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Design and Synthesis of Chiral Stationary Phase Derived from (*S*)-[10]Paracyclophane-13-carboxylic Acid for the HPLC Separation of Enantiomers

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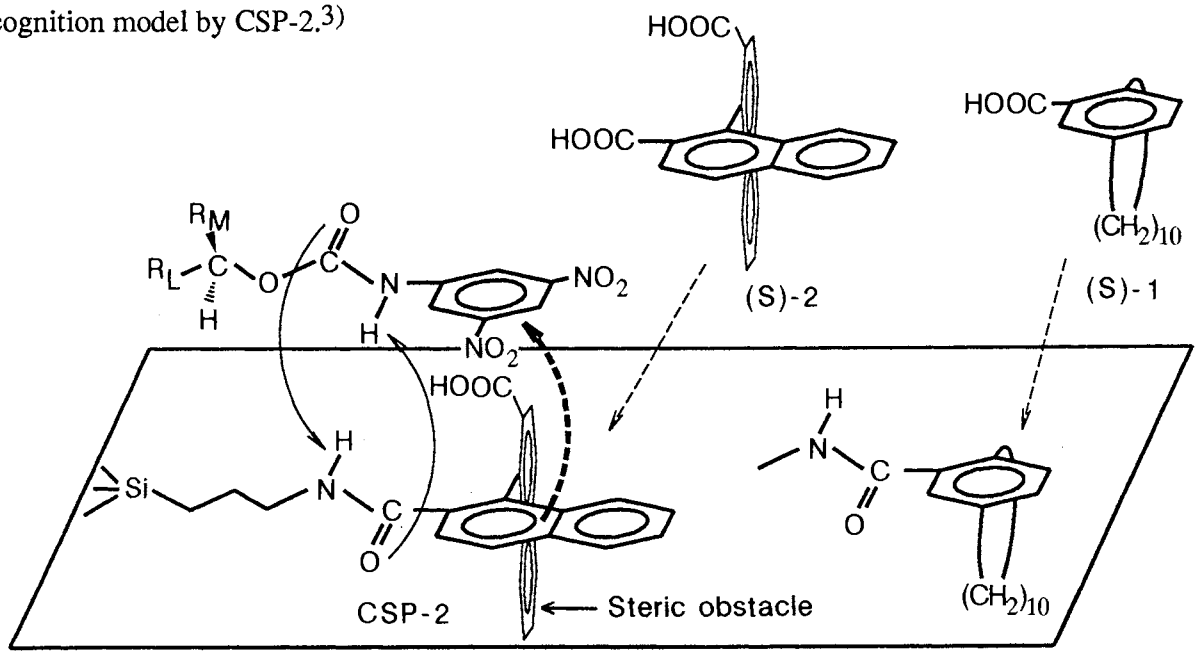
Homochiral (*S*)-[10]paracyclophane-13-carboxylic acid ((*S*)-**1**) could conveniently be obtained on a preparative scale via fractional crystallization of the (*S*)-1-phenylethylamide diastereomers. (*S*)-**1** was used for the first time as a stereodifferentiating element with planar chirality for a new chiral stationary phase (CSP) for HPLC. The CSP, which was prepared by bonding (*S*)-**1** to γ-aminopropylsilanized silica gel via amide linkage, recognized a wide range of enantiomers by HPLC.

A variety of CSPs have been developed for direct separation of enantiomers by HPLC; C-centro-chirality of amines, amino acids and the like, and helical structure of chiral polymers have been utilized as chirality recognizing element.[1] In a previous paper we have described that a chiral stationary phase (CSP-2) derived from axially chiral 1,1'-binaphthalene-2,2'-dicarboxylic acid (*S*)-**2** efficiently differentiates enantiomeric alcohols as 3,5-dinitrophenylcarbamates,[2] and also propose a chiral recognition model by CSP-2.[3]

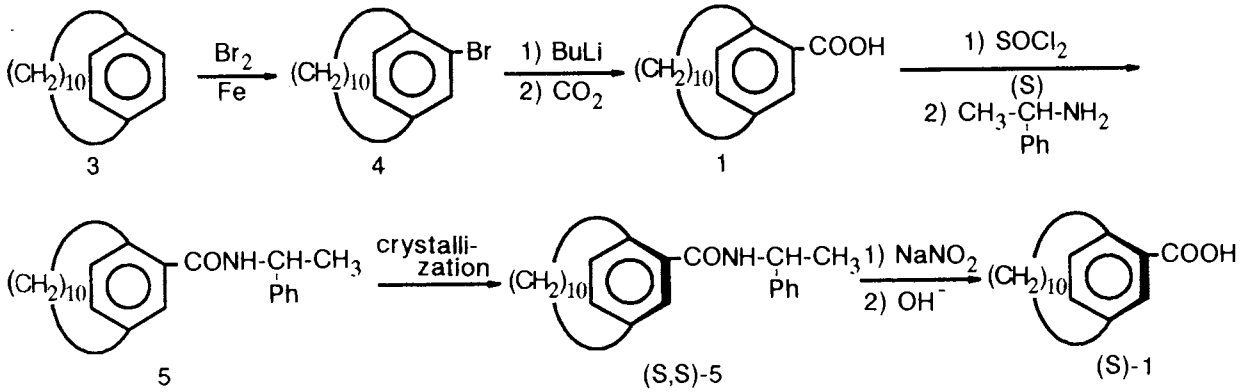


Scheme 1.

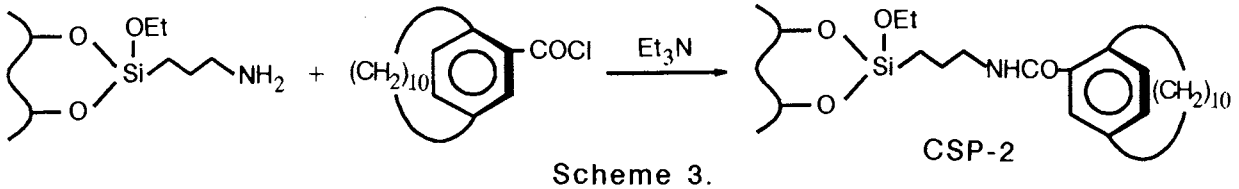
In this model, as is shown in Scheme 1, the solute interacts with CSP-2 with π-π interaction between the 3,5-dinitrophenyl ring and the relevant naphthalene ring, and the dipole-stacking interaction between the amide bond and the urethane bond, with the steric obstacle imposed by the other naphthalene ring of the (*S*)-binaphthyl unit forcing the solute to approach to the CSP-2 only from the upper side. This model suggests that the necessities for the chiral recognition of the enantiomeric 3,5-dinitrophenyl carbamates are an aromatic plane to donate π-electrons to the 3,5-dinitrophenyl ring, an amide bond for dipole stacking interaction with the urethane bond, and an obstacle to shield one side of the aromatic plane from the approach of the solute. Thus, it occurred to us that a planar chiral paracyclophane-carboxylic acid is one of the promising candidates for the CSP, because it has the π-plane shielded on one side and carboxylic function for introduction of the amide linkage.

Herein we wish to report that our expectation was realized by the fact that the silica gel stationary phase chirally modified with atropisomeric **1** via amide bond (CSP-1) showed discrimination for a wide range of enantiomers such as 3,5-dinitrophenyl derivatives of amino acids, amines, alcohols, and carboxylic acids, and biaryls.

Optically active **1** was prepared as follows (Scheme 2). [10]Paracyclophane (**3**)[4] was brominated by bromine to give 13-bromide (**4**), which was lithiated by butyllithium and then treated with carbon dioxide to give 13-carboxylic acid (**1**) in 47% yield based on **4**. Treatment of **1** with thionyl chloride gave the acid chloride, which in turn allowed to react with (*S*)-1-phenylethylamine to give the pair of the diastereomeric amides ((*R*,*S*)- and (*S*,*S*)-**5**) in quantitative yield. One crystallization of the amide mixture from acetonitrile gave (*S*,*S*)-**5** in 46% yield based on one of the enantiomers of **1** (>98% d.e. by HPLC on silica-gel column). Nitrosoation[5] followed by alkaline hydrolysis of (*S*,*S*) **5** gave (*S*)-**1**[6] in 88% yield, which was turned out to be almost 100% e.e. by HPLC;[7] $[\alpha]_D^{20}$ -81.4° (c 1.03, $CHCl_3$).



Scheme 2.

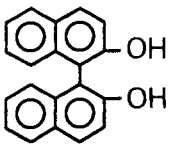
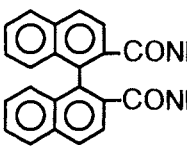


Scheme 3.

CSP-1 was prepared as follows (Scheme 3). To a slurry of an aminopropylsilanized silica-gel in THF were added the acid chloride of (*S*)-**1** and triethylamine. The slurry was irradiated with ultrasound for 8h at 70°C. The modified silica-gel was collected and washed (THF, methanol, acetone, and ether) and then dried under reduced pressure to afford CSP-1 (paracyclophane-residue content, 0.48 mmol/g gel). The CSP-1 was then slurry packed to a stainless-steel column (250 mm long, 4.6 mm i.d.) using conventional techniques. Samples of racemic amino acids, amines, alcohols, and carboxylic acids were converted into 3,5-dinitrophenyl derivatives (Table 1). Hexane-2-propanol mixture was used as eluent and solutes were detected by ultraviolet detector at 254 nm.

Results of the HPLC separation of the enantiomeric derivatives on CSP-1 are summarized in Table 1. This new chiral stationary phase showed appreciable differentiation for the above enantiomeric 3,5-dinitrophenyl derivatives with separation factor (α) up to ca. 1.1. The solutes which had aromatic group attaching to the asymmetric carbon tended to be separated better than those without aryl ring, but in case of amine derivatives, the reverse tendency was found in that only 2-octylamine derivative was separated. Figure 1 shows chromatograms of 3,5-dinitrophenyl derivatives of 1-phenyl-1-cyclohexylmethanol and 2-phenylpropionic acid. CSP-1 also differentiated atropisomeric 1,1'-binaphthyl compounds having polar functional groups, such as hydroxyl and amide, on 2,2'-position with separation factor of ca. 1.1.

Table 1. HPLC separation of derivatives of enantiomers on CSP-1

R_1	R_2	Eluent[a]	k_1'[b]	α
Amino acid derivatives[c]				
CH_3 (Ala)		A	6.50(*S*)	1.05
iso-C_4H_9 (Leu)		A	2.34(*S*)	1.10
CH_2Ph (Phe)		A	3.44(*S*)	1.13
Amine derivatives[d]				
CH_3	n-C_6H_{13}	B	3.65	1.11
CH_3	Ph	D	2.93	1.00
CH_3	1-Naph	D	2.79	1.00
Alcohol derivatives[e]				
CH_3	n-C_8H_{17}	B	3.36	1.06
CH_3	Ph	C	4.91(*S*)	1.04
cyclohexyl	Ph	C	3.76(*S*)	1.10
Carboxylic acid derivatives[f]				
CH_3	n-C_8H_{17}	C	5.81	1.04
CH_3	Ph	D	5.65	1.11
cyclohexyl	Ph	D	4.14	1.15
Binaphthyls				
		B	3.23	1.11
		C	2.82(*S*)	1.10

a) Hexane-2-PrOH (A: 99:1, B: 98:2, C: 97:3, D: 95:5), 1 ml/min. b) Capacity factor of first eluting enantiomer. c) $R_1CH(COOBu)$-NHCO-3,5-NO_2-C_6H_3 d) R_1CHR_2-NHCO-3,5-NO_2-C_6H_3 e) R_1CHR_2-OCONH-3,5-NO_2-C_6H_3 f) R_1CHR_2-CONH-3,5-NO_2-C_6H_3

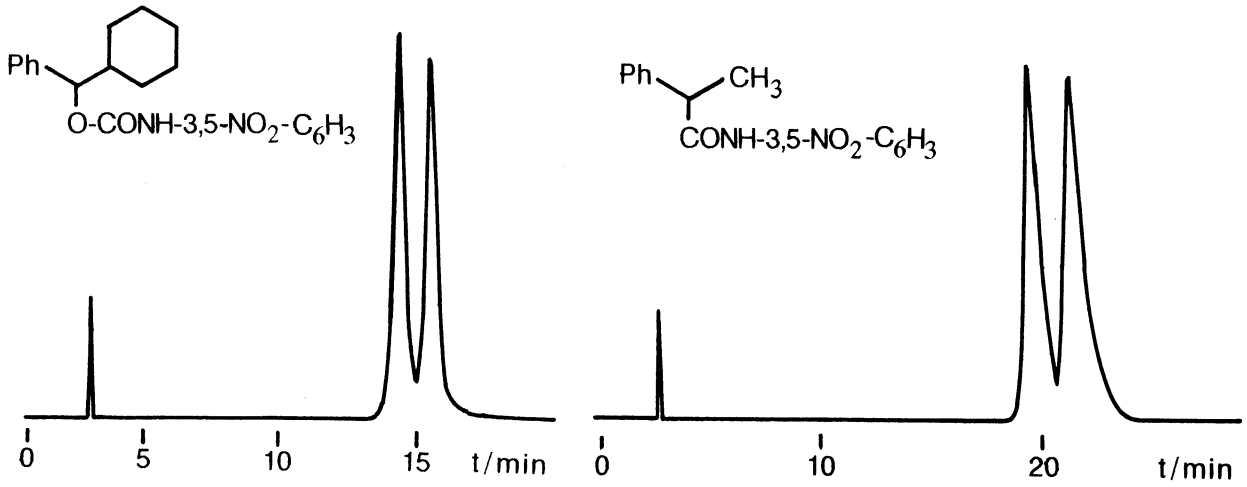


Fig. 1. Resolution of 3,5-dinitrophenyl derivatives of 1-phenyl-1-cyclohexylmethanol and 2-phenylpropionic acid.

The elution order of the typical solutes is suggestive; (*S*)-enantiomers eluted first for amino acids, alcohols, and biaryls, while (*R*)-enantiomers eluted first for carboxylic acids. These elution orders were consistent with those obtained on CSP-2 comprised of (*S*)-1,1'-binaphthyl-2,2'-dicarboxylic acid. This fact suggests that the chiral recognition mechanism by CSP-1 is essentially similar to that by CSP-2, as is depicted in Scheme 1. The inferior donating ability of the phenyl ring of CSP-1 as compared with naphthyl ring of CSP-2 may explain the lower discrimination ability of the former CSP than the latter.

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4) T. Otsubo and S. Misumi, *Synth. Commun.*, **8**, 285 (1978).
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6) The absolute configuration was determined by X-ray crystalography: S. Ôi, N. Harada, H. Uda, A. Okamura, and S. Miyano, to be published.
7) The acid was converted to *N*-butylamide and subjected to HPLC using *N*-3,5-dinitrobenzoyl-D-phenylglicine bonded to silica-gel as a chiral stationary phase (hexane-2-propanol (3%)).

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