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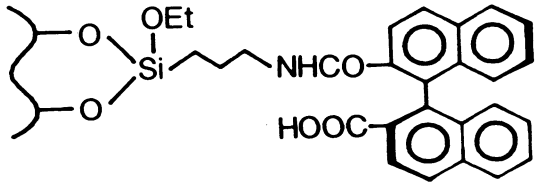
HPLC Separation of Enantiomers on a Chiral Stationary Phase Containing 1,1'-Bianthracene-2,2'-dicarboxylic Acid Bonded to Silica Gel

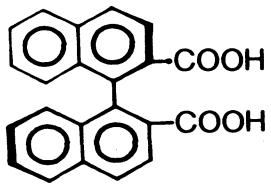
Shuichi ÔI, Masayuki SHIJO, and Sotaro MIYANO*
Department of Biochemistry and Engineering, Faculty of Engineering,
Tohoku University, Aramaki-Aoba, Aoba-ku, Sendai 980

A chiral stationaly phase (CSP) comprised of axially chiral 1,1'-bianthracene-2,2'-dicarboxylic acid chemically bonded to aminopropylsilanized silica gel was prepared for HPLC separation of enantiomers. This phase showed far better discrimination for a wide range of aromatic and aliphatic alcohols and diols as 3,5-dinitrophenylcarbamates than that which was prepared from 1,1'-binaphthalene-2,2'-dicarboxylic acid.

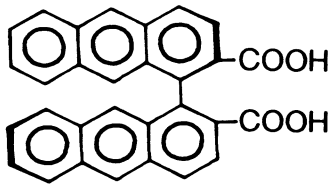
A variety of CSPs have been developed for direct separation of enantiomers by HPLC; C-centro chirality of amines, amino acids and the like, and herical structure of chiral polymers have been utilized as chirality recognizing element.[1] Although it is well documented that axially chiral 1,1'-binaphthalenes are excellent chiral auxiliaries in various asymmetric reactions,[2] there have been only a handful of reports in which those atropisomers are utilized for CSPs.[3,4] Recently, we reported efficient differentiation of enantiomeric alcohols as 3,5-dinitrophenylcarbamates by use of CSP-1, which was comprised of 3-aminopropylsilanized silica gel modified with axially chiral 1,1-binaphthalene-2,2'-dicarboxylic acid.[5,6]



CSP-1



(R)-1



(R)-2

By the use of CSP-1 which contained (R)-axially chiral binaphthalene structure, the carbamates from (R)-R_1R_2CH-OH consistently eluted faster than those from (S)-alcohols. The separation factors (α)[7] increased with the increase of the difference of the steric bulks between R_1 and R_2. From these chromatographic data, we devised a chiral recognition model by CSP-1 which is schematically shown in Fig. 1: When the solute 3,5-dinitrophenylcarbamate interacts with the CSP, the π-π interaction between the 3,5-dinitrophenyl ring and the relevant naphthalene ring (denoted as (a) in Fig. 1), and the dipole-stacking interaction between the

amide bond and the urethane bond (b) seem to play a critical role. Steric obstacle imposed by the other naphthalene ring (c) of the (R)-binaphthyl unit forces the solute to approach to the CSP only from the upper side. Thus, the carbamate from (S)-R_1R_2CH-OH should associate more strongly with the CSP than those of (R)-alcohols, because in the former carbamates, the smallest ligand, i.e. hydrogen, on the chiral carbon directs toward the alkyl chain of the CSP (d) (Fig. 1), while in the latter carbamates, the medium ligand R_M is disposed toward the CSP. The model depicted in Fig. 1 suggests that axially chiral 1,1'-bianthracene-2,2'-dicarboxylic acid (2) should be a far better chiral element than 1, because not only steric obstacle depicted (c) but also the π-donating ability would become more effective in case of 2 than 1.

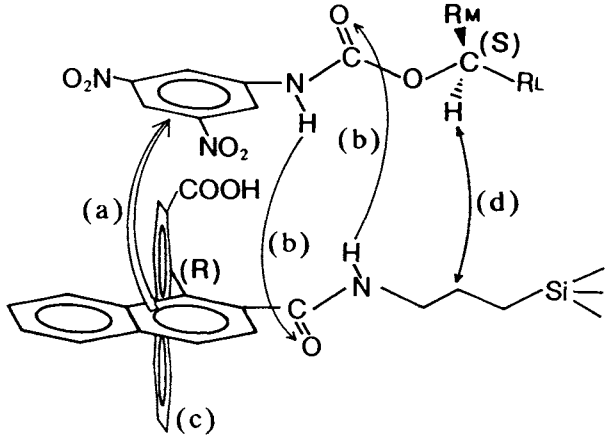
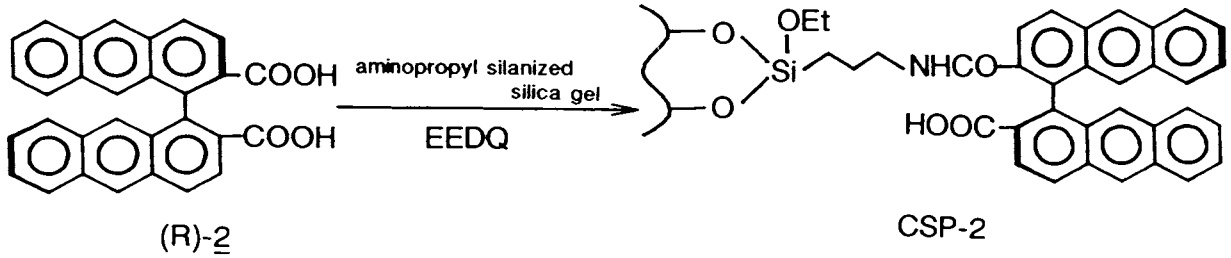


Fig. 1. Chiral recognition model by CSP-1.

Herein we wish to report that our expectation was realized by the fact that the silica gel stationary phase chirally modified with atropisomeric 2 (CSP-2) showed excellent discrimination for a wide range of enantiomeric alcohols and diols as 3,5-dinitrophenylcarbamates.

The CSP-2 was prepared as follows (Scheme 1). To a slurry of an aminopropylsilanized silica gel in DMF which contained 1.01 mmol $-NH_2$/g silica were added optically pure (R)-2[8] (ca. 0.7 equiv.) and N-ethoxycarbonyl-2-ethoxy-1,3-dihydroquinoline (EEDQ, 1.4 equiv. of 2). The slurry was irradiated with ultrasound for 8 h at 25 °C. The modified silica gel was collected and washed (THF, methanol, acetone and ether) and then dried under reduced pressure to afford CSP-2 (bianthryl-residue content, 0.26 mmol/g gel).



(R)-2 CSP-2

Scheme 1.

The CSP-2 was then slurry packed to a stainless-steel column (250 mm long, 4.6 mm i.d.) using conventional techniques. Samples of racemic alcohols (ca. 20 mg) were treated with an excess of 3,5-dinitrophenyl isocyanate in the presence of triethylamine in dioxane for 1 h at 100 °C to form the corresponding carbamates, which were separated by TLC and then subjected to the HPLC analysis. These solutes were detected by ultraviolet detector at 254 nm.

Results of the HPLC separation of the carbamates of alcohols and diols on

CSP-2 are summarized in Table 1. In the series of straight chain aliphatic alcohols (R_1R_2CH-OH), the most simple 2-butanol could be separated well (run 1, Fig. 2),[9] and the separation factor (α) became larger with the increase of the difference of the lengths between the alkyl groups R_1 and R_2 (runs 1 - 4). CSP-2 differentiated structually different R_1 and R_2 of even the same carbon number (runs 5, 6). Aryl alkyl carbinols (R_1 = Ar) were nicely separated with separation factor (α) > 2, while it declined with the bulk of the alkyl group R_2 becoming larger (runs 7 - 11). Even β-chiral alcohols containing phenyl residue could be differentiated (runs 15, 16). All the carbamates of 1,2-diols ($RCH(OH)CH_2OH$) examined were separated well, the α increasing with the chain length of the alkyl substituent (runs 17 - 20), and among the 1,2-diols the best separation was achieved in 1-phenyl-1,2-ethanediol (run 20).

Table 1. HPLC separation of carbamates of enantiomeric alcohols and diols[a]

Run	Compound	α / Mobile phase[c]	Config.[b]	Run	Compound	α / Mobile phase[c]	Config.[b]
1	CH_3-CH(OY)-C_2H_5	1.13 / A		11	CH_3-CH(OY)-(2-Naph)	3.10 / B	
2	CH_3-CH(OY)-n-C_3H_7	1.20 / A	(R)	12	Ph-CH(OY)-(2-Naph)	1.28 / B	
3	CH_3-CH(OY)-n-C_6H_{13}	1.56 / A	(R)	13	CH_3-CH(OY)-CH_2Ph	1.59 / B	(R)
4	CH_3-CH(OY)-n-C_8H_{17}	1.72 / A		14	C_2H_5-CH(OY)-CH_2Ph	1.49 / B	
5	n-C_3H_7-CH(OY)-i-C_3H_7	1.05 / A		15	CH_3-CH(CH_2OY)-Ph	1.13 / B	
6	n-C_4H_9-CH(OY)-i-C_4H_9	1.27 / A		16	C_2H_5-CH(CH_2OY)-Ph	1.22 / B	(S)
7	CH_3-CH(OY)-Ph	2.31 / B	(R)	17	C_2H_5-CH(OY)-CH_2(OY)	1.27 / C	
8	n-C_3H_7-CH(OY)-Ph	2.04 / B		18	n-C_4H_9-CH(OY)-CH_2(OY)	1.55 / C	
9	i-C_3H_7-CH(OY)-Ph	2.16 / B		19	n-C_6H_{13}-CH(OY)-CH_2(OY)	1.80 / C	(S)
10	cyclohexyl-CH(OY)-Ph	1.99 / B	(R)	20	Ph-CH(OY)-CH_2(OY)	2.73 / C	(S)

a) Y = -CONH-3,5-dinitrophenyl. b) First eluting enantiomer. c) A: hexane-i-PrOH (8:2), B: hexane-EtOH (8:2), C: hexane-EtOH-MeOH (7:1:2), 1 ml/min.

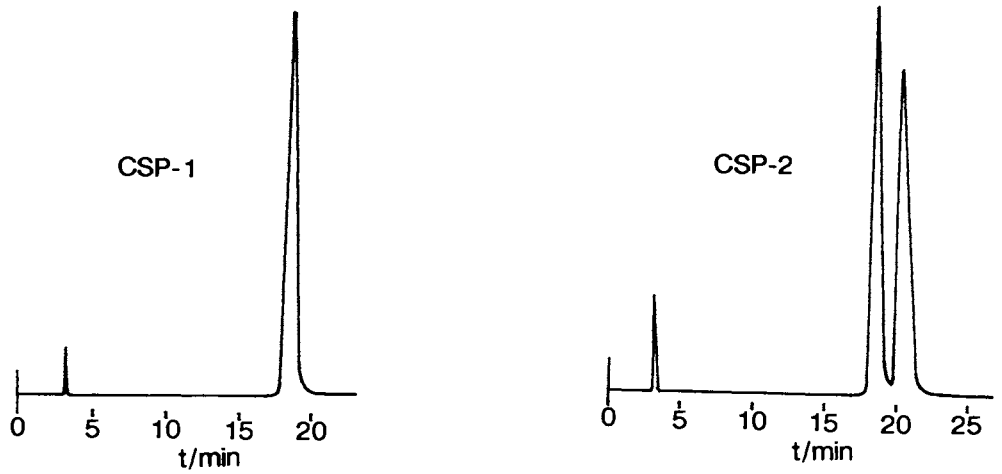


Fig. 2. Resolution of (RS)-2-butanol as the carbamate by CSP-1 and CSP-2 (CSP-1: hexane-i-PrOH (9:1), CSP-2: hexane-i-PrOH (8:2), 1 ml/min).

As was stated before, the CSP-2 showed identical elution order for a pair of carbamates from enantiomeric alcohols or 1,2-diols with that of CSP-1, but with far better discriminating ability in case of CSP-2 (see Fig. 2). These facts strongly suggest that the mode of chiral recognition by CSP-2 is similar to that by CSP-1 which is schematically shown in Fig. 1.

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5) S. Ôi, M. Shijo, J. Yamashita, and S. Miyano, Chem. Lett., 1988, 1545.
6) We have prepared the CSP-1s from both (S)- and (R)-1, and in previous paper,[5] results were reported on the separation of enantiomeric carbamates by use of CSP-1 prepared from (S)-1.
7) Separation factor is defined as the ratio of the capacity factors of the both eluting enantiomers.
8) Prepared by the literature method, $[\alpha]_{546}^{20}$ -435.6° (c 0.84, acetone); F. Bell, D. H. Waring, J. Chem. Soc., 1949, 1579.
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