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Journal of Chromatography A, 757 (1997) 73–79

JOURNAL OF CHROMATOGRAPHY A

Enantiomeric separation of diols and β-amino alcohols by chiral stationary phase derived from (*R*,*R*)-tartramide

Yoshio Machida*, Hiroyuki Nishi, Kouji Nakamura, Hideo Nakai, Tadashi Sato

Analytical Research Laboratory, Tanabe Seiyaku Co., Ltd., 16-89, Kashima 3-chome, Yodogawa-ku, Osaka 532, Japan

Received 14 May 1996; revised 11 July 1996; accepted 23 July 1996

Abstract

A novel chiral stationary phase (CSP) having a (*R*,*R*)-tartramide derivative as a chiral moiety was synthesized. This CSP showed good chiral recognition for 1,2-diols, bi-β-naphthol and β-amino alcohols (β-blockers) without any derivatization. The driving force of enantiomeric separation was assumed to be the dual hydrogen-bonding association and $\pi-\pi$ interaction between the solute enantiomers and the chiral moiety of CSP.

Keywords: Enantiomer separation; Chiral stationary phases, LC; Diols; β-Amino alcohols

1. Introduction

The preparation of enantiomerically active compounds has become very important in many branches of chemistry. For a long time the major source of optically active compounds was nature. In the last few decades, numerous synthetic strategies and methods have been developed to prepare an increasing number of optically active building blocks, or chiral auxiliary reagents. Many approaches have been made on the basis of optically active catalysts that transfer their chiral information during the creation step of new centers of chirality. Therefore, the recognition of molecular chirality is a subject of great interest because of the need to determine enantiomeric compositions and absolute configurations of enantiomers. Chromatographic techniques, especially high-performance liquid chromatography (HPLC), have been used extensively to achieve enantiomer separation. There are principally three ways to perform enantiomer separation. The first is to use the formation of diastereoisomers by using optically active reagents, which are separated on an achiral column. The second is to use chiral mobile phase additives and the last uses chiral stationary phases (CSPs). Various kinds of CSPs, based on amino acid derivatives [1–3], cellulose [4], cyclodextrins [5], ovomucoid [6], bovine serum albumin [7], antibiotics [8–10] and crown ether [11], have been developed and applied to direct resolution of enantiomers. We have been investigating the enantiomeric separation by CSPs [12–15] having a (*R*,*R*)-tartramide moiety. Dual hydrogen-bonding between the solute enantiomers and the tartramide moiety of CSP seems to be essential for chiral recognition [13–15]. The separation of broad categories of enantiomers has been achieved using the CSP derived from (*R*,*R*)-tartramide [12]. There is, however, still a need to expand the scope of chiral recognition due to the lack of CSPs that are capable of resolving all enantiomers. In this work, we designed and prepared a novel CSP derived from (*R*,*R*)-tartramide,

* Corresponding author.

0021-9673/97/$17.00
PII S0021-9673(96)00658-9

in which the isopropyl moiety in the previous CSP [12] was replaced by a *p*-chlorophenyl moiety. The novel CSP was applied to the enantiomeric separation of 1,2-diols and β-blocker and we expected an additional function through π–π interaction.

2. Experimental

2.1. General

The HPLC system consisted of a LC-5A high-pressure pump and a SPD-6A variable-wavelength UV detector (Shimadzu, Kyoto, Japan), operating at 254 nm. Samples were applied to the column with a Rheodyne Model 7125 injector equipped with a 50-μl sample loop. Peak integration was carried out with a Shimadzu Chromatopac C-R5A data processor. IR spectra were measured on a Shimadzu FTIR-8100M spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AC-200 instrument at 200 MHz in the ^{2}H lock mode, with tetramethylsilane as an internal standard. Optical rotations were measured on a Perkin-Elmer 241 automatic digital polarimeter in a 10-cm cell. Mass spectra were measured on a JEOL JMS-DX-300 with chemical ionization.

2.2. Materials

The solvents used for HPLC were distilled before use. Tetrahydrofuran (THF) was distilled from benzophenone ketyl. 2-Propanol, *n*-hexane, pyridine and dichloromethane were distilled from calcium hydride. Chloroform was distilled from diphosphorus pentoxide. Benzene was distilled from sodium metal. These materials were stored under nitrogen. Other solvents and reagents used were of reagent-grade purity. Water-sensitive reactions were carried out in a nitrogen atmosphere.

2.3. Preparation of the chiral stationary phase

2.3.1. (R,R)-N-p-Chlorophenyldiacetyltartaric acid monoamide (2)

A mixture of (*R,R*)-diacetyltartaric acid anhydride (8.80 g, 40.7 mmol) and *p*-chloroaniline (10.99 g, 86.1 mmol) in dichloromethane (30 ml) was stirred at room temperature for 1 h under an atmosphere of nitrogen. The solvent was removed under reduced pressure. Diethylether (600 ml) was added to the residual oil. The organic layer was washed successively with 5 *M* HCl (200 ml) and a saline solution (200 ml) and was dried (Na_2SO_4) and concentrated under reduced pressure. Recrystallization from a mixture of 2-propanol and *n*-hexane gave 10.26 g (73%) of pure (**2**) as a colorless crystal: mp, 122.2–122.5°C. IR(KBr), 3341, 2977, 1754, 1680, 1595, 1526, 1246 and 1067 cm^{-1}. $[\alpha]_D^{20} = -12.65°$ (1.02 w/v %, ethanol).

^{1}H NMR ($CDCl_3$), δ 2.12 (s, 3 H), 2.24 (s, 3 H), 3.95–4.13 (m, 1 H, (disappeared with ^2H_2O)), 5.69 (d, 1 H, *J*=2.6 Hz), 5.84 (d, 1 H, *J*=2.6 Hz), 7.30 (d, 2 H, *J*=8.9 Hz), 7.47 (d, 2 H, *J*=8.9 Hz) 7.99 (br.s, 1 H (disappeared with ^2H_2O)). High resolution MS, *m/z* 343.0459 (M^+, calculated for $C_{14}H_{14}NO_7Cl$ 343.0494).

2.3.2. (R,R)-N-(p-Chlorophenyl)-N′-(10-undecenyl)-diacetyltartramide (3)

A mixture of N-hydroxy-5-norbornene-2,3-dicarboximide (0.53 g, 2.96 mmol), (**2**) (1.00 g, 2.91 mmol) and 1,3-dicyclohexyl-carbodiimide (0.62 g, 3.00 mmol) in THF (20 ml) was stirred at 0°C for 3 h under an atmosphere of nitrogen. The reaction mixture was added to a mixture of 10-undecenylamine (0.52 g, 3.07 mmol) [7] and triethylamine (0.33 g, 3.26 mmol) in THF (10 ml) at 0°C. After the mixture was stirred at this temperature for 2 h, the reaction mixture was poured into 1.2 *M* HCl (100 ml) and was extracted with ethyl acetate (150 ml×4). The extract was washed with water (150 ml), saline (150 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed on silica gel (Wakogel C-100) with *n*-hexane–ethyl acetate (8:2, v/v) to give 1.11 g (77%) of (**3**) as a white solid; mp, 159.3–1.59.9°C. IR(KBr), 3341, 2977, 1754, 1680, 1595, 1246 and 1067 cm^{-1}. $[\alpha]_D^{20} = -8.78°$ (0.501 w/v %, ethanol). ^{1}H NMR ($CDCl_3$), δ 1.23 (s, 12 H), 1.36–1.45 (m, 2 H), 1.94–2.12 (m, 2 H), 2.14 (s, 3 H), 2.16 (s, 3 H), 3.10–3.35 (m, 2 H), 4.90–5.04 (m, 2 H), 5.70 (d, 1 H, *J*=4.0 Hz), 5.74–5.91 (m, 1 H), 5.77 (d, 1 H, *J*=4.0 Hz), 6.48 (t, 1 H, *J*=6.0 Hz (disappeared with ^2H_2O)), 7.23 (d, 2 H, *J*=8.9 Hz), 7.46 (d, 2 H, *J*=8.9 Hz), 9.28 (s, 1 H, (disappeared with ^2H_2O)).

High resolution MS, *m/z* 494.2086 (M^+, calculated for $C_{25}H_{34}N_2O_6Cl$ 494.2197).

2.3.3. (R,R)-N-[(11-Chlorodimethylsilyl)undecyl]-N′-(p-chlorophenyl)diacetyltartramide (4)

A 2-propanol solution (0.1 ml) of chloroplatinic acid (0.64 mol/l) was added, at room temperature, to a mixture of (**3**) (1.40 g, 2.83 mmol) in chloroform (10 ml). After the mixture was stirred for 5 min, dimethylchlorosilane (5 ml) was added. The mixture was then heated to reflux for 30 min. The solvent and the excess silane were removed in vacuo and the residue was co-evaporated twice with chloroform to afford (**4**) as a slightly brown gum. This material was used in the next step without further purification.

2.3.4. Modified gel (5)

A suspension containing 3.0 g of porous silica (Develosil 100-5, 5 μm 100 Å, Nomura Chemicals, Tokyo) in benzene (20 ml) was concentrated to ca. 15 ml under an atmosphere of nitrogen. To this azeotropically dried mixture was added a solution of (**4**) in pyridine (10 ml), at room temperature. After the mixture was gently stirred for 24 h, the modified gel was collected by filtration and washed successively with chloroform, methanol, acetone and *n*-hexane: IR(KBr), 2932, 2860, 1765, 1667 and 1560 cm^{-1}. On analysis, it was found that C=8.75% and N=0.45%.

2.3.5. Trimethylsilylated gel (6)

(Trimethylsilyl)imidazole (10 ml, Tokyo Kasei) was added to a suspension of modified gel (**5**) (3.44 g) in chloroform (30 ml). After the mixture was refluxed for 12 h under a nitrogen atmosphere, the silica gel was collected by filtration and washed as described in Section 2.3.4. IR(KBr), 2930, 2859, 1765, 1665 and 1561 cm^{-1}. On analysis, it was found that C=9.35% and N=0.43%.

2.3.6. Aminolysis of (6)

To a suspension of modified gel (**6**) (520 mg) in methanol (5 ml) was added 0.6 *M* ammonia in methanol (10 ml), at 0°C. After the mixture was stirred gently for 5 h at the same temperature, the silica gel was collected by filtration and washed with methanol, acetone and *n*-hexane; IR(KBr), 2932, 2861, 1665 and 1561 cm^{-1}. On analysis, it was found that C=8.20% and N=0.49%.

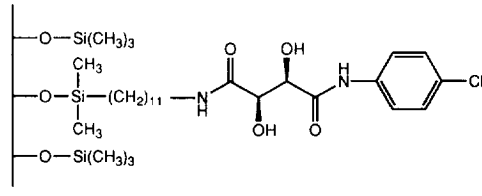
2.4. Chromatographic conditions

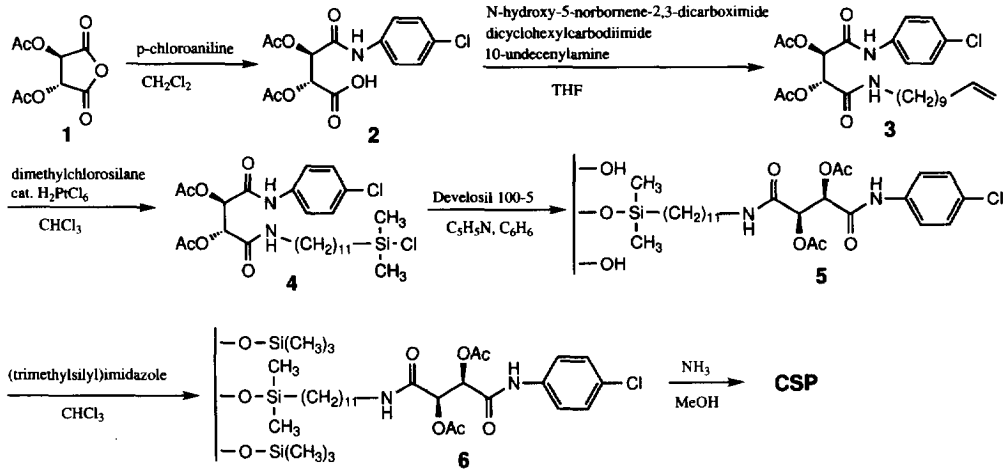
The modified gel (CSP) was slurry-packed in a stainless-steel HPLC column (15×0.2 cm I.D.) in Shinwa Kako Chromato Packings Center. Two columns were connected in series (CSP) and chromatographic runs were performed at a constant flow-rate of 0.2 ml/min and a constant temperature of 25°C. The eluate was detected at 254 nm. The dead time of the column was determined by injection of toluene. Typically, 10 μl of a 1% solution of racemate dissolved in chloroform or the mobile phase used for chromatography were injected.

3. Results and discussion

3.1. Preparation of chiral stationary phase

The CSP was prepared from (*R,R*)-diacetyltartaric acid anhydride, as shown in Scheme 1. The half amide (**2**), readily prepared from (*R,R*)-diacetyltartaric acid anhydride with *p*-chloroaniline (73% yield), was condensed with N-hydroxy-5-norbornene-2,3-dicarboximide and 1,3-dicyclohexylcarbodimide, subjected to aminolysis with 10-undecenylamine in the presence of triethylamine to give olefin derivative (**3**) at a yield of 77%. Hydrosilylation of (**3**) with dimethylchlorosilane in the presence of a catalytic amount of chloroplatinic acid afforded monochlorosilane derivative (**4**). The modified silica gel, (**5**), obtained from the reaction of porous silica gel (Develosil 5 μm) with monochlorosilane derivative (**4**), was found to contain 0.15 mmol/g of tartramide moiety, by elemental analysis of nitrogen. Trimethylsilylation of (**5**) with (trimethylsilyl)imidazole afforded trimethylsilylated silica gel (**6**). Deacetylation of the acetyl groups of (**6**) by 0.6 *M* NH_3 in methanol afforded the CSP.





Scheme 1. Synthesis of a chiral stationary phase derived from (*R*,*R*)-tartramide.

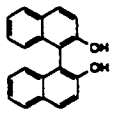
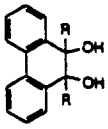
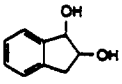
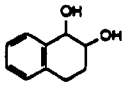
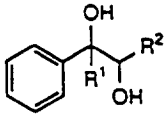
3.2. Enantiomeric separation of aromatic, alicyclic and aliphatic diols

The CSP gave good chiral recognition for aromatic, alicyclic and aliphatic diols. Chromatographic results are summarized in Table 1. The aromatic diol, bi-β-naphthol, was resolved with a separation factor (α) of 1.07 on the CSP (Fig. 1, entry 1). For alicyclic diols, both *trans*-9,10-disubstituted-9,10-dihydrophenanthrene-9,10-diols and indan-1,2-diols were resolved with good separation factors (α, 1.07–1.35). Separation of enantiomers of these solutes is shown in Fig. 2. *trans*-9,10-Dihydrophenanthrene-9,10-diols were resolved with a separation factor of 1.35 (entry 2), although *trans*-9,10-dimethyl (or diethyl)-9,10-dihydrophenanthrene-9,10-diol gave a value of 1.12 (or 1.11) (entries 3 and 4). An increase in steric bulkiness of the alkyl substituent at asymmetric centers of the solutes caused a reduction in the separation factors. *cis*-Indan-1,2-diol afforded a greater separation factor than the corresponding *trans* isomer (entries 5 and 6). Although *trans*-tetralin-1,2-diol was resolved with a separation factor of 1.26, the *cis* isomer was not resolved (entries 7 and 8). Enantioselectivity in this type of CSP is ascribed to the dual hydrogen-bonding association between the solute enantiomers and the tartramide moiety of the CSP. A specific distance between the two hydroxy functions of the enantiomer is presumed to be essential for chiral recognition (although this distance differs for the *cis* and *trans* isomers).

The threo isomers of 2-alkyl-1-phenyl-1,2-ethanediol afforded greater separation factors than the corresponding erythro isomers (entries 10 and 11). In the threo family of 2-alkyl-1-phenyl-1,2-ethanediol, an increase in steric bulkiness of the alkyl substituent at asymmetric centers of the solutes reduced the separation factors (Fig. 3, entries 9, 10, 12 and 13).

In the previous CSP [12], for both alicyclic and aliphatic diols, it was shown that an increase in steric bulkiness of the alkyl substituent at asymmetric centers of the solutes caused enhancement of the separation factors. The opposite enantioselectivity was observed between the previous CSP [12] and the novel CSP. This result suggests that steric interactions between substituents at the asymmetric centers of the solutes and the chiral moiety of the CSP during their association contribute to the generation of differences in the stability of the diastereomeric complexes. Whereas the association mode in the case of the previous CSP [12] is considered to be based on two hydrogen bonds and, therefore, additional steric interactions contribute essentially to the chiral interaction, the newly synthesized CSP provides the third interaction site in the form of the $\pi-\pi$ system and thus makes the above steric interaction totally superfluous.

Table 1
Chromatographic resolution of enantiomers on CSP

Entry	Structure	R^1	R^2		k'	α	R_s	Strong solvent in *n*-hexane (%, v/v)
Aromatic diol								
1					5.53	1.07	1.55	CH_2Cl_2(10)
Alicyclic diol								
2		H		trans	9.46	1.35	3.49	CH_2Cl_2(10), Et_2NH(1)
3		Me		trans	3.08	1.12	2.03	CH_2Cl_2(10), Et_2NH(1)
4		Et		trans	2.14	1.11	1.87	CH_2Cl_2(10), Et_2NH(1)
5				trans	6.97	1.07	1.12	CH_2Cl_2(50)
6				cis	2.70	1.11	1.78	CH_2Cl_2(50)
7				trans	3.35	1.26	3.33	CH_2Cl_2(50)
8				cis	2.27	1.00	–	CH_2Cl_2(50)
Aliphatic diol								
9		H	H		4.91	1.13	1.84	THF(10)
10		H	Me	threo	2.47	1.13	1.91	THF(10)
11		H	Me	erythro	2.61	1.02	0.52	THF(10)
12		H	Ph	threo	1.95	1.05	0.83	THF(10)
13		H	i-Pr	threo	1.34	1.02	0.43	THF(10)
14		Me	H		2.39	1.08	1.06	THF(10)
β-Blocker (β-aminoalcohol)								
15	propranol				3.68	1.05	0.90	CH_2Cl_2(5), Et_2NH(1)
16	methoprolol				3.03	1.04	0.58	CH_2Cl_2(5), Et_2NH(1)
17	bisoprolol				3.68	1.03	0.64	CH_2Cl_2(5), Et_2NH(1)

The mobile phase is described in the table. Flow-rate, 0.2 ml/min. k'=Capacity factor for the first-eluted enantiomer. The separation factor, α, is the ratio of the capacity factors of the enantiomers. R_s (resolution)=2×(distance of the two peak positions)/(sum of the bandwidths of the two peaks).

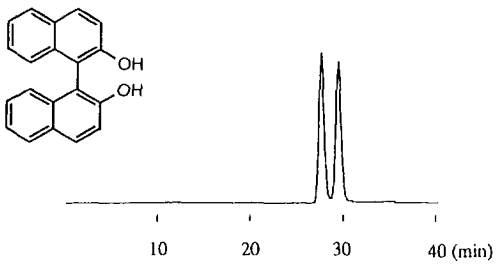


Fig. 1. Enantiomeric resolution of aromatic diol.

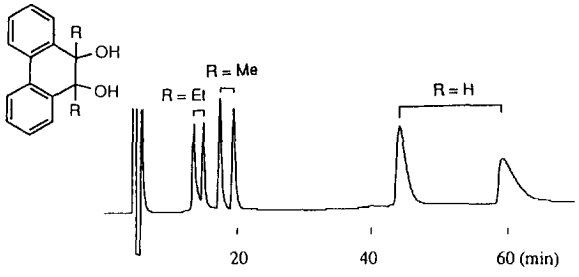


Fig. 2. Enantiomeric resolution of alicyclic diol.

3.3. Enantiomeric separation of β-blockers (β-amino alcohols)

β-Blockers have an amino alcohol structure with a secondary hydroxy and a secondary amine function accessible for derivatization in a molecule. 2-Amino-1,2-diphenylethanol and 2-amino-3-phenyl-1-propanol, as β-amino alcohols, were not resolved on the previous CSP [12]. These β-amino alcohols had to be converted to their urea derivatives through reaction with phenyl isocyanate for successful enantioseparation to take place. However, the newly synthesized CSP was capable of chiral recognition for β-blockers such as propranolol, metoprolol and bisoprolol, with a separation factor of 1.03–1.05 without any derivatization (entries 15, 16 and 17). Enantioselectivity is considered to be due to dual hydrogen-bonding association and $\pi-\pi$ interaction between the solute enantiomers and the tartramide moiety of the CSP.

Furthermore, promethazine hydrochloride and N-3,5-dinitrobenzoyl-1-phenylethylamine were recognised chirally on the novel CSP with a separation factor of 1.03. Replacement of the isopropyl group by the *p*-chlorophenyl group may have contributed to the successful chiral recognition of these solutes.

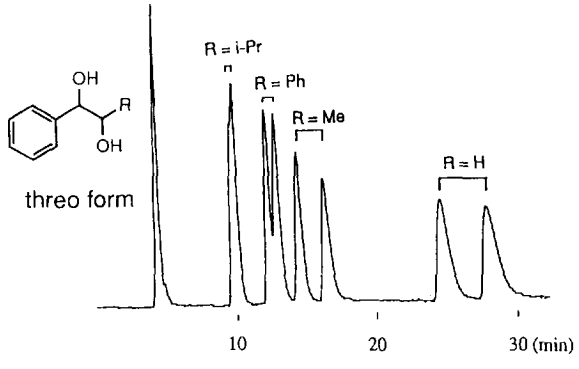


Fig. 3. Enantiomeric resolution of aliphatic diol.

4. Conclusion

The novel CSP gave good chiral recognition for aromatic, alicyclic and aliphatic diols and β-blockers. In particular, the novel CSP showed successful enantiomer separation for some blockers that were not separated directly by the previous CSP [12]. The difference between the previous CSP and the novel CSP is replacement of the isopropyl group with a *p*-chlorophenyl group. There were two systems for chiral recognition of the novel CSP. One was dual hydrogen-bonding between the solute enantiomers and the tartramide moiety of the CSP. The other was $\pi-\pi$ interaction between the solute enantiomers and the *p*-chlorophenyl moiety of the CSP.

Acknowledgments

The authors are grateful to Dr. N. Shirai (Nagoya City University) for measurement of mass spectra. The authors thank Dr. Y. Dobashi (Tokyo College of Pharmacy) for the generous gift of samples of 1,2-diols.

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