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Journal of Chromatography A, 959 (2002) 75–83

JOURNAL OF CHROMATOGRAPHY A

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Liquid chromatographic resolution of racemic amines, amino alcohols and related compounds on a chiral crown ether stationary phase

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Received 4 January 2002; received in revised form 10 April 2002; accepted 15 April 2002

Abstract

A chiral stationary phase (CSP) based on diphenyl-substituted 1,1′-binaphthyl crown ether was applied in resolving various racemic amines, amino alcohols and α-aminocarbonyl compounds including pharmaceutically important compounds such as amphetamine analogues, mexiletine, norepinephrine and norephedrine. The resolution was quite successful. In order to find out the effects of mobile phase additives on the chromatographic resolution behaviors, four selected racemic compounds were resolved on the CSP with the variation of the type and content of organic, acidic and cationic modifiers in aqueous mobile phase and with the variation of column temperature. The resolution behaviors were quite dependent on the type and the content of organic, acidic and cationic modifiers in aqueous mobile phase and on column temperature.

Keywords: Chiral stationary phases, LC; Enantiomer separation; Amines; Amino alcohols; Crown ethers

1. Introduction

Chiral stationary phases (CSPs) based on chiral crown ethers have been known to be very effective in resolving racemic compounds containing a primary amino group. For example, Cram and coworkers utilized bis-(1,1′-binaphthyl)-22-crown-6 immobilized on polystyrene or silica gel as CSPs in separating the enantiomers of racemic α-amino acids and their derivatives [1,2]. Disubstituted 1,1′-binaphthyl-20-crown-6 dynamically coated on octadecyl silica gel has also been utilized as a CSP (a related CSP has been commercialized as CROWNPAK CR by Daicel Chemical Industries) in resolving racemic α-amino acids and other racemic compounds containing a primary amino group [3–5]. In recent years, CSPs based on (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid have also been developed and successfully utilized in resolving various racemic compounds containing a primary amino group [6–13].

Very recently, we reported a short communication paper concerning the development of a new CSP

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0021-9673/02/$ – see front matter
PII: S0021-9673(02)00431-4

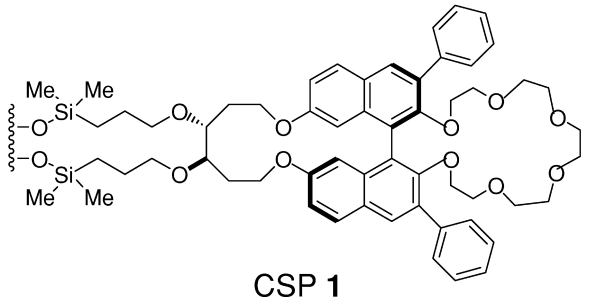


Fig. 1. Structure of CSP **1**.

(CSP **1**) (Fig. 1) [14]. The chiral crown ether moiety of CSP **1** bears some similarity to the commercial CROWNPAK CR, but differs in that it is covalently bonded to silica gel. Consequently, covalently linked CSP **1** is useful in a variety of mobile phases. In the previous paper, we reported that CSP **1** is very effective in resolving various natural and unnatural α-amino acids. However, CSP **1** has not been utilized in resolving other racemic compounds containing a primary amino group. In this study, we wish to extend the use of CSP **1** to the resolution of racemic amines, amino alcohols and the related compounds.

2. Experimental

Chromatography was performed with an HPLC system consisting of a Waters model 515 HPLC pump, a Rheodyne model 7725i injector with a 20-μl sample loop, a YoungLin M720 Absorbance detector (variable wavelength) and a YoungLin Autochro Data Module (Software: YoungLin Autochro-WIN 2.0 plus). The temperature of the chiral column was controlled by using a Julabo F30 Ultratemp 2000 cooling circulator. The chiral column prepared by packing CSP **1** into a 250×4.6-mm I.D. stainless steel empty column was available from the previous study [14]. All analytes used in this study were available from previous study [10] or purchased from Aldrich. Injection samples were prepared by dissolving analytes in methanol at a concentration of 1.0 mg/ml and an injection size of 3 μl was typically used. Elution orders were determined by injecting configurationally known samples available from Aldrich.

3. Results and discussion

CSP **1** was applied in resolving various racemic amines (**2**), amino alcohols (**3**) and α-amino carbonyl compounds (**4**). The chromatographic resolution results are summarized in Table 1. The data shown in Table 1 were obtained under identical chromatographic conditions given in the footnote to Table 1. The chromatographic conditions utilized in obtaining data shown in Table 1 were not optimized for any racemate but generally quite useful. Sulfuric acid added to the mobile phase is necessary for protonation of the primary amino group of analytes to enhance the complexation of the ammonium ion ($R\text{-}NH_3^+$) inside the cavity of the crown ether ring of the CSP [15]. Under the mobile phase condition of the given pH (1.06) in Table 1, amino groups of all analytes seem to be fully protonated. Ammonium acetate added to the mobile phase is used to reduce the retention time of the two enantiomers on the chiral column, by competing with the ammonium ion of analytes for complexation inside the cavity of crown ether ring of the CSP [14]. Especially, it is interesting to note that pharmaceutically important compounds such as amphetamine analogues (**2e**, **2f**), mexiletine (**2g**), norepinephrine (**3b**) and norephedrine (**3f**) were resolved with reasonable separation factors on CSP **1**. While most of analytes contain aromatic functional groups, the non-aromatic analyte (**4b**) was also resolved very well. Consequently, the presence of aromatic functional groups in analytes seems to be not essential for the chiral recognition.

The organic and acidic modifiers and the cationic modifiers in mobile phase and the column temperature are expected to influence the enantioselectivity of CSP **1**. In order to investigate the effects of mobile phase modifiers and the column temperature on the enantioselectivity, we selected four racemic compounds (**2c**, **2o**, **3f** and **4b**), which are resolved well on CSP **1** as shown in Table 1 and Fig. 2, and tested their resolutions with the variation of the type and content of organic and acidic modifiers and cationic modifiers in aqueous mobile phase and with the variation of column temperature.

Table 1
Resolution of various amines (**2**), amino alcohols (**3**) and α-amino carbonyl compounds (**4**) on CSP **1**

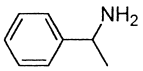
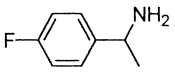
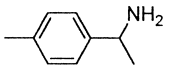
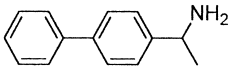
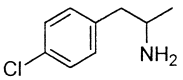
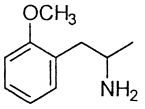
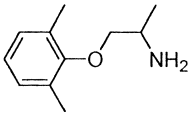
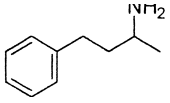
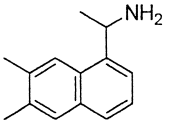
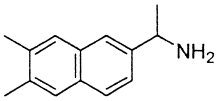
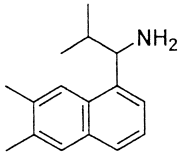
	Analytes	k_1[a]	k_2[b]	α[c]	R_S[d]	Conf.[e]
2a		1.07	1.92	1.80	3.80	*S*
2b		0.83	1.84	2.23	3.39	
2c		0.99	1.92	1.78	3.54	*S*
2d		1.59	2.59	1.62	3.11	
2e		0.73	1.09	1.49	2.27	
2f		0.84	2.00	2.37	3.33	
2g		0.34	0.40	1.16	0.44	
2h		2.82	3.41	1.21	1.94	
2i		3.31	3.86	1.16	1.33	
2j		2.67	3.53	1.32	2.43	
2k		0.32	0.47	1.47	1.60	

Table 1. Continued

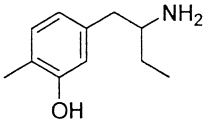
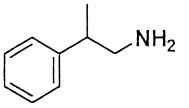
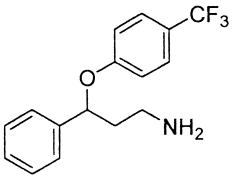
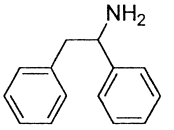
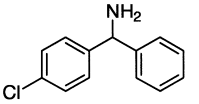
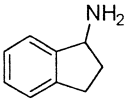
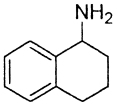
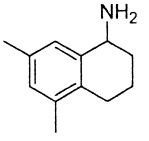
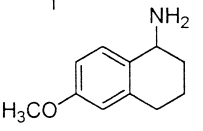
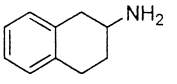
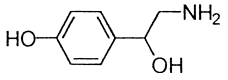
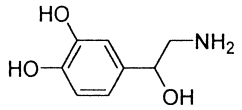
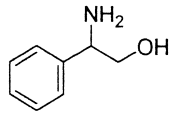
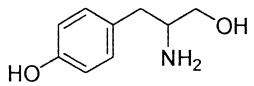
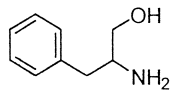
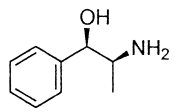
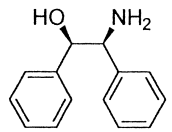
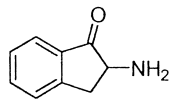
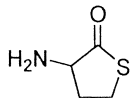
	Analytes	k_1[a]	k_2[b]	α[c]	R_S[d]	Conf.[e]
2l		0.26	0.30	1.16	0.43	
2m		1.73	2.30	1.33	1.85	*S*
2n		2.69	3.28	1.22	1.47	
2o		0.52	1.57	3.00	6.60	
2p		0.65	0.77	1.20	0.71	
2q		1.49	3.28	2.20	5.88	*S*
2r		0.37	0.78	2.11	3.25	
2s		0.67	1.64	2.45	4.67	
2t		0.46	0.92	2.01	3.57	
2u		2.75	4.45	1.62	4.30	

Table 1. Continued

	Analytes	k_1 [a]	k_2 [b]	α [c]	R_S [d]	Conf. [e]
3a		1.05	1.05	1.00		
3b		0.89	0.97	1.09	0.44	
3c		0.40	0.47	1.18	0.57	
3d		0.31	0.36	1.16	0.62	
3e		0.34	0.41	1.20	0.67	*R*
3f		0.31	0.65	2.09	3.06	(1*R*,2*S*)
3g		0.19	0.33	1.77	1.68	(1*S*,2*R*)
4a		2.07	2.53	1.22	1.82	
4b		0.66	1.02	1.55	2.14	

Mobile phase, 80% CH_3CN in $H_2O+H_2SO_4$ (10 m*M*)+ CH_3COONH_4 (1 m*M*). Flow rate, 0.5 ml/min; detection, 225 nm UV; temperature, 20 °C.

[a] Retention factor of the first eluted enantiomer.

[b] Retention factor of the second eluted enantiomer.

[c] Separation factor.

[d] Resolution factor.

[e] Absolute configuration of the second eluted enantiomer. For blanks, the elution orders were not determined.

First of all, the effects of organic modifiers on the enantioselectivity exerted by CSP **1** were investigated with the variation of the type and content of organic modifiers in aqueous mobile phase. In this study, we actually investigated two different organic modifiers such as methanol and acetonitrile. The chromatographic resolution results are summarized in Table 2. As shown in Table 2, the retention factors (k_1) generally decrease as the content of organic modifier in aqueous mobile phase increases except for the resolution of α-amino carbonyl compound, homocysteine thiolactone **4b**. In the resolution of homocysteine thiolactone **4b**, the retention factor (k_1) does not show any significant trends. The separation (α) and the resolution factors (R_S), in general, increase as the content of organic modifier in aqueous mobile phase increases. All of these trends with the variation of the content of organic modifier in aqueous mobile phase are consistent with those for the resolution of α-amino acids on CSP **1** [14].

The effects of acidic modifiers in aqueous mobile phase on the resolution of selected racemic compounds (**2c**, **2o**, **3f** and **4b**) on CSP **1** are summarized in Table 3. The retention factors (k_1) are significantly diminished as the concentration of acidic modifier in aqueous mobile phase increases. These trends are somewhat different from those for the resolution of α-amino acids on CSP **1**. In the resolution of α-amino acids on CSP **1**, the retention factors (k_1) were reported to show a maximum at a certain concentration of acidic modifier [14]. The initial increase in k_1 for the resolution of α-amino acids on CSP **1** was rationalized by increased complexation of the primary ammonium ion ($R\text{-}NH_3^+$) inside the cavity of the crown ether ring of the CSP, while the decrease in k_1 at higher acid concentrations was assumed to be a result of the greater ionic strength of the mobile phase. In this instance, the continuous decrease in k_1 with the increase in the acid concentration for the resolution of racemic compounds **2c**, **2o**, **3f** and **4b** shown in Table 3 might be rationalized to stem from the increased ionic strength of the mobile phase. Enantioselectivity (α) for the resolution of racemic compounds **2c**, **2o** and **3f** increases slightly as the concentration of acidic modifier in aqueous mobile phase increases and these trends are consistent with those for the resolution of

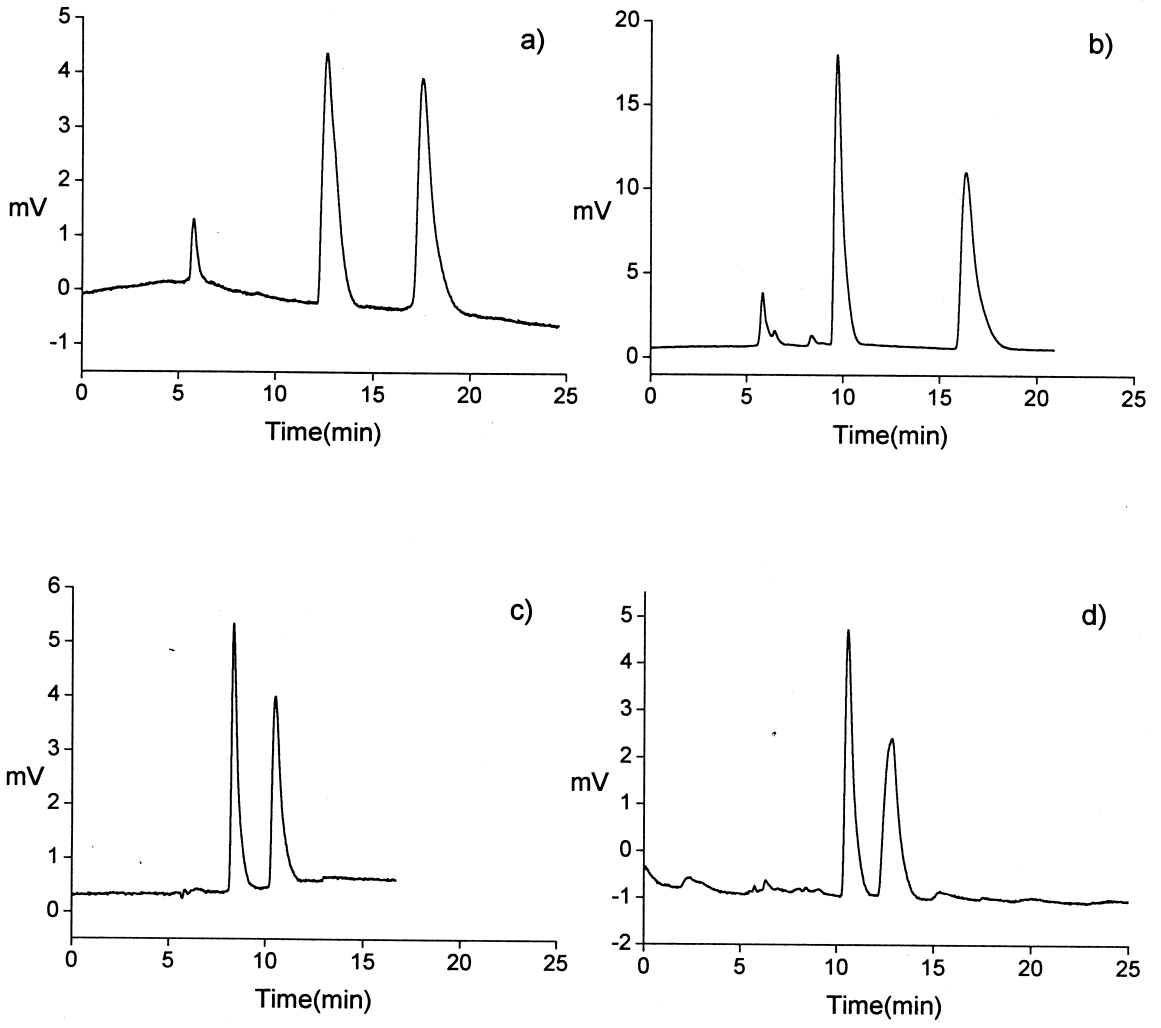


Fig. 2. Representative chromatograms for the resolution of (a) α-(4-methylphenyl)ethylamine **2c**, (b) 1,2-diphenylethylamine **2o**, (c) norephedrine **3f** and (d) homocysteine thiolactone **4b** on CSP **1**. For chromatographic conditions, see the footnote to Table 1.

α-amino acids on CSP **1** [14]. On the contrary, enantioselectivity (α) for the resolution of homocysteine thiolactone **4b** shows a maximum at a certain concentration of acidic modifier. Resolution factors (R_S), however, do not show significant trends with the variation of the content of acidic modifier in aqueous mobile phase as shown in Table 3. The use of perchloric acid or trifluoroacetic acid as an acidic modifier in aqueous mobile phase was also effective for the resolution of racemic compounds **2c**, **2o**, **3f** and **4b**. However, sulfuric acid seems to be better as an acidic modifier than perchloric or trifluoroacetic acid in terms of the resolution (R_S).

The effects of cationic modifiers in aqueous mobile phase on the resolution of four selected racemic compounds (**2c**, **2o**, **3f** and **4b**) on CSP **1** are summarized in Table 4. The cationic modifier added to mobile phase might compete with the ammonium ion of analytes ($R\text{-}NH_3^+$) for complexation inside the cavity of crown ether ring of the CSP. In this instance, the concentration of cationic modifier in mobile phase is expected to influence the retention of

Table 2
Resolution of selected racemic compounds (**2c**, **2o**, **3f** and **4b**) on CSP **1** with the variation of the type and the content of organic modifier in aqueous mobile phase[a]

Organic modifier (%)	**2c**			**2o**			**3f**			**4b**		
	k_1[b]	α[c]	R_S[d]	k_1^b	α^c	R_S^d	k_1^b	α^c	R_S^d	k_1^b	α^c	R_S^d
CH_3CN (20)	4.30	1.68	2.31	9.40	2.57	5.63	0.80	1.86	3.08	0.54	1.40	1.62
CH_3CN (50)	2.22	1.70	3.75	2.00	2.71	6.29	0.60	1.93	3.83	0.74	1.43	2.10
CH_3CN (80)	0.99	1.78	3.54	0.52	3.00	6.60	0.31	2.09	3.06	0.66	1.55	2.14
CH_3OH (50)	2.60	1.49	1.78	3.49	2.52	4.00	0.79	1.95	2.56	0.72	1.57	1.89
CH_3OH (80)	0.92	1.71	2.59	0.60	2.67	5.50	0.45	2.07	3.76	0.69	1.55	2.71

[a] Mobile phase, organic modifier (%) in $H_2O+H_2SO_4$ (10 m*M*)+CH_3COONH_4 (1 m*M*); flow rate, 0.5 ml/min; detection, 225 nm UV; temperature, 20 °C.
[b] Retention factor of the first eluted enantiomer.
[c] Separation factor.
[d] Resolution factor.

Table 3
Resolution of selected racemic compounds (**2c**, **2o**, **3f** and **4b**) on CSP **1** with the variation of the type and the content of acidic modifier in aqueous mobile phase[a]

Acidic modifier (m*M*)	**2c**			**2o**			**3f**			**4b**		
	k_1[b]	α[c]	R_S[d]	k_1^b	α^c	R_S^d	k_1^b	α^c	R_S^d	k_1^b	α^c	R_S^d
H_2SO_4 (1)	1.49	1.60	4.00	0.85	2.48	7.11	0.65	1.75	3.81	1.21	1.34	2.50
H_2SO_4 (5)	1.11	1.65	3.33	0.54	2.97	5.00	0.35	2.02	2.90	0.72	1.59	2.75
H_2SO_4 (10)	0.99	1.78	3.54	0.52	3.00	6.60	0.31	2.09	3.06	0.66	1.55	2.14
H_2SO_4 (20)	0.91	1.82	4.18	0.48	3.12	6.45	0.27	2.20	3.08	0.59	1.51	2.25
$HClO_4$ (10)	1.06	2.58	3.30	0.69	3.26	5.85	0.42	2.21	2.57	0.93	1.57	1.81
CF_3COOH (10)	1.11	2.76	2.60	0.82	3.07	7.09	0.52	2.08	2.54	0.91	2.05	3.12

[a] Mobile phase, CH_3CN (80%) in H_2O+Acidic modifier (m*M*)+CH_3COONH_4 (1 m*M*); flow rate, 0.5 ml/min; detection, 225 nm UV; temperature, 20 °C.
[b] Retention factor of the first eluted enantiomer.
[c] Separation factor.
[d] Resolution factor.

Table 4
Resolution of selected racemic compounds (**2c**, **2o**, **3f** and **4b**) on CSP **1** with the variation of the type and the content of the inorganic modifier in aqueous mobile phase[a]

Inorganic modifier (m*M*)	**2c**			**2o**			**3f**			**4b**		
	k_1[b]	α[c]	R_S[d]	k_1^b	α^c	R_S^d	k_1^b	α^c	R_S^d	k_1^b	α^c	R_S^d
CH_3COONH_4 (1)	0.99	1.78	3.54	0.52	3.00	6.60	0.31	2.09	3.06	0.66	1.55	2.14
CH_3COONH_4 (5)	0.64	1.69	2.13	0.29	3.24	4.78	0.17	2.35	2.15	0.40	1.68	2.31
NH_4Cl (1)	1.23	2.40	3.01	0.83	3.01	6.52	0.51	2.08	2.57	1.07	1.50	1.54
KCl (0.5)	0.67	1.72	1.56	0.39	2.74	3.70	0.25	2.08	2.19	0.54	1.54	1.96
KCl (1)	0.43	1.74	1.66	0.23	3.00	3.24	0.15	2.27	1.62	0.35	1.57	1.71

[a] Mobile phase, CH_3CN (80%) in $H_2O+H_2SO_4$ (10 m*M*)+inorganic modifier (m*M*); flow rate, 0.5 ml/min; detection, 225 nm UV; temperature, 20 °C.
[b] Retention factor of the first eluted enantiomer.
[c] Separation factor.
[d] Resolution factor.

analytes on the CSP. As expected, the retention (k_1) of analytes is decreased more significantly at the higher concentration of cationic modifier than at the lower concentration of cationic modifier. The retention (k_1) of analytes with the use of potassium chloride as an inorganic modifier is more significantly reduced than with the use of ammonium acetate as shown in Table 4. The stability constant of the complex between 18-crown-6 and cations has been known to be much greater with K^+ than with NH_4^+ ion [16]. In this instance, potassium chloride is expected to compete with the ammonium ion of analytes ($R\text{-}NH_3^+$) for complexation inside the cavity of crown ether ring of the CSP more effectively and consequently reduces the retention (k_1) more significantly than ammonium acetate. There was no much difference in enantioselectivity (α) when ammonium acetate or potassium chloride was used as a cationic modifier. However, the resolution (R_S) was generally greater when ammonium acetate was used as a cationic modifier than when potassium chloride was used. The use of ammonium chloride as a cationic modifier in aqueous mobile phase was observed to be equally effective as the use of ammonium acetate as shown in Table 4.

The effects of column temperature on the resolution of four selected racemic compounds **2c**, **2o**, **3f** and **4b** on CSP **1** are demonstrated in Table 5. As shown in Table 5, all three chromatographic parameters such as the retention (k_1), the separation (α) and the resolution factors (R_S) improve continuously as column temperature decreases. At lower temperature, the diastereomeric complexes formed between the individual enantiomers of an analyte and the chiral crown ether moiety of the CSP are expected to become energetically more favorable and this is more significant with the more stable diastereomeric complex. Consequently, the retention (k_1) and the separation factors (α) improve as the column temperature decreases. The improved enantioselectivity (α) at lower temperature makes the distance wider between the two chromatographic peaks corresponding to the two enantiomers and consequently the resolution (R_S) is also expected to improve at lower temperature.

Finally, CSP **1** was demonstrated to be very useful in the determination of the optical purity of enantiomerically enriched samples. For example, the chromatogram for the resolution of a commercial sample of optically active **2c** (Aldrich, $R{:}S = 1{:}99$, 98% ee) on CSP **1** in Fig. 3a shows the two peaks corresponding to the two enantiomers present in the sample. Another chromatogram for the resolution of a commercial sample of optically active norephedrine **3f** (Aldrich, optical purity is not known) shown in Fig. 3b demonstrated that the optical purity of the sample is also 98% ee. As shown in Fig. 3, the minor enantiomers present in the optically active samples are clearly shown and consequently their detection limit can be more lowered. However, enantiomerically more enriched samples are not available and the detection limit of the optical purity was not checked further.

In summary, in this study, we demonstrated that CSP **1** was quite successful for resolving various racemic amines (**2**), amino alcohols (**3**) and α-aminocarbonyl compounds (**4**). Especially, the resolution of pharmaceutically important compounds such as amphetamine analogues (**2e**, **2f**), mexiletine (**2g**), norephineprine (**3b**) and norephedrine (**3f**) was noteworthy. In order to find out the effects of mobile phase additives on the chromatographic resolution

Table 5
Resolution of selected racemic compounds (**2c**, **2o**, **3f** and **4b**) on CSP **1** with the variation of column temperature[a]

Column temp. (°C)	**2c**			**2o**			**3f**			**4b**		
	k_1[b]	α[c]	R_S[d]	k_1[b]	α[c]	R_S[d]	k_1[b]	α[c]	R_S[d]	k_1[b]	α[c]	R_S[d]
30	0.88	1.70	3.30	0.48	2.33	3.85	0.37	1.65	2.25	0.74	1.39	1.79
20	0.99	1.78	3.54	0.52	3.00	6.60	0.31	2.09	3.06	0.66	1.55	2.14
10	1.37	1.95	5.60	0.73	3.18	8.25	0.53	2.16	4.25	1.05	1.60	2.93

[a] Mobile phase, CH_3CN (80%) in $H_2O + H_2SO_4$ (10 m*M*) + CH_3COONH_4 (1 m*M*); flow rate, 0.5 ml/min; detection, 225 nm UV.
[b] Retention factor of the first eluted enantiomer.
[c] Separation factor.
[d] Resolution factor.

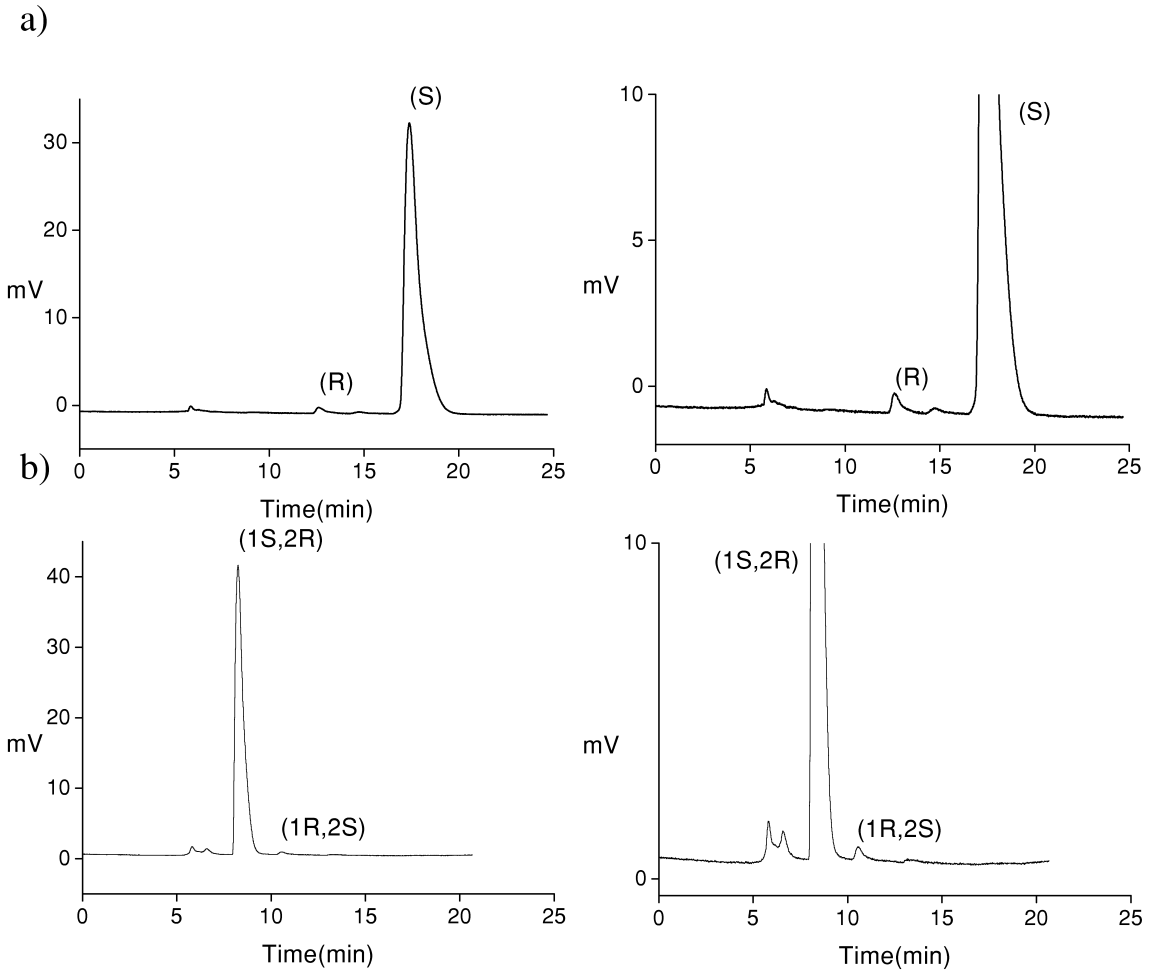


Fig. 3. Examples for the optical purity determination of enantiomerically enriched samples on CSP **1**: (a) (left) the chromatogram for the resolution of a commercial sample of optically active **2c** (Aldrich, *R*:*S* = 1:99), (right) the expanded chromatogram and (b) (left) the chromatogram for the resolution of a commercial sample of optically active norephedrine **3f** (Aldrich), (right) the expanded chromatogram. For the chromatographic conditions, see the footnote to Table 1.

behaviors, four selected racemic compounds (**2c**, **2o**, **3f** and **4b**) were resolved on CSP **1** with the variation of the type and content of organic, acidic and cationic modifiers in aqueous mobile phase and with the variation of column temperature. All of the three chromatographic parameters such as retention (k_1), separation (α) and resolution factors (R_S) were found controllable to some extent by varying the type and content of organic, acidic or cationic modifiers in mobile phase or by varying column temperature. CSP **1** was also demonstrated to be useful in the determination of optical purity of enantiomerically enriched samples. However, the chiral recognition mechanism is not clear except that the diastereoselective complexation of the primary ammonium group ($R\text{-}NH_3^+$) of analytes inside the chiral crown ether ring of the CSP might be responsible. Further studies are expected to be necessary to elucidate the more detailed chiral recognition mechanism.

Acknowledgements

This work was supported from the Ministry of Health and Welfare, Korea (Grant No. HMP-00-B-21500-0107).

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