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Journal of Chromatography A, 805 (1998) 85–92

JOURNAL OF CHROMATOGRAPHY A

Enantiomer separation of amino compounds by a novel chiral stationary phase derived from crown ether

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Received 29 August 1997; received in revised form 29 December 1997; accepted 5 January 1998

Abstract

A novel chiral stationary phase (CSP-18C6I) was prepared by immobilizing (+)-18-crown-6 tetracarboxylic acid on 3-aminopropylsilanized silica-gel to separate enantiomers of drugs having a primary amino group. The chiral crown ether was combined with 3-aminopropyl silica gel (0.85 mmol of amine per gram of gel) to provide CSP-18C6I having a chiral selector loading of 0.26 mmol per gram of gel. This CSP-18C6I showed good chiral recognition for thirteen out of eighteen DL-amino acids and seven racemic aminoalcohols using a dilute aqueous solution of perchloric acid as the eluent. Afloqualone (a muscle relaxant), primaquine (an antimalarial), and 1-(1-naphthyl)ethylamine (1-NEA) were resolved on the CSP-18C6I. Furthermore, alanine-β-naphthylamide (Ala-β-NA), which is hydrophobic and did not elute within 60 min by the commercially available CROWNPAK CR(+) with 15% methanol and a column temperature of 40°C, was successfully enantioseparated by the novel CSP-18C6I. © 1998 Elsevier Science B.V.

Keywords: Enantiomer separation; Stationary phases, LC; Crown ethers; Amino acids; Amino alcohols; Primary amines

1. Introduction

The separation of enantiomers is a subject of great interest because the antipode of a chiral drug is regarded as one of the impurities from the viewpoint of quality control [1]. One enantiomer sometimes shows high toxicity while another is effective. Recently, chromatographic techniques, especially high-performance liquid chromatography (HPLC) with chiral stationary phases (CSPs), have been extensively used to achieve direct enantiomer separation. Various kinds of CSPs based on amino acid derivatives [2–4], cellulose [5], cyclodextrins [6], ovomucoid [7], bovine serum albumin [8], antibiotics [9–11], and crown ethers [12,13] are commercially available.

Crown ethers, first introduced by Pedersen in 1967 [14,15], are synthesized as cyclic polyethers. Cram and his co-workers reported chromatographic resolution of enantiomers as 'host–guest complexation' by using CSPs attached chiral crown ethers to polystyrene [16] or silica-gel [17]. Optically active crown ethers form complexes enantioselectively with optically active primary amines (in the form of ammonium cations). In 1987, Shinbo and his co-workers [12,13] reported chromatographic separation of underivatized DL-amino acids by using the CSP, where hydrophobic chiral crown ether was dynamically coated on an ODS column. However, in this type of immobilized stationary phase, there is a disadvantage. That is, only aqueous solutions of

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0021-9673/98/$19.00
PII S0021-9673(98)00013-2

inorganic species can be used as the mobile phase. As the crown ether is embedded in the alkyl chain of reversed-phase silica-gels support by the hydrophobic interaction, the passage of methanol-containing solution through the CSP leads to desorption of the coated crown ether from the support.

Our major aim is to separate enantiomeric drugs, which are hydrophobic and have a primary amino group, using HPLC with an aqueous mobile phase. Our attention was attracted to (+)-18-crown-6 tetracarboxylic acid as a chiral moiety, because (+)-18-crown-6 tetracarboxylic acid, which is the only commercially available chiral crown ether, has been successfully employed as a chiral selector for the capillary electrophoresis enantiomer separation [18–23]. In this work, we designed and prepared a novel CSP (CSP-18C6I) immobilized chiral crown ether [(+)-18-crown-6 tetracarboxylic acid]. Then, some characteristics of the CSP-18C6I were investigated, and finally the CSP-18C6I was applied to the enantiomer separation of amino acids, aminoalcohols, afloqualone (a muscle relaxant), primaquine (an antimalarial) and some hydrophobic amino compounds such as Ala-β-NA, which are all primary amines.

2. Experimental

2.1. Apparatus

The HPLC system consisted of an LC-10AD high-pressure pump and an SPD-10A variable-wavelength UV detector (Shimadzu, Kyoto, Japan), operating at 200 nm or 254 nm. Samples were applied to the column with a Rheodyne Model 7725i injector equipped with a 50-μl sample loop. Peak integration was carried out with Shimadzu Chromatopac C-R7A and C-R7A plus data processors. Elemental analysis was performed on a Perkin Elmer PE-240.

2.2. Materials

Solvents and reagents used were of reagent-grade purity. Water-sensitive reactions were carried out in a nitrogen atomosphere. Acetonitrile, methanol, 2-propanol and tetrahydrofuran of HPLC grade, and ethanol and perchloric acid (70%) of analytical reagent grade were purchased from Katayama Kagaku Kogyo (Osaka, Japan). (+)-18-Crown-6 tetracarboxylic acid was purchased from Aldrich Chemicals (Milwaukee, WI, USA). Enantiomers of drugs or compounds tested were amino acids, aminoalcohols, and some other amino compounds. The structures of some of the solutes are shown in Fig. 1. Afloqualone was obtained from Tanabe Seiyaku, (Osaka, Japan), and the others were purchased from Aldrich Chemicals, Katayama Kagaku Kogyo, Nacalai Tesque (Kyoto, Japan), Tokyo Kasei Kogyo (Tokyo, Japan), and Wako Pure Chemicals (Tokyo, Japan).

2.3. Preparation of the chiral stationary phase

2.3.1. Modified gel (1)

A mixture of the 3-aminopropylsilanized silica-gel (1.50 g, Develosil NH_2-10, 10 μm, Nomura Chemical, Tokyo) (found: C=3.00%, H=1.01%, N=1.19%; calculated: 0.85 mmol of amine per gram of gel based on N), (+)-18-crown-6 tetracarboxylic acid (0.66 g, 1.50 mmol) and *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) (0.74 g, 3.00

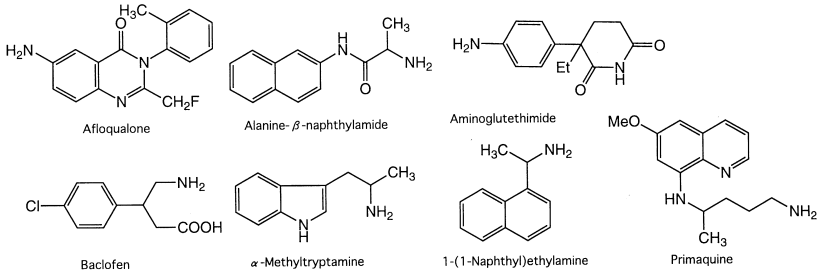


Fig. 1. Structures of some amino compounds.

mmol) in benzene (30 ml) was heated to reflux for 2 h under a nitrogen atomosphere. The silica-gel was collected by filtration and washed successively with tetrahydrofuran, methanol, acetone, and diethyl ether. On analysis, it was found that C=7.97% and N=1.06%. It was also found that the chiral crown ether of 0.26 mmol per gram of gel was introduced from the increase of C%.

2.3.2. Acetylated gel

To a suspension of modified gel(1) (1.50 g) in benzene (30 ml), was added pyridine (5 ml) and acetic anhydride (1 ml), at 0°C. After the mixture was stirred for 2 h at room temperature, the silica-gel (acetylated gel) was collected by filtration and washed successively with tetrahydrofuran, methanol, acetone, and diethyl ether. On analysis, it was found that C=8.31% and N=0.89%.

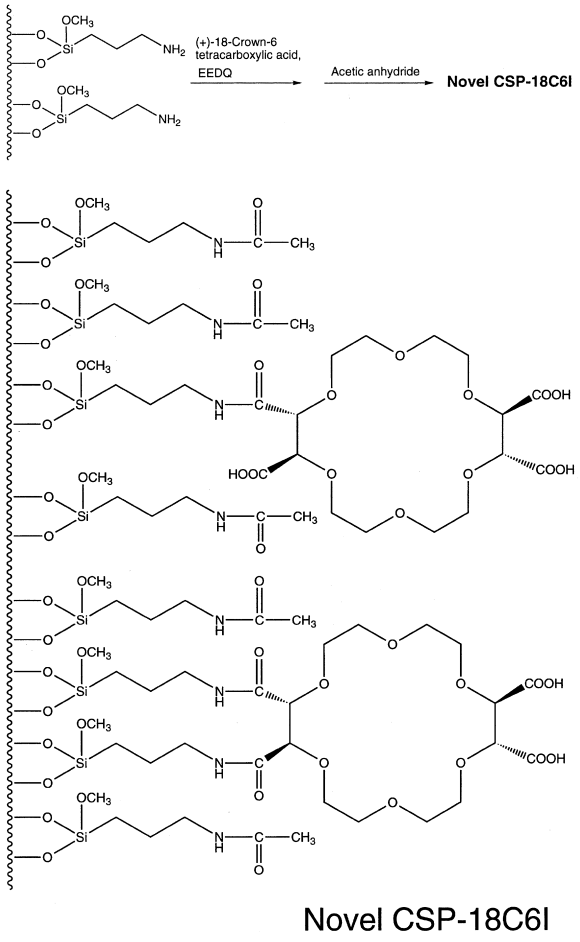
2.4. Chromatographic conditions

The acetylated gel was slurry-packed in a stainless-steel HPLC column (15 cm×0.2 cm I.D.). Two columns, connected in series, were used for the enantiomer separation. Chromatographic runs were performed at a constant flow-rate of 0.3 ml/min and a constant temperature of 25°C except for the investigation of the effect of column temperature. The eluate was detected at 200 nm or 254 nm. Typically, 2 μl of a 1% solution of racemate dissolved in mobile phases or 0.1 *M* hydrochloric acid was injected.

3. Results and discussion

3.1. Characterization of CSP-18C6I

According to the procedures described in Section 2, a (+)-18-crown-6 tetracarboxylic acid immobilized packing material, CSP-18C6I, was prepared (Scheme 1). By elemental analysis of nitrogen, the chiral crown ether was combined with 3-aminopropyl silica gel (0.85 mmol of amine per gram of gel) to provide CSP-18C6I having a chiral selector loading of 0.26 mmol per gram of gel. Judging from the amount of chiral selector immobilized, one chiral moiety seems to be introduced per four amino



Scheme 1. Synthesis of the chiral stationary phase.

residues and the bonding form seems to be mono or bifunctional linking as described in Scheme 1.

At first, the effect of organic solvents (acetonitrile, methanol, ethanol, 2-propanol and tetrahydrofuran) in the eluent on the enantioselectivity was investigated by adding each organic solvent to the 10 m*M* perchloric acid. The capacity factors, k_1 and k_2 ($k_1 < k_2$), and the separation factors, $\alpha(=k_2/k_1)$, and the resolutions, R_s, obtained for Ala-β-NA and 1-NEA, are summarized in Table 1. Acetonitrile and tetrahydrofuran gave smaller capacity factors and larger separation factors and resolutions, compared with the other solvents (methanol, ethanol and 2-propanol). This may be interpreted by the high peak theoretical plate numbers in use of acetonitrile and tetrahydrofuran. Further, high pressure (about 130 kg/cm^2)

Table 1
Effect of an organic modifier on the enantioselectivity

	50% Acetonitrile			50% Methanol			50% Ethanol			50% Isopropanol			50% Tetrahydrofuran		
	k_1	α	R_s	k_1	α	R_s	k_1	α	R_s	k_1	α	R_s	k_1	α	R_s
Alanine-β-naphthylamide	2.80	1.48	2.23	14.1	1.25	1.40	9.96	1.41	1.82	8.12	1.51	1.93	2.43	1.76	2.56
1-(1-Naphthyl)ethylamine	2.69	1.48	2.13	8.92	1.44	2.17	9.04	1.47	2.12	9.56	1.48	2.04	3.75	1.58	2.05

Mobile phase: 50% polar solvent to the 10 m*M* perchloric acid, column temperature: 25°C.

was observed in the use of alcohols. Therefore, we selected acetonitrile as the organic modifier for this CSP-18C6I. Typical chromatograms of enantiomers of Ala-β-NA and 1-NEA are shown in Fig. 2. The mobile phases used were a mixture of acetonitrile and 10 m*M* perchloric acid (50:50). The column temperature was set at 25°C.

Secondly, the effect of the concentration of the solvent (acetonitrile) on the enantioselectivity was investigated by adding acetonitrile (30–70%) to the 10 m*M* perchloric acid. These effects in high concentration of organic solvents cannot be investigated on CROWNPAK CR(+), because CROWNPAK CR(+) is a dynamic coated CSP, as mentioned above. The results obtained for Ala-β-NA and 1-NEA are summarized in Table 2. An increase of acetonitrile concentration led to a decrease of the capacity factor as in the reversed-phase HPLC. Some hydrophobic interaction seems to be contributed to the retention of the hydrophobic analytes. On the one hand, an increase of acetonitrile concentration led to increases of the separation factor and resolution of Ala-β-NA, an increase of the separation factor of 1-NEA. These results are different from those obtained in the reversed or normal-phase HPLC, where larger k' values usually give larger α and R_s values. High concentration of acetonitrile may contribute to the effective complexation between the analyte and

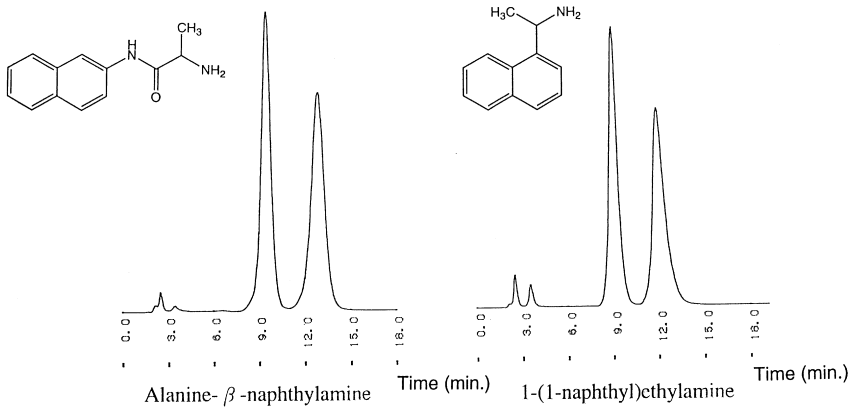


Fig. 2. Enantiomer separation of amino compounds. Mobile phase: acetonitrile–10 m*M* perchloric acid (50:50); column temperature: 25°C; detection: 254 nm.

Table 2
Effect of the concentration of acetonitrile on the enantioselectivity

	30%			40%			50%			60%			70%		
	k_1	α	R_s	k_1	α	R_s	k_1	α	R_s	k_1	α	R_s	k_1	α	R_s
Alanine-β-naphthylamide	7.02	1.38	1.61	3.48	1.42	2.21	2.80	1.48	2.23	2.10	1.58	2.33	1.89	1.65	2.45
1-(1-Naphthyl)ethylamine	5.75	1.58	2.76	3.35	1.45	2.43	2.69	1.48	2.13	2.02	1.50	1.86	1.75	1.50	1.85

Mobile phase: % acetonitrile to the 10 m*M* perchloric acid, column temperature: 25°C.

Table 3
Effect of the concentration of perchloric acid (buffer pH) on the enantioselectivity

	40 m*M* (pH 1.40)			10 m*M* (pH 1.95)			5 m*M* (pH 2.24)			2 m*M* (pH 2.63)			1 m*M* (pH 2.94)		
	k_1	α	R_s	k_1	α	R_s	k_1	α	R_s	k_1	α	R_s	k_1	α	R_s
Alanine-β-naphthylamide	1.99	1.48	2.23	2.80	1.48	2.23	3.62	1.46	2.16	5.18	1.43	1.99	8.75	1.41	2.37
1-(1-Naphthyl)ethylamine	1.97	1.36	1.78	2.69	1.48	2.13	2.89	1.64	1.98	3.21	1.12	0.97	3.27	1.07	0.87

Mobile phase: 50% acetonitrile to the 10~40 m*M* perchloric acid, column temperature: 25°C.

the chiral crown ether, or contribute to the reduction of peak tailings of the analytes.

Thirdly, the effect of the concentration of perchloric acid (1~40 m*M*=pH 2.94~1.40) in the eluent, in other words, the effect of buffer pH, on the enantioselectivity, was investigated. The concentration of acetonitrile was fixed at 50%. The results are summarized in Table 3. An increase of the concentration of perchloric acid led to a decrease of the capacity factor. These results were quite different with those obtained from CROWNPAK CR(+), where an increase of perchloric acid (a decrease of the buffer pH) leads to an increase of the capacity factor [12]. The opposite tendency of the capacity factors observed between the CSP-18C6I and CROWNPAK CR(+) may be explained by the electrostatic interactions. That is, in CSP-18C6I, there are two or three carboxy groups (see Scheme 1). The pK_a values of four carboxyl groups of (+)-18-crown-6 tetracarboxylic acid are 2.13, 2.84, 4.29, and 4.88 [24]. Therefore, above pH 2, these carboxyl groups of CSP-18C6I must dissociate and can contribute to the electrostatic interaction with the cationic analyte. The pH value was found to be one of the useful parameters for manipulating the retention in the CSP-18C6I.

Finally, the effect of column temperature on the enantioselectivity was investigated. The improvement of enantioselectivity was obtained with decreasing temperature as in CROWNPAK CR(+) [12]. Cram and co-workers [15] observed that the difference in the stability of two diastereomeric (host–guest) complexes was formed between the chiral crown ether, and each enantiomer increases with a decrease of the temperature. The results shown in Table 4 were consistent with this observation.

3.2. Enantiomer separation of amino acids

The CSP-18C6I gave good chiral recognition for DL-amino acids. These were eluted and resolved with 10 m*M* perchloric acid alone in this CSP. The results are summarized in Table 5. Typical separations of some DL-amino acids are shown in Fig. 3. DL-Arginine and DL-histidine, both basic amino acids, were resolved with separation factors of 1.48 and 1.41 (entry 2, 5). However, acidic amino acids, such as DL-asparagine and DL-aspartic acid, were not resolved on the CSP-18C6I (entry 3, 4). These enantioselectivities can probably be discussed with the electrostatic interactions between the carboxyl groups of the crown ether and DL-amino acids. The k' values of acidic amino acids were smaller than those of basic ones. This means that there was no useful interaction between the acidic amino acids and the CSP-18C6I. On the other hand, polar DL-amino acids gave low, and hydrophobic DL-amino acids gave high retention as in the reversed-phase HPLC (entry 1, 10). This can be interpreted by the contribution of the hydrophobic interaction as mentioned in Section 3.1. DL-Amino acids having one bulky substituent group at

Table 4
Effect of column temperature on the enantioselectivity

	10°C			20°C			25°C			35°C			40°C		
	k_1	α	R_s	k_1	α	R_s	k_1	α	R_s	k_1	α	R_s	k_1	α	R_s
Alanine-β-naphthylamide	5.48	1.53	2.43	3.47	1.49	2.25	2.80	1.48	2.23	1.88	1.45	1.98	1.55	1.43	1.86
1-(1-Naphthyl)ethylamine	4.88	1.53	2.46	3.20	1.48	2.16	2.69	1.48	2.13	1.86	1.40	1.90	1.56	1.39	1.79

Mobile phase: 50% acetonitrile to the 10 m*M* perchloric acid.

Table 5
Enantiomer separation of amino acids on CSP-18C6I

Entry	Amino acids	k_1	k_2	α	R_s
1	Alanine (Ala)	0.60	0.67	1.12	0.41
2	Arginine (Arg)	0.58	0.86	1.48	1.30
3	Asparagine (Asn)	0.34	–	1.00	–
4	Aspartic acid (Asp)	0.44	–	1.00	–
5	Histidine (His)	0.39	0.55	1.41	0.82
6	Leucine (Leu)	0.63	0.83	1.32	0.89
7	Isoleucine (Ile)	0.39	–	1.00	–
8	Norleucine (Nleu)	0.74	0.99	1.34	0.92
9	Methionine (Met)	0.90	1.11	1.23	0.73
10	Phenylalanine (Phe)	1.22	1.87	1.53	1.61
11	Threonine (Thr)	0.41	–	1.00	–
12	Tryptophan (Trp)	2.76	3.88	1.41	1.77
13	Tyrosine (Tyr)	0.94	1.32	1.40	1.30
14	Valine (Val)	0.39	–	1.00	–
15	Phenylglycine (PheG)	1.87	3.57	1.91	2.68
16	α-Amino-*n*-butyric acid	0.44	0.51	1.16	0.47
17	DOPA	0.80	1.15	1.44	1.33
18	Kynurenine	3.00	3.88	1.29	1.10

Mobile phase: 10 m*M* perchloric acid, column temperature: 25°C.

the β-carbon atom showed a large enantioselectivity (entry 10, 12, 13, 15, 17, 18), and DL-amino acids having more than one substituent group at the β-carbon atom did not give an enantioseparation (entry 7, 11, 14). These can be interpreted by the steric hindrance in the formation of the complexes. Relatively small k' values were obtained for these three DL-amino acids, as in the acidic amino acids.

As for the elution order of DL-forms, L-amino acids eluted prior to D-forms. It was found that D-amino acids form more stable complexes with the CSP-18C6I. CROWNPAK CR(+) also showed the same enantioselectivity. That is, L-amino acids eluted prior to D-forms. These results suggest that the chiral recognition mechanism of the CSP-18C6I is similar to those in CROWNPAK CR(+) for DL-amino acids [13].

3.3. Enantiomer separation of aminoalcohols

The CSP-18C6I gave good chiral recognition for aminoalcohols. These were resolved with 10 m*M* perchloric acid alone, as in DL-amino acids. The results are summarized in Table 6. 2-Amino-1-phenylethanol, norephedrine (2-methyl derivatized form), and 2-amino-1,2-diphenylethanol (2-phenyl derivatized form), were resolved with separation factors of 1.29, 1.38 and 1.78 using 10 m*M* perchloric acid solution alone as the eluent. The aminoalcohols having no bulky substituent group at the phenyl group (R^2=H compounds in Table 6) showed large R_s values (entry 19, 23, 25) and this seems to be effective for the chiral recognition on CSP-18C6I. Typical separations of some racemic aminoalcohols are shown in Fig. 4. On the other hand, norphenylephrine, octopamine, and normethanephrine (3-hy-

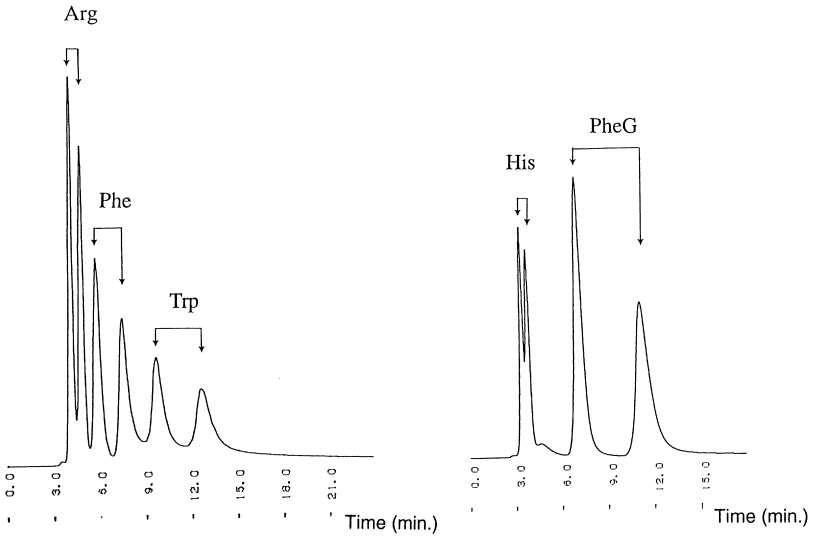
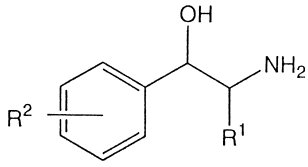


Fig. 3. Enantiomer separation of amino acids. Mobile phase: 10 m*M* perchloric acid; column temperature: 25°C; detection: 200 nm.

Table 6
Enantiomeric separation of aminoalcohols on CSP-18C6I

Entry	Aminoalcohols		R^1	R^2	k_1	k_2	α	R_s
19	2-Amino-1-phenylethanol		H	H	6.20	8.02	1.29	1.25
20	Norphenylephrine		H	3-OH	5.95	7.03	1.18	1.17
21	Octopamine		H	4-OH	4.88	5.46	1.12	0.79
22	Normetanephrine		H	3-OH, 4-OH	7.09	7.64	1.08	0.56
23	Norephedrine		Me	H	1.54	2.13	1.38	1.39
24	4-Hydroxynorephedrine		Me	4-OH	1.08	1.45	1.34	1.15
25	2-Amino-1,2-diphenylethanol		Ph	H	2.36	4.20	1.78	2.74

Mobile phase: 10 m*M* perchloric acid, column temperature: 25°C.

droxyphenyl, 4-hydroxyphenyl and 4-hydroxy-3-methoxyphenyl derivatized form), which have substituents in the benzene ring, gave lower R_s values than that in 2-amino-1-phenylethanol (entry 19, 20, 21, 22). 2-Aminoethanol derivatives (R^1=H compounds in Table 6) gave high retentions and 2-aminopropanol derivatives (R^1=Me compounds) gave low retentions. These results suggest that steric hindrance between the enantiomers and the crown ether moiety strongly contributes to the differences in the stability of the diastereomeric complexes.

3.4. Enantiomer separation of other amino compounds

The CSP-18C6I also gave good chiral recognition for some other amino compounds. The results are summarized in Table 7. Afloqualone (muscle relaxant), α-methyltryptamine, and 1-NEA were resolved on the CSP-18C6I with separation factors of 1.07, 1.07 and 1.48. Furthermore, Ala-β-NA, which is hydrophobic and did not elute within 60 min by the commercially available CROWNPAK CR(+) with 15% methanol and column temperature 40°C [23], was successfully enantioseparated by the novel CSP-18C6I, with a separation factor of 1.48 within a relatively short time (see Fig. 2). Primaquine (antimalarial), where the distance of amino group and the asymmetric center is long, was also successfully enantioseparated by the CSP-18C6I.

4. Conclusion

The novel CSP (CSP-18C6I) was prepared by immobilizing, (+)-18-crown-6 tetracarboxylic acid on silica-gel. There is no restriction for use of organic solvents in this novel CSP. The CSP-18C6I

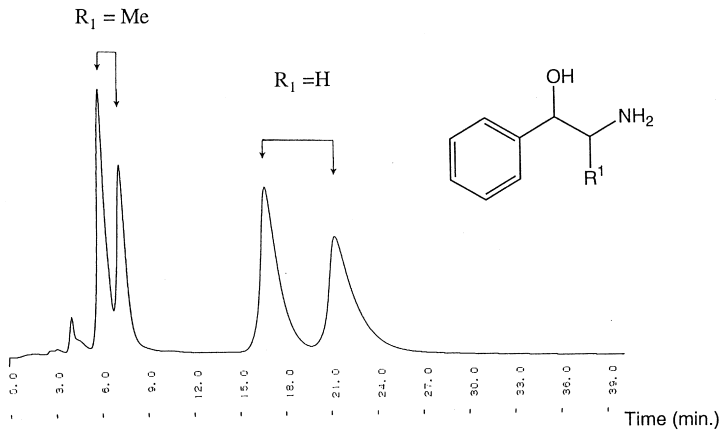


Fig. 4. Enantiomer separation of aminoalcohols. Mobile phase: 10 m*M* perchloric acid; column temperature: 25°C; detection: 200 nm.

Table 7
Enantiomer separation of other amino compounds on CSP-18C6I

Entry	Amino compounds	k_1	k_2	α	R_s	% Acetonitrile[a]
26	Afloqualone	9.29	9.92	1.07	0.49	10
27	Alanine-β-naphthylamide	2.80	4.16	1.49	2.23	50
28	Aminoglutethimide	4.24	4.24	1.00	–	20
29	Baclofen	8.63	8.63	1.00	–	30
30	α-Methyltryptamine	3.00	3.21	1.07	0.48	20
31	1-(1-Naphthyl)ethylamine	2.69	3.97	1.48	2.13	50
32	Primaquine	8.38	9.22	1.10	0.62	20

Column temperature: 25°C.
[a] % acetonitrile in the eluent (10 m*M* perchloric acid).

gave good chiral recognition for primary amino compounds such as amino acids, aminoalcohols, etc. Thirteen from among eighteen amino acids, and seven aminoalcohols were enantioseparated using a dilute aqueous solution of perchloric acid as the eluent. Afloqualone, primaquine, and 1-NEA were resolved on the CSP-18C6I. Ala-β-NA, which is a hydrophobic amino compound and did not elute within 60 min under 40°C and 15% methanol mobile phase on CROWNPAK CR(+), was finely enantioseparated with a separation factor of 1.48 within a short time (ca. 15 min). However, there is still a need to expand the scope of chiral recognition of this CSP, because some of the analytes were not enantioseparated. In the future, we plan to synthesize other novel CSPs derived from the same chiral crown ether through the modification of the CSP-18C6I, or changing the spacer length or structures, expecting the wide scope of chiral recognition.

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