H_{23}NO_3$, C 78.57, H 5.83, N 3.52%.

Preparation of stationary phases

CSP 1. A solution of (a*S*)-**1a'** (1.74 g, 5.10 mmol) in benzene (50 ml) and triethylamine (10 ml) was added to a slurry of 11-aminoundecylsilanized silica gel (3.30 g) in benzene (70 ml). The slurry was irradiated with ultrasound under a nitrogen atmosphere in the water-bath of an ultrasound laboratory cleaner (35 W, 41 kHz) which was maintained at 70°C. After 5 h of irradiation, the modified silica gel was collected and washed exhaustively with benzene, THF, methanol, acetone and diethyl ether and then dried under reduced pressure to a constant mass to afford 3.82 g of CSP 1. Analysis: found, C 19.41, H 2.07, N 1.26%; calculated, 0.54 mmol/g gel based on C.

CSP 2. A solution of (a*S*)-**1b** (1.50 g, 4.38 mmol) and 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) (1.63 g, 6.62 mmol) in DMF (50 ml) was added to 3-aminopropylsilanized silica gel (3.00 g). The slurry was heated at 70°C for 8 h under ultrasound irradiation as above. The modified silica gel was successively washed with DMF, THF, methanol, acetone and diethyl ether and then dried under reduced pressure to afford 3.40 g of CSP 2. Analysis: found, C 17.89, H 2.41, N 1.32%; calculated, 0.47 mmol/g gel based on C.

CSP 3. CSP 3 (3.29 g) was similarly prepared as above by the treatment of (a*S*)-**1c** (1.03 g, 2.93 mmol) and 3-aminopropylsilanized silica gel (3.00 g) in the presence of EEDQ (1.50 g, 6.09 mmol). Analysis: found, C 13.88, H 1.81, N 1.60%; calculated, 0.26 mmol/g gel based on C.

CSP 4. CSP 4 (3.13 g) was similarly prepared as above by the treatment of (a*S*)-**1d** (1.70 g, 4.60 mmol) and 3-aminopropylsilanized silica gel (3.00 g) in the presence of EEDQ (2.50 g, 10.2 mmol). Analysis: found, C 10.56, H 1.41, N 1.53%; calculated, 0.19 mmol/g gel based on C.

CSP 5. CSP 5 (3.58 g) was similarly prepared as above by the treatment of (a*S*)-**1d** (2.00 g, 5.41 mmol) and 11-aminoundecylsilanized silica gel (3.30 g) in the presence of EEDQ (2.50 g, 10.2 mmol). Analysis: found, C 15.96, H 2.47, N 1.28%; calculated, 0.31 mmol/g gel based on C.

CSP 6. CSP 6 (3.46 g) was similarly prepared as above by the treatment of (a*S*)-**1e** (2.00 g, 5.03 mmol) and 11-aminoundecylsilanized silica

gel (3.30 g) in the presence of EEDQ (2.50 g, 10.2 mmol). Analysis: found, C 14.11, H 2.31, N 1.21%; calculated, 0.20 mmol/g gel based on C.

CSP 7. CSP 7 (3.73 g) was prepared according to the method used for the preparation of CSP 1 by using (a*S*)-**1f′** (1.21 g, 3.49 mmol) and 11-aminoundecylsilanized silica gel (3.30 g). Analysis: found, C 19.52, H 1.84, N 0.75%; calculated, 0.55 mmol/g gel based on C.

Preparation of the derivatized enantiomeric analytes

Typical examples of the preparation of the derivatized enantiomeric analytes for the HPLC analysis are as follows.

*N-(3,5-Dinitrobenzoyl)alanine butyl ester (**3a**).* To a solution of alanine (50 mg, 0.56 mmol) in 1 *M* $NaHCO_3$ (5 ml) was added a solution of 3,5-dinitrobenzoyl chloride (258 mg, 1.1 mmol) in THF (2 ml), and then the mixture was stirred at room temperature for 1 h. After the solution had been acidified with 2 *M* HCl, the resulting precipitate was extracted with ethyl acetate and dried over $MgSO_4$. After filtration, the solvent was evaporated *in vacuo* and the residue was treated with butanol containing dry HCl at 100°C for 1 h, and then subjected to TLC to give a sample of **3a**.

*N - (3,5-Dinitrobenzoyl) - 1 - phenylethylamine (**4a**).* 1-Phenylethylamine (20 mg, 0.17 mmol) and triethylamine (20 μl) were added to a solution of 3,5-dinitrobenzoyl chloride (76 mg, 0.33 mmol) in THF (1 ml). After the solution had been stirred at room temperature for 10 min, 3-dimethylaminopropylamine (20 μl) was added to remove excess of acid chloride and then the mixture was subjected to TLC to give a sample of **4a**.

*1-Phenylethyl 3,5-dinitrophenylcarbamate (**5a**).* A solution of 1-phenylethanol (20 mg, 0.16 mmol), 3,5-dinitrophenyl isocyanate (67 mg, 0.32 mmol) and one drop of triethylamine in dioxane (1 ml) was stirred at 100°C for 1 h. To the solution was added 3-dimethylaminopropylamine (20 μl) to remove excess of isocyanate and the mixture was subjected to TLC to give a sample of **5a**.

*2,2′-Bis(butylcarbamoyl)-1,1′-binaphthyl (**6e**).* A mixture of 1,1′-binaphthyl-2,2′-dicarboxylic acid (**1b**) (20 mg, 0.06 mmol) in thionyl chloride (0.5 ml) was stirred at 50°C for 1 h. After the excess of thionyl chloride had been distilled out under reduced pressure, butylamine (0.5 ml) was added. The mixture was stirred at room temperature for 10 min and then subjected to TLC to give a sample of **6e**.

Other biaryls used for the derivatization were those prepared in this laboratory and reported elsewhere [25,26].

RESULTS AND DISCUSSION

The preparation of the CSPs was easily accomplished by treating atropisomerically pure 2′-substituted-1,1′-binaphthyl-2-carboxylic acids (**1b–e**) or acid chlorides (**1a′** and **f′**) with 3-aminopropyl- and/or 11-aminoundecylsilanized silica gel with the aid of a condensing agent, EEDQ or triethylamine, which allowed the covalent bonding of the axially dissymmetric binaphthyl residue to the support via an amide linkage (Scheme 1). From microanalytical results and the increase in mass of the silica gel after bonding the chiral selectors, the contents of the binaphthyl residue of these CSPs were calculated to be in the range 0.19–0.55 mmol/g silica gel. It should be noted that both of the chiral precursors, (a*S*,1*S*)-2′-(N-1-phenylethyl)carbamoyl-1,1′-binaphthyl-2-carboxylic acid (**2**) for the synthesis of CSP 1-CSP 6 (Scheme 2) and (a*S*)-2′-methoxy-1,1′-binaphthyl-2-carboxylic acid (**1f**) for CSP 7, are readily available in substantial amounts as reported previously [23,24]. Treatment of **2** with thionyl chloride gave (a*S*)-2′-cyano-1,1′-binaphthyl-2-carbonyl chloride (**1a′**) (the von Braun reaction), alkaline hydrolysis of which afforded (a*S*)-2′-carbamoyl-1,1′-binaphthyl-2-carboxylic acid (**1c**) or (a*S*)-1,1′-binaphthyl-2,2′-dicarboxylic acid (**1b**), depending on the reaction conditions. Treatment of **1b** with 1,3-dicyclohexylcarbodiimide (DCC) followed by reaction with ethylamine and diethylamine gave (a*S*)-2′-ethylcarbamoyl- (**1d**) and (a*S*)-2′-diethylcarbamoyl-1,1′-binaphthyl-2-carboxylic acid (**1e**), respectively (Scheme 2).

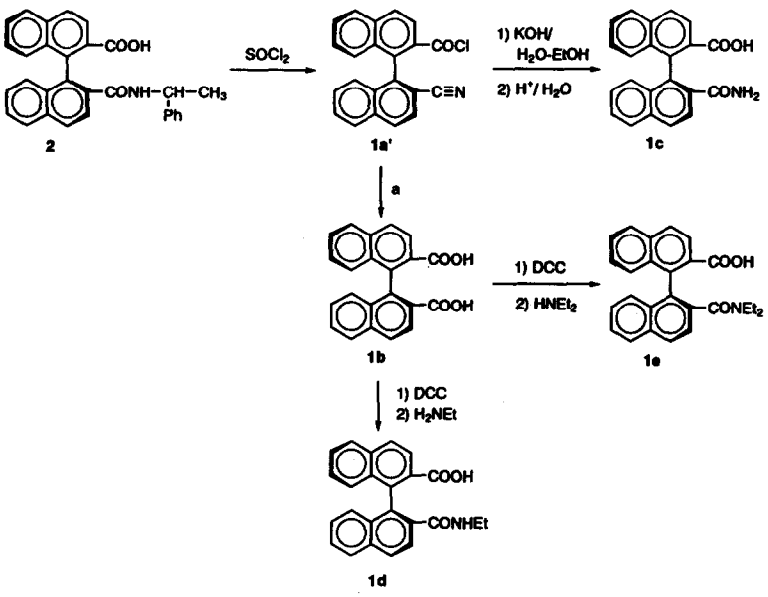
The resulting CSPs were slurry packed into 250 × 4.6 mm I.D. stainless-steel columns by using conventional methods. Enantiomeric sam-

TABLE I

RESOLUTION OF ENANTIOMERIC ANALYTES ON AXIALLY DISSYMMETRIC 1,1'-BINAPHTHYL-BASED CHIRAL STATIONARY PHASES

Mobile phases: hexane–2-propanol, (A) 95:5, (B) 90:10, (C) 85:15 and (D) 80:20. Flow-rate: 1 ml/min. k_1' = Capacity factor for the initially eluted enantiomer. The configuration of the initially eluted enantiomer is indicated in parentheses. The separation factor, α, is the ratio of the capacity factors of the enantiomers.

Compound	CSP 1			CSP 2			CSP 3			CSP 4			CSP 5			CSP 6			CSP 7		
	Eluent	k_1'	α	Eluent	k_1'	α	Eluent	k_1'	α	Eluent	k_1'	α	Eluent	k_1'	α	Eluent	k_1'	α	Eluent	k_1'	α
3a	D	3.82(*S*)	1.08	B	4.58(*S*)	1.13	A	8.24(*S*)	1.13	B	5.18(*S*)	1.03	B	5.60(*S*)	1.04	B	5.69(*S*)	1.03	B	8.58	1.00
3b	D	2.63(*S*)	1.08	B	2.64	1.00	A	4.34(*S*)	1.21	B	3.08(*S*)	1.04	B	3.18(*S*)	1.05	B	3.61	1.00	B	4.41	1.00
3c	D	2.39(*S*)	1.06	B	2.71	1.00	A	4.58(*S*)	1.14	B	3.40(*S*)	1.02	B	3.71(*S*)	1.06	B	3.99	1.00	B	4.73(*R*)	1.04
3d	D	4.88(*R*)	1.18	B	4.27(*R*)	1.15	A	6.63	1.00	B	4.56(*R*)	1.03	B	5.17	1.00	B	5.52	1.00	B	8.17(*R*)	1.27
3e	D	4.93(*S*)	1.11	B	5.20(*S*)	1.14	A	8.20(*S*)	1.22	B	5.61(*S*)	1.12	B	6.87(*S*)	1.17	B	6.60(*S*)	1.07	B	12.29(*S*)	1.09
4a	D	8.24(*S*)	1.17	C	6.55(*S*)	1.17	B	8.41(*S*)	1.06	D	4.46	1.00	D	6.51(*R*)	1.03	D	6.30	1.00	D	10.91(*S*)	1.04
4b	D	13.13	1.09	C	7.90	1.07	B	10.83	1.04	D	5.12	1.04	D	8.09	1.10	D	8.43	1.00	D	14.78	1.10
4c	D	3.49	1.00	B	5.34	1.00	A	10.38	1.00	D	2.14	1.00	D	2.62	1.00	D	3.00	1.00	D	3.84	1.10
5a	D	6.26(*S*)	1.40	C	3.86(*S*)	1.54	B	5.62(*S*)	1.28	D	2.98(*S*)	1.20	D	4.77(*S*)	1.22	D	4.84(*S*)	1.12	D	8.64(*S*)	1.29
5b	D	5.56	1.40	C	3.44	1.53	B	5.03	1.32	D	2.74	1.22	D	4.06	1.24	D	4.37	1.13	D	7.32	1.32
5c	D	5.15	1.35	C	3.33	1.43	B	4.67	1.29	D	2.60	1.21	D	3.76	1.21	D	4.01	1.11	D	7.16	1.22
5d	D	2.25	1.25	B	3.93(*S*)	1.21	A	6.33(*S*)	1.10	D	1.78	1.05	D	2.08	1.06	D	2.45	1.03	D	3.20	1.18
6a	D	4.65	1.00	C	3.41(*S*)	1.09	B	4.37(*S*)	1.05	D	5.29	1.00	D	6.43(*S*)	1.11	D	7.22(*S*)	1.04	D	6.05(*S*)	1.08
6b	B	3.22	1.00	B	1.22	1.00	A	3.03	1.04	A	3.12	1.05	A	3.96	1.00	A	2.29	1.00	B	2.30	1.00
6c	B	1.97	1.00	B	1.46	1.00	A	1.82	1.00	A	1.78	1.00	A	1.98	1.00	A	1.30	1.00	B	1.50	1.00
6d	B	4.96	1.03	B	3.06(*S*)	1.09	A	4.33(*S*)	1.13	A	4.10(*S*)	1.10	A	3.96(*S*)	1.13	A	2.89	1.00	B	2.97	1.00
6e	B	3.82(*S*)	1.17	C	5.41(*S*)	1.38	B	8.30(*S*)	1.47	D	3.03(*S*)	1.29	D	3.34(*S*)	1.35	D	2.30(*S*)	1.11	B	9.79(*S*)	1.24
6f	B	10.13(*R*)	1.14	C	4.58(*R*)	1.21	B	6.52(*R*)	1.31	B	8.40(*R*)	1.19	B	7.29(*R*)	1.18	B	4.88(*R*)	1.09	B	7.25(*R*)	1.23
6g	B	8.63	1.14	C	3.25	1.26	B	4.89	1.34	B	6.96	1.28	B	7.39	1.27	B	5.33	1.10	B	5.80	1.18
6h	B	7.40(*S*)	1.10	C	3.24(*S*)	1.13	B	5.16(*S*)	1.16	B	6.93(*S*)	1.17	B	6.37(*S*)	1.16	B	4.79(*S*)	1.06	B	5.73(*S*)	1.15



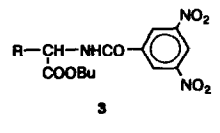
Scheme 2. (a): (1) KOH–aq. EtOH; (2) NaOH–H_2O; (3) H^+/H_2O (see ref. 23).

ples of amino acids and amines as the 3,5-dinitrobenzamides, alcohols as the 3,5-dinitrophenylcarbamates, 1,1′-bi-2-naphthol and biarylcarboxylic acids as the N-butylamides, are summarized in Scheme 3. They were eluted with hexane–2-propanol mixtures, the composition of which was varied to adjust the capacity factor, k', in a comparable range, and Table I lists the chromatographic data. Although the analytes examined are relatively limited, inspection of Table I allows the following comments on the structural factors of CSP 1–CSP 7 and their chromatographic behaviour. These CSPs show appreciable selectivity for many of the analytes with separation factors, α, of up to 1.54. Typical chromatograms are shown in Fig. 1.

The elution order is consistent in that, where the absolute stereochemistry of the samples is known, the *S*-enantiomers are eluted prior to the *R*-counterparts on the CSPs bearing a*S*-axial chirality, only two obvious exceptions being the derivatized leucine **3c** on CSP 7 and the 1-phenylethylamine derivative **4a** on CSP 5. The inconsistency of the elution order of the derivatized phenylglylcine **3d** compared with the other amino acid derivatives (**3a–c** and **e**) may need some comments here. As will be discussed later, the binaphthyl-based CSPs seem to discriminate

Amino acid derivatives:

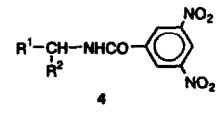
R	3
CH_3 (Alanine)	3a
$CH(CH_3)_2$ (Valine)	3b
$CH_2CH(CH_3)_2$ (Leucine)	3c
Ph (Phenylglycine)	3d
CH_2Ph (Phenylalanine)	3e



3

Amine derivatives:

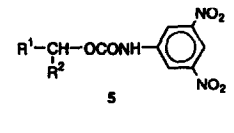
R^1	R^2	4
CH_3	Ph	4a
CH_3	1-Naph	4b
CH_3	$(CH_2)_5CH_3$	4c



4

Alcohol derivatives

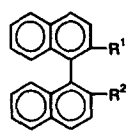
R^1	R^2	5
CH_3	Ph	5a
CH_2CH_3	Ph	5b
$(CH_2)_2CH_3$	Ph	5c
CH_3	$(CH_2)_5CH_3$	5d



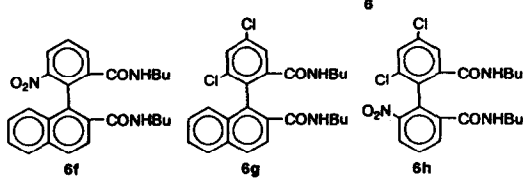
5

Biaryl derivatives

R^1	R^2	6
OH	OH	6a
H	CONHBu	6b
CH_3	CONHBu	6c
OCH_3	CONHBu	6d
CONHBu	CONHBu	6e



6



Scheme 3.

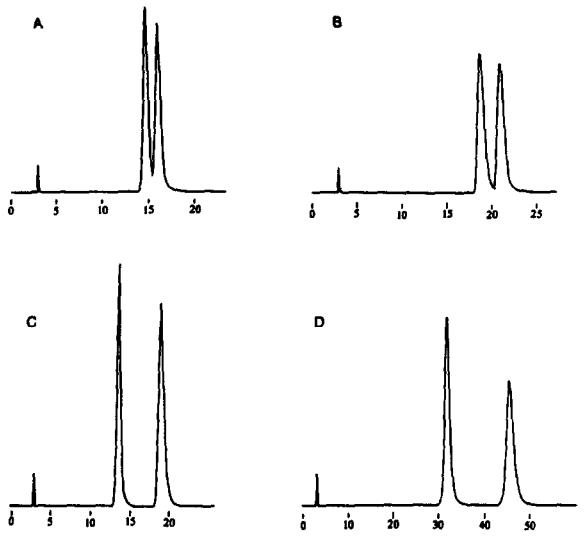


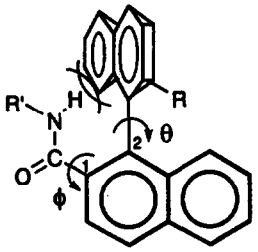
Fig. 1. Chromatographic separation of enantiomers. (A) N-(3,5-Dinitrobenzoyl)alanine butyl ester on CSP 2; (B) N-(3,5-dinitrobenzoyl)-1-phenylethylamine on CSP 2; (C) 1-phenylpropyl 3,5-dinitrophenylcarbamate on CSP 2; (D) 2,2′-bis(butylcarbamoyl)-1,1′-binaphthyl on CSP 3. Chromatographic conditions as in Table I.

a pair of enantiomers by the spatial arrangement of the steric bulk of the three substituents attached to the chiral carbon centre. For the amino acid derivatives **3**, the smallest substituent is hydrogen throughout **3a–e**, and hence the steric repulsion caused by the R or COOBu group on approach to the chiral selectors should be compared. It seems that the CSPs recognize that the effective exclusion size of the sp^2-hybridized COOBu group is larger than the sp^3-hybridized CH_3 (**3a**), $CH(CH_3)_2$ (**3b**), $CH_2CH(CH_3)_2$ (**3c**) and CH_2Ph (**3e**) to elute the *S*-isomers first, but smaller than sp^2-hybridized Ph (**3d**) to elute the *R*-isomer first. The apparent inversion of the elution order of **6f** is because of the inversion of the substituent priority sequence about the substituents on the biaryl residue. In conclusion, it may be said that axial chirality of the binaphthyl chiral selector is the main determinant for the stereoselectivity, almost irrespective of the 2′-substituent.

CSP 4 and 5 have the same chiral binaphthyl residue but connecting arms of different length. Interestingly, the chromatographic behaviours of the two CSPs are similar for different types of analytes, except that the k' values on CSP 5 are slightly larger than those on CSP 4. This may be ascribed in part to a higher loading rate of the chiral selector on CSP 5 than on CSP 4. The insensitivity to the length of the connecting arms seems to stem from the structure of the bulky and rigid binaphthyl selector moiety, implying some clues for the chiral discrimination mechanism (see below).

The most characteristic feature of these chiral phases is the good separability of alcohol enantiomers as the 3,5-dinitrophenylcarbamates, whereas the separations of amino acids and amines as the 3,5-dinitrobenzamides are poor to fair. Roughly, the discriminating abilities of these CPSs for the derivatized aryl carbinols **5a–c** decrease in the order CSP 2 > CSP 1 > CSP 7 > CSP 3 > CSP 5 ≥ CSP 4 > CSP 6, as judged by the α values. This order is nearly in accordance with the reverse of the bulk of the 2′-substituent, suggesting that steric hindrance imposed by the 2′-substituent reduces the chiral discriminating ability. It seems that the presence of protic hydrogen on the 2′-substituent compensates to some extent the repulsive Van der Waals steric effect via hydrogen bonding between the CSP and analyte, as discussed later.

In a control experiment, derivatization of 1-phenylethanol into the phenylcarbamate, in place of the 3,5-dinitrophenylcarbamate (**5a**), dramatically reduced both k' {from 5.62 [eluted with hexane–2-propanol (90:10)] (Table 1) to 2.35 [eluted with hexane–2-propanol (95:5)]} and α (from 1.28 to 1.00) on CSP 3, showing the critical importance of the π-donor–acceptor interaction between the π-basic naphthalene plane of the CSP and the π-acidic 3,5-dinitrophenyl ring of the analyte. In a previous study, (a*S*)-2′-methoxy-1,1′-binaphthyl-2-carboxylic acid (**1f**) was converted into the (*S*)-1-phenylethylamide (**7a**) (Fig. 2) [27]. An X-ray crystal analysis of **7a** showed that the dihedral angle θ between the two naphthalene planes is 97.5°, and that the –CO–NH–CH– atoms are almost on a same plane, the –CO–NH– linkage being an *s-trans* conformation and the dihedral angle ϕ of C_1–C_2–C=O being 52.6°. It has been shown that, for the 1-phenylethyl ester of **1f**, the plane containing the –CO–O–CH– atoms is coplanar



7a ; R = OCH_3, R' = (*S*)-$CH(CH_3)Ph$

7b ; R = CN, COOH, $CONH_2$, CONHEt, $CONEt_2$, OCH_3

R' = $-(CH_2)_n-Si\lessdot$ n = 3, 11

Fig. 2. Schematic view of 2'-substituted-1,1'-binaphthyl-2-carboxylic acid derivatives (7).

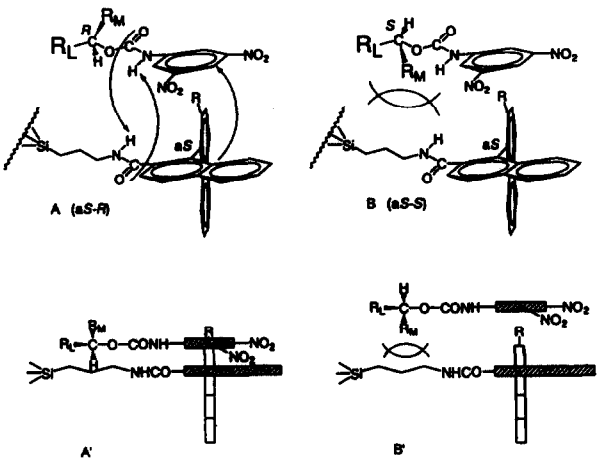


Fig. 3. Chiral discrimination models of alcohol derivatives. (A) Schematic representation of the adsorbate of (*R*)-alcohol derivatives on (a*S*)-CSPs; (A') side view of A; (B) schematic representation of the adsorbate of (*S*)-alcohol derivatives on (a*S*)-CSPs; (B') side view of B.

with the connected naphthalene plane [24], and therefore the deviation of the –CO–NH–CH– plane of **7a** from the coplanarity with the connected naphthalene plane is ascribed to the steric repulsion between the other naphthalene plane and the amide hydrogen, as depicted schematically in Fig. 2. This means that the side of the naphthalene plane against the amide hydrogen is severely blocked by the R' group of **7**, *e.g.*, the 1-phenylethyl moiety in the case of **7a**, which in turn means that the lower side of the –CO–NH–CH– plane is almost completely blocked by the relevant naphthalene ring. Although CSP 1–CSP 7 are carrying the solid silica gel support at the end of the alkyl chain connecting to the amido nitrogen at the 2'-position and conformational changes by dissolution must be taken into account, it may not be unreasonable to assume that the stable conformation of the binaphthyl selectors of the CSPs is similar to that of **7a** (Fig. 2, **7b**).

On the basis of the chromatographic results (Table I) and the X-ray crystal analysis of the model compound (**7a**, Fig. 2), a probable chiral discrimination mechanism for the 3,5-dinitrophenyl-derivatized alcohols by the binaphthyl-based CSPs is as shown in Fig. 3. As stated above, the plane containing the –CO–NH–CH– linkage has open space only above the plane of the connected naphthalene nucleus. Hence the most favourable approach of the analyte towards the chiral selector should occur from the upper side of the horizontal naphthalene plane, as only this approach can provide two cooperative attractive interactions between the CSP and analyte via the dipole stacking interaction and the π-donor–acceptor interaction. The steric hindrance imposed by the 2'-substituent can be substantially avoided by the approach of the analyte from the direction parallel to the –CO–NH–CH– plane, which is tilted several tens of degrees (*ca.* 50°) from the horizontal naphthalene plane. Obviously, the smaller is the R group on the 2'-position, the easier will be the π-donor–acceptor interaction between the 3,5-dinitrophenyl ring and the horizontal naphthalene ring. However, when the R group bears protic hydrogen, the 2'-substituent may be expected to form hydrogen bonds with one of the two nitro groups of the 3,5-dinitrophenyl ring.

Under these circumstances, inspection of the space-filling CPK (Corey–Pauling–Koltun) molecular models indicates that the most bulky substituent R_L linked to the chiral carbon centre of the analyte is most comfortably located by being arranged parallel to the CSP-connecting chain as shown in Fig. 3A' and B' for steric reasons and probably for lipophilic interaction. Comparison of Fig. 3A' and B' clearly indicates

that the carbamate of (*R*)-R_1R_2CHOH should associate more strongly with the CSP of the (a*S*)-binaphthyl axis than that of the (*S*)-alcohol, because in the former carbamate, the smallest ligand, *i.e.*, hydrogen, on the chiral carbon atom is directed toward the alkyl chain of the CSP (Fig. 3A′), whereas in the latter carbamate, the medium ligand R_M must be disposed toward the CSP against increased steric repulsion (Fig. 3B′). The space between the chiral binaphthyl moiety and the silica gel support given by the trimethylene bridge, $-(CH_2)_3-$, seems to be wide enough to accommodate the relevant analyte moiety, rendering the α value almost independent of the length of the connecting arm.

As can be seen from Fig. 3, the 3,5-dinitrophenyl nucleus of the analyte can overlap with the other two sides of the naphthalene planes of the CSP. These π-donor–acceptor interactions will contribute to the retention, but seem to be non-stereoselective because the chiral moiety of the analyte is diposed apart from the sterically effective bulk of the CSP. In this respect, comparison of the chromatographic behaviours of structurally closely related **4a** and **5a** is of interest. Inspection of Table I reveals that the retention of **4a** is always longer than that of **5a** but the relationship of the stereoselectivity is reversed between the two throughout CSP 1–CSP 7. The longer retention of **4a** may be ascribed to the enhanced, non-stereoselective π-donor–acceptor interaction with the CSPs: the π-acidity of **4a** should be significantly stronger than that of **5a**, as the 3,5-dinitrophenyl nucleus of the former bears an electron-withdrawing carbonyl substituent whereas that of the latter bears a highly electron-donating amino substituent. On the other hand, the lower resolution of **4a** on these CSPs may be ascribed to the lack, or at least the reduction, of the cooperative, stereoselective dipole stacking interaction because of the mismatched direction of the amide dipoles of the analyte and the CSP (Fig. 4). The inferior resolution of the other amines and amino acids as the 3,5-dinitrobenzamines may have the same basis, but at present further explanations of the HPLC results in Table I are difficult because of the too many alternatives for plausible CSP–analyte interactions.

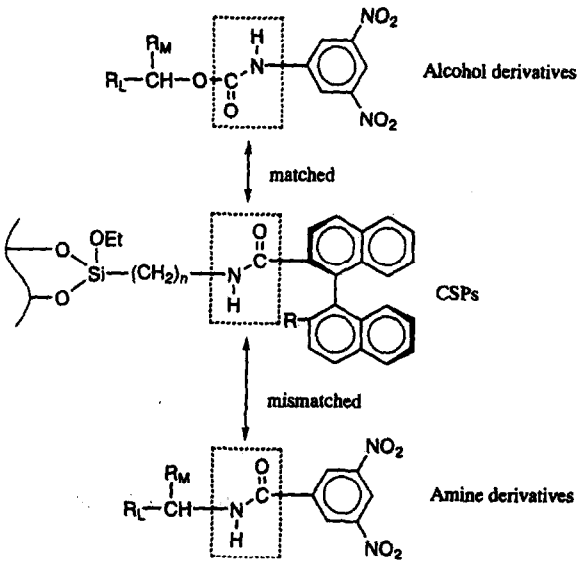


Fig. 4. Matched and mismatched dipole stacking interaction of alcohol and amine derivatives, respectively, on (a*S*)-CSPs.

The chiral discrimination model depicted in Fig. 3 implies that the stronger is the π-donating character of the horizontal naphthalene plane, the better is the separation to be expected. This has been exemplified by the far better chiral discrimination ability of an axially dissymmetric bianthracene-based CSP [28]. Another interesting extension of the model is that the minimum requirement for a CSP to separate enantiomeric alcohols as the 3,5-dinitrophenylcarbamates is a chiral π-donor plane connected to the amide linkage $-CO-NH-(CH_2)_n-Si\equiv$, the soundness of the idea has also been reported in a preliminary communication by preparing a CSP derived from chiral (*S*)-[10]paracyclophane-13-carboxylic acid [14].

A second characteristic feature of the CSPs is their performance with respect to the axially dissymmetric biaryl enantiomers (**6**). It seems that the presence of polar functional groups, such as hydroxyl or carbamoyl, at both of the 2- and 2′-positions in the biaryl analytes is required for chiral discrimination by the CSPs. Thus, the separability of the biaryl analytes **6** is in the order of 2,2′-bis(butylcarbamoyl)biaryls (**6e–h**) followed by 2′-methoxy-2-butylcarbamoyl-1,1′-binaphthyl (**6d**) and then 1,1′-bi-2-naphthol (**6a**).

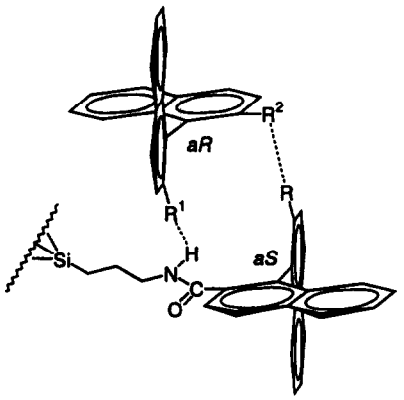
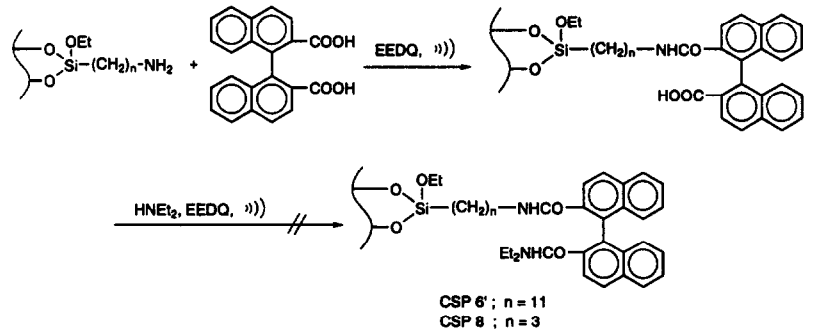


Fig. 5. Chiral discrimination model of (a*R*)-biaryls on (a*S*)-CSPs.

2-Butylcarbamoyl-1,1′-binaphthyl (**6b**) is only partially separable on CSP 3 and CSP 5, but the 2′-methyl analogue (**6c**) shows no indication of separation on these CSPs. The separation of **6e** is a typical example of the discrimination of the biaryl analytes **6** by the biaryl-based CSPs; the separability of **6e** decreases in the order CSP 3 > CSP 2 > CSP 5 > CSP 4 > CSP 7 > CSP 1 > CSP 6. This seems to imply that the hydrogen-bonding ability of the 2′-substituent of the binaphthyl selector is more important than the steric size for the resolution of the biaryl analytes. Fig. 5 shows a probable model for the more retained biaryl analyte, where the hydrogen bonding between the 2,2′-substituents on both the CSP and the heterochiral analyte plays a critical role. A similar chiral discrimination model of 1,1′-bi-2-naphthol on a CSP derived from *trans*-1,2-diaminocyclohexane has been proposed [29].

Considering the above resolution results for the CSPs for both the C-centrochiral and the axially chiral analytes (Table I), a carboxyl function should be the substituent of choice for the 2′-position (CSP 2), because it is small in size and bears protic hydrogen for hydrogen bonding. On the other hand, CSP 6 is the least effective because the 2′-diethylcarbamoyl group is the largest in bulk and bears no protic hydrogen. In this regard, we previously claimed the preparation of the CSPs (CSP 6′ and CSP 8 in Scheme 4) which had a 2′-diethylcarbamoyl substituent on the binaphthyl moiety. The performance of these CSPs, however, was far different from that of CSP 6 prepared in this work, which definitely bears a 2′-diethylcarbamoyl substituent. They were, on the other hand, similar to that of CSP 2, indicating that CSP 6′ and CSP 8 had, in fact, a free 2′-carboxyl rather than a 2′-diethylcarbamoyl substituent. It should be considered that the treatment of the binaphthyl-modified silica with diethylamine in the presence of EEDQ retained the 2′-carboxyl group almost intact because of the steric congestion (Scheme 4), and the previously reported structures of CSP 6′ and CSP 8 must be revised to those bearing 2′-carboxyl function.

In conclusion, we have reported here that an efficient and stable CSP for the separation of a wide range of enantiomers by HPLC is readily prepared by bonding axially dissymmetric 1,1′-binaphthyl-2,2′-dicarboxylic acid (**1b**) to 3-aminopropylsilanized silica gel [30].



Scheme 4.

ACKNOWLEDGEMENTS

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