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Liquid chromatographic direct resolution of aryl α-amino ketones on a residual silanol group-protecting chiral stationary phase based on optically active (3,3′-diphenyl-1,1′-binaphthyl)-20-crown-6☆

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ABSTRACT

A residual silanol group-protecting chiral stationary phase (CSP) based on optically active (3,3′-diphenyl-1,1′-binaphthyl)-20-crown-6 was successfully applied to the resolution of racemic cathinone and it analogue aryl α-amino ketones. The separation factors (α) and the resolutions (R_S) for 12 analytes were in the ranges of 2.85–16.12 and 6.49–19.64, respectively. The chromatographic resolution behaviors were investigated as a function of the content and type of organic and acidic modifiers and the ammonium acetate concentration in aqueous mobile phase. The practical usefulness of the CSP in the determination of the enantiomeric purity of optically active cathinone and in the preparative resolution of racemic cathinone was demonstrated.

1. Introduction

Optically active aryl α-amino ketones have been used as precursors of biologically active ingredients such as ephedrine [1]. Moreover, aryl α-amino ketones belong to a family of drugs employed in the clinical treatment of nicotine dependence [2]. Especially, cathinone, the (*S*)-enantiomer of α-aminopropiophenone, is the main psychoactive alkaloid found in the leaves of the khat plant [3] and has a pharmacological profile closely resembling that of amphetamine [4]. Consequently, cathinone shows an amphetamine-like stimulating effect on the central nervous system and in this context, it is forensically significant for both legal and intelligence purposes [5]. Furthermore, cathinone is known to be more active than its antipode, the (*R*)-enantiomer of α-aminopropiophenone [6] and consequently only the (*S*)-enantiomer (cathinone) is controlled under international conventions [5]. In this context, the methods used for the synthesis of optically active aryl α-amino ketones and those used for the exact determination of the enantiomeric composition of aryl α-amino ketones are important.

Several effective methods have been developed for the synthesis of optically active aryl α-amino ketones [7,8]. For the exact determination of the enantiomeric composition of optically active compounds, liquid chromatographic chiral stationary phase (CSP) methods are known to be the most accurate and convenient and, consequently, various CSPs have developed and applied to the resolution of racemic compounds [9,10]. For example, racemic cathinone have been resolved by liquid chromatography on a CSP based on (3,3′-diphenyl-1,1′-binaphthyl)-20-crown-6 dynamically coated on octadecylsilica gel [11], on a CSP based on cellobiohydrolase (CBH-I) [12], or on CSPs based on (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid [13]. Among others, the resolution of racemic cathinone on a CSP based on (3,3′-diphenyl-1,1′-binaphthyl)-20-crown-6 dynamically coated on octadecylsilica gel was reported to be quite effective [11]. However, the CSP has a critical problem in that a mobile phase containing more than 15% methanol in water cannot be used because of the dynamically coated nature of the CSP. In order to solve this problem, a covalently bonded CSP (CSP **1**, Fig. 1) was developed in our laboratory

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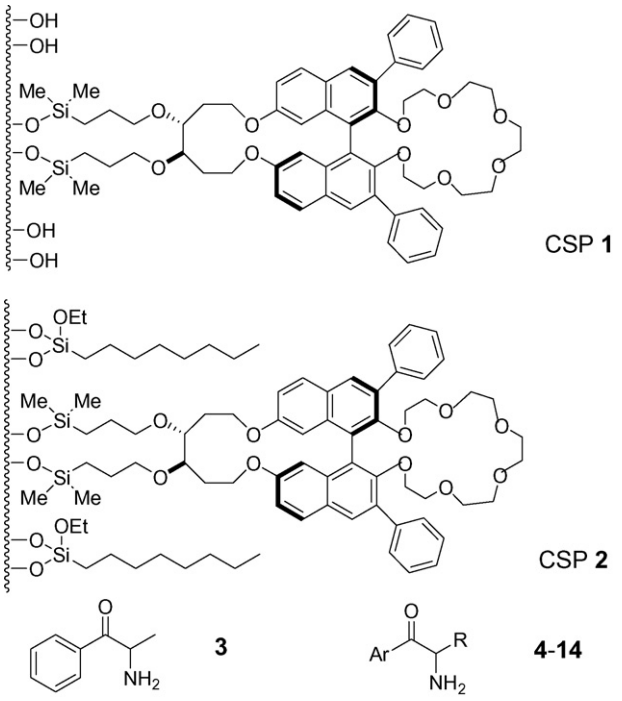

Fig. 1. Structures of CSP **1**, CSP **2**, cathinone (**3**) and cathinone analogues **4**–**14**. For R and Ar groups, see Table 1.

[14]. CSP **1** was quite effective for the resolution of racemic α-amino acids [14], non-cyclic and cyclic amines [15], amino alcohols [15], fluoroquinolone antibacterials [16] and tocainide (antiarrhythmic agent) [17]. CSP **1** was also quite effective for the resolution of aryl α-amino ketones including racemic cathinone [18].

Recently, we developed a residual silanol group-protecting CSP (CSP **2**, Fig. 1) by treating CSP **1** with *n*-octyltriethoxysilane [19]. The *n*-octyl groups introduced in CSP **2** are believed to play a dual role, protecting the residual silanol groups and increasing the lipophilicity of the CSP. The residual silanol group-protection and the improved lipophilicity of the CSP were proved to enhance the chiral recognition ability of the CSP in the resolution of α-amino acids, amines and amino alcohols [19]. However, CSP **2** has not yet been applied to the resolution of aryl α-amino ketones yet. In this study, we attempted to demonstrate that the introduction of the residual silanol protecting *n*-octyl groups in CSP **2** improves its chiral recognition ability significantly in the resolution of aryl α-amino ketones including cathinone.

2. Experimental

Chromatography was performed with an HPLC system consisting of a Waters model 515 HPLC pump (Milford, MA, USA), a Rheodyne model 7725i injector (Rohnert Park, CA, USA) with a 20 μl sample loop, a YoungLin M720 absorbance UV detector (variable wavelength, Seoul, Korea) 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 (Seelbach, Germany). The chiral column (150 mm × 4.6 mm i.d.) packed with CSP **2** (loadings of chiral selectors and octadecyl chains are 0.10 and 0.18 mmol, respectively) was available from a prior study [19]. Racemic and optically active aryl α-amino ketones including cathinone (**3**) and its analogues (**4**–**14**) (Fig. 1) prepared from the corresponding α-amino acids were available from a prior study [18]. Injection samples were prepared by dissolving each of racemic and optically active aryl α-amino ketones (**3**–**14**) in water (usually 2.5 mg/ml). The usual injection volume was 3.0 μl. For the loading capacity study, the same chromatography system with a 500 μl sample loop was used and the injection sample was prepared by dissolving 5.0 mg of racemic cathinone (**3**) in 1.0 ml of water.

3. Results and discussion

3.1. Resolution of aryl α-amino ketones

CSP **2** was applied to the resolution of cathinone (**3**) and its analogue aryl α-amino ketones (**4**–**14**). The chromatographic results on CSP **2** are summarized and compared to those on CSP **1** in Table 1. For the purpose of comparison, an identical mobile phase consisting of 50% acetonitrile in water containing sulfuric acid (10 mM) and ammonium acetate (1 mM) was used on the two CSPs.

As shown in Table 1, the chiral recognition ability of CSP **2** for the resolution of cathinone (**3**) and its analogue aryl α-amino ketones (**4**–**14**) was considerably improved in every case compared to that of CSP **1** in terms of both the separation factors (α) and the resolutions (R_S). The removal of the non-enantioselective interaction between the analytes and the residual silanol group and the improved lipophilicity in CSP **2** might enhance the chiral recognition ability of the CSP for the resolution of cathinone (**3**) and its analogue aryl α-amino ketones (**4**–**14**), as proposed previously for the resolution of α-amino acids, amines and amino alcohols [19]. However, the precise reason for the significantly improved chiral recognition ability of CSP **2** is not clear yet and needs further study. The improved lipophilicity of CSP **2** compared to that of CSP **1** is

Table 1
Comparison of the resolution of cathinone (**3**) and its analogue aryl α-amino ketones (**4**–**14**) on CSP **1** and CSP **2**[a]

Analytes			CSP **1**			CSP **2**		
	R	Ar	k_1	α	R_S	k_1	α	R_S
3	Methyl	Phenyl	0.64 (*S*)	4.38	5.57	1.73 (*S*)	6.66	10.16
4	Methyl	4-Methylphenyl	0.78 (*S*)	5.12	8.89	2.53 (*S*)	6.98	14.15
5	Isopropyl	Phenyl	0.42 (*S*)	2.69	4.27	1.15 (*S*)	5.08	14.48
6	Isopropyl	4-Methylphenyl	0.31 (*S*)	2.32	3.09	0.56 (*S*)	4.78	9.29
7	Isobutyl	Phenyl	0.46 (*S*)	7.83	9.78	1.11 (*S*)	15.46	18.97
8	Isobutyl	4-Methylphenyl	0.53 (*S*)	8.58	9.48	1.54 (*S*)	16.12	19.64
9	Benzyl	Phenyl	0.66 (*S*)	5.38	11.10	2.06 (*S*)	8.27	19.58
10	Benzyl	4-Methylphenyl	0.75 (*S*)	5.67	8.58	2.68 (*S*)	8.52	14.94
11	2-(Methylthio)ethyl	Phenyl	0.64 (*S*)	7.02	9.02	1.80 (*S*)	11.17	18.30
12	2-(Methylthio)ethyl	4-Methylphenyl	0.77 (*S*)	7.70	9.06	2.56 (*S*)	11.59	19.20
13	Isopropyl	1-Naphthyl	0.39 (*S*)	1.72	2.60	0.84 (*S*)	2.85	6.49
14	Isopropyl	2-Naphthyl	0.40 (*S*)	2.78	5.55	0.90 (*S*)	5.58	13.70

[a] Chromatographic data on CSP **1** are quoted from Ref. [18]. Mobile phase: 50% acetonitrile in water containing sulfuric acid (10 mM) and ammonium acetate (1 mM); flow rate: 0.5 ml/min; detection: 254 nm UV; column temperature: 20 °C; k_1: retention factor of the first eluted enantiomer. The absolute configuration of the first eluted enantiomer is presented in the parentheses; α: separation factor; R_S: resolution.

Table 2
Resolution of selected aryl α-amino ketones (**3**, **8** and **10**) on CSP **2** with the variation of the type and the content of organic modifier in aqueous mobile phase[a]

Mobile phase	**3**			**8**			**10**		
	k_1	α	R_S	k_1	α	R_S	k_1	α	R_S
30% CH_3CN + 10 mM H_2SO_4 + 1 mM $CH_3CO_2NH_4$	5.64	6.39	5.40	10.75	16.02	12.76	22.95	8.47	9.23
50% CH_3CN + 10 mM H_2SO_4 + 1 mM $CH_3CO_2NH_4$	1.73	6.66	10.16	1.54	16.12	19.64	2.68	8.52	14.94
80% CH_3CN + 10 mM H_2SO_4 + 1 mM $CH_3CO_2NH_4$	1.10	8.25	9.36	0.41	20.16	17.71	0.64	10.26	13.84
80% CH_3OH + 10 mM H_2SO_4 + 1 mM $CH_3CO_2NH_4$	0.77	7.82	7.74	0.40	13.69	11.03	0.63	7.59	9.07
80% CH_3CH_2OH + 10 mM H_2SO_4 + 1 mM $CH_3CO_2NH_4$	0.68	6.72	6.56	0.36	11.54	8.77	0.61	7.09	7.66

[a] Flow rate: 0.5 ml/min; detection: 254 nm UV; column temperature: 20 °C; k_1: retention factor of the first eluted enantiomer; α: separation factor; R_S: resolution.

evidenced from the retention factors. In reversed phase chromatography, the retention factors of analytes should be greater on more lipophilic CSPs than on less lipophilic ones. As shown in Table 1, the retention factors (k_1) on CSP **2** are greater in every case than those on CSP **1**, indicating that CSP **2** is more lipophilic than CSP **1**. The residual silanol protecting *n*-octyl groups of CSP **2** are thought to be responsible for its improved lipophilicity.

The effect of the structural variation of the analytes on the chiral recognition was generally identical on the two CSPs. For example, when the aryl group (Ar) of the analytes was changed from phenyl to 4-methylphenyl, the separation factors were always improved on the two CSPs, except for the resolution of analytes **5** and **6**. When the aryl group of analyte **5** was changed from the phenyl to the relatively larger 2-naphthyl group (analyte **14**), the separation factor was slightly improved on the two CSPs. However, when the aryl group of analyte **5** was changed from the phenyl to the 1-naphthyl group (analyte **13**), the separation factor was significantly decreased on the two CSPs. In addition, the elution orders determined by injecting configurationally known samples were identical on the two CSPs. From these results, we can conclude that an identical chiral recognition mechanism operates on the two CSPs, although the details of the chiral recognition mechanism are not clear yet.

3.2. Effect of mobile phase modifiers and column temperature on the resolution of aryl α-amino ketones

The chromatographic behaviors for the resolution of α-aryl amino ketones including cathinone on CSP **1** have been reported to be dependent on the content and the type of organic and acidic modifiers and the ammonium acetate concentration in aqueous mobile phase [18]. Similarly, the chromatographic behaviors for the resolution of the three selected analytes including cathinone (**3**, **8** and **10**) on CSP **2** were investigated as a function of the content and the type of organic and acidic modifiers, the ammonium acetate concentration in aqueous mobile phase and the column temperature.

3.2.1. Effect of organic modifiers

The chromatographic results for the resolution of the three selected analytes (**3**, **8** and **10**) on CSP **2** as a function of the content and the type of organic modifiers in aqueous mobile phase at the constant concentrations of the acidic modifier (sulfuric acid) and ammonium acetate and at a constant column temperature are summarized in Table 2. As shown in Table 2, the retention factors (k_1) for the first eluted enantiomers always decrease as the content of acetonitrile in aqueous mobile phase is increased. The decreasing trends of the retention factors on CSP **2** with increasing acetonitrile content in aqueous mobile phase are exactly consistent with those on CSP **1** [18], but these trends on CSP **2** are much more significant than those on CSP **1**, as shown in Fig. 2. The retention behaviors for the resolution of racemic compounds on crown ether-based CSPs have been proposed to stem from the balance between the lipophilic interaction of the analytes with the CSP and the hydrophilic interaction of the analytes with the mobile phase [20]. In reverse phase chromatography, the former interaction is an important factor for the retention of the analytes, especially when the CSP is lipophilic. CSP **1** is quite lipophilic, because of the 3,3′-diphenyl-1,1′-binaphthyl group and CSP **2** should be even more lipophilic, because of the additional *n*-octyl groups. With increasing the content of organic modifier (acetonitrile in this case) in

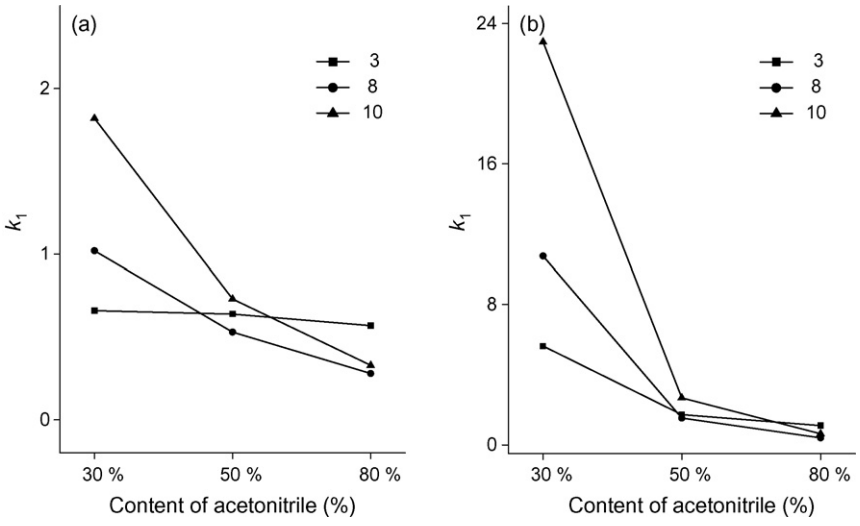

Fig. 2. Trends of the retention factors (k_1) for the resolution of cathinone (**3**) and its analogues (**8** and **10**) on (a) CSP **1** and (b) CSP **2** as a function of the content of acetonitrile in aqueous mobile phase containing sulfuric acid (10 mM) and ammonium acetate (1 mM) at 20 °C. Flow rate: 0.5 ml/min; detection: 254 nm UV. The retention factor data for the plots on CSP **1** are quoted from Ref. [18].

Table 3
Resolution of selected aryl α-amino ketones (**3**, **8** and **10**) on CSP **2** with the variation of the type and the content of acidic modifier in aqueous mobile phase[a]

Mobile phase	**3**			**8**			**10**		
	k_1	α	R_S	k_1	α	R_S	k_1	α	R_S
80% CH_3CN + 0.5 mM H_2SO_4 + 1 mM $CH_3CO_2NH_4$	2.04	5.94	9.89	0.48	20.01	15.80	0.94	9.41	14.76
80% CH_3CN + 1 mM H_2SO_4 + 1 mM $CH_3CO_2NH_4$	1.14	7.34	9.97	0.35	23.02	16.62	0.48	11.60	15.80
80% CH_3CN + 5 mM H_2SO_4 + 1 mM $CH_3CO_2NH_4$	0.97	9.26	10.04.	0.38	22.25	16.48	0.62	10.77	14.88
80% CH_3CN + 10 mM H_2SO_4 + 1 mM $CH_3CO_2NH_4$	1.10	8.25	9.36	0.41	20.16	17.71	0.64	10.26	13.84
80% CH_3CN + 10 mM $HClO_4$ + 1 mM $CH_3CO_2NH_4$	1.26	8.02	9.97	0.43	20.51	18.701	0.71	10.19	15.36
80% CH_3CN + 10 mM CH_3CO_2H + 1 mM $CH_3CO_2NH_4$	2.90	6.33	8.94	1.21	14.76	17.73	1.79	7.91	14.63

[a] Flow rate: 0.5 ml/min; detection: 254 nm UV; column temperature: 20 °C; k_1: retention factor of the first eluted enantiomer; α: separation factor; R_S: resolution.

aqueous mobile phase, the polarity of the mobile phase decreases and, consequently, the lipophilic interaction of the analytes with the CSP decreases, thereby resulting in a decrease of the retention factors. The decreasing trends of the retention factors should be more significant with the more lipophilic CSP.

In general, the separation factors increase as the content of acetonitrile in aqueous mobile phase is increased. However, the resolution factors show a maximum at 50% acetonitrile in an aqueous mobile phase containing a certain amount of acidic modifier (sulfuric acid) and ammonium acetate. As an organic modifier, methanol and ethanol were also used, but acetonitrile was most effective in terms of both the separation factors and the resolutions as shown in Table 2.

3.2.2. Effect of acidic modifiers

The acidic modifier added to the mobile phase has been believed to be used to protonate the primary amino group of the analytes and the resulting primary ammonium ions ($R\text{-}NH_3^+$) have been known to be essential for the chiral recognition through the enantioselective complexation inside the cavity of the crown ether ring of the CSP [20]. The chromatographic results for the resolution of the selected analytes (**3**, **8** and **10**) on CSP **2** as a function of the content and the type of acidic modifier in aqueous mobile phase at a constant concentration of organic modifier (acetonitrile in this case) and ammonium acetate are summarized in Table 3. Previously, the retention factors (k_1) for the resolution of aryl α-amino ketones on CSP **1** were reported to decrease as the content of sulfuric acid in aqueous mobile phase is increased [18]. However, the trends of the retention factors for the resolution of aryl α-amino ketones on CSP **2** as a function of the content of sulfuric acid in aqueous mobile phase are somewhat different from those on CSP **1**. As shown in Table 3, the retention factors for the resolution of aryl α-amino ketones on CSP **2** decrease initially as the content of sulfuric acid in aqueous mobile phase is increased, but they increase as the content of sulfuric acid in aqueous mobile phase is increased further. Consequently, the retention factors show a minimum value when the content of sulfuric acid in aqueous mobile phase reaches 1 mM for analytes **8** and **10** or reaches 5 mM for analyte **3**. In contrast, the separation factors and the resolutions show their highest values when the content of sulfuric acid in aqueous mobile phase reaches 1 mM for analytes **8** and **10** or reaches 5 mM for analyte **3**. However, the reason for these characteristic chromatographic behaviors is not clear yet. In addition to sulfuric acid, perchloric and acetic acid were also tested as an acidic modifier. As shown in Table 3, these three different acidic modifiers are all effective as an acidic modifier, but acetic acid is slightly worse than the other two acids in terms of the separation factors. In addition, the retention factors are more than two times larger when acetic acid is used as an acidic modifier compared with those observed when sulfuric acid or perchloric acid is used.

3.2.3. Effect of ammonium acetate concentration

Ammonium acetate has been used as an important inorganic modifier in aqueous mobile phase in order to control the retention behaviors for the resolution of racemic α-amino acids, amines and amino alcohols on CSP **1** [14–17] and CSP **2** [19]. The ammonium ions (NH_4^+) compete with the primary ammonium ions ($R\text{-}NH_3^+$) of the analytes for the complexation inside the cavity of the crown ether ring of the CSPs and, consequently, the retention times of the analytes are diminished by adding ammonium acetate to the aqueous mobile phase. The chromatographic results for the resolution of the three selected aryl α-amino ketones (**3**, **8** and **10**) on CSP **2** as a function of the ammonium acetate concentration in aqueous mobile phase are summarized in Table 4. As shown in Table 4, the three selected analytes are resolved quite well, but the retention factors are quite large without ammonium acetate in aqueous mobile phase. As the content of ammonium acetate in aqueous mobile phase is increased, the retention factors decrease significantly, but the separation factors increase. The addition of ammonium acetate (0.5 mM) to aqueous mobile phase also improves the resolutions, but further addition of ammonium acetate (1 mM) does not improve the resolutions any more.

3.2.4. Effect of column temperature

The resolution of the three selected aryl α-amino ketones (**3**, **8** and **10**) on CSP **2** as a function of the column temperature is also summarized in Table 4. As the column temperature is lowered

Table 4
Resolution of selected aryl α-amino ketones (**3**, **8** and **10**) on CSP **2** with the variation of the ammonium acetate concentration in aqueous mobile phase and the column temperature[a]

Mobile phase	**3**			**8**			**10**		
	k_1	α	R_S	k_1	α	R_S	k_1	α	R_S
80% CH_3CN + 10 mM H_2SO_4 + 0 mM $CH_3CO_2NH_4$, 20 °C	7.83	6.75	6.21	3.11	17.88	11.97	4.82	9.18	9.53
80% CH_3CN + 10 mM H_2SO_4 + 0.5 mM $CH_3CO_2NH_4$, 20 °C	1.76	8.02	9.36	0.68	19.19	17.74	1.06	9.94	14.95
80% CH_3CN + 10 mM H_2SO_4 + 1 mM $CH_3CO_2NH_4$, 20 °C	1.10	8.25	9.36	0.41	20.16	17.71	0.64	10.26	14.84
80% CH_3CN + 10 mM H_2SO_4 + 1 mM $CH_3CO_2NH_4$, 30 °C	0.81	7.64	8.71	0.30	18.80	17.25	0.48	9.61	14.19
80% CH_3CN + 10 mM H_2SO_4 + 1 mM $CH_3CO_2NH_4$, 20 °C	1.10	8.25	9.36	0.41	20.16	17.71	0.64	10.26	14.84
80% CH_3CN + 10 mM H_2SO_4 + 1 mM $CH_3CO_2NH_4$, 10 °C	1.20	9.81	8.67	0.42	25.65	15.84	0.72	11.94	14.19

[a] Flow rate: 0.5 ml/min; detection: 254 nm UV; k_1: retention factor of the first eluted enantiomer; α: separation factor; R_S: resolution.

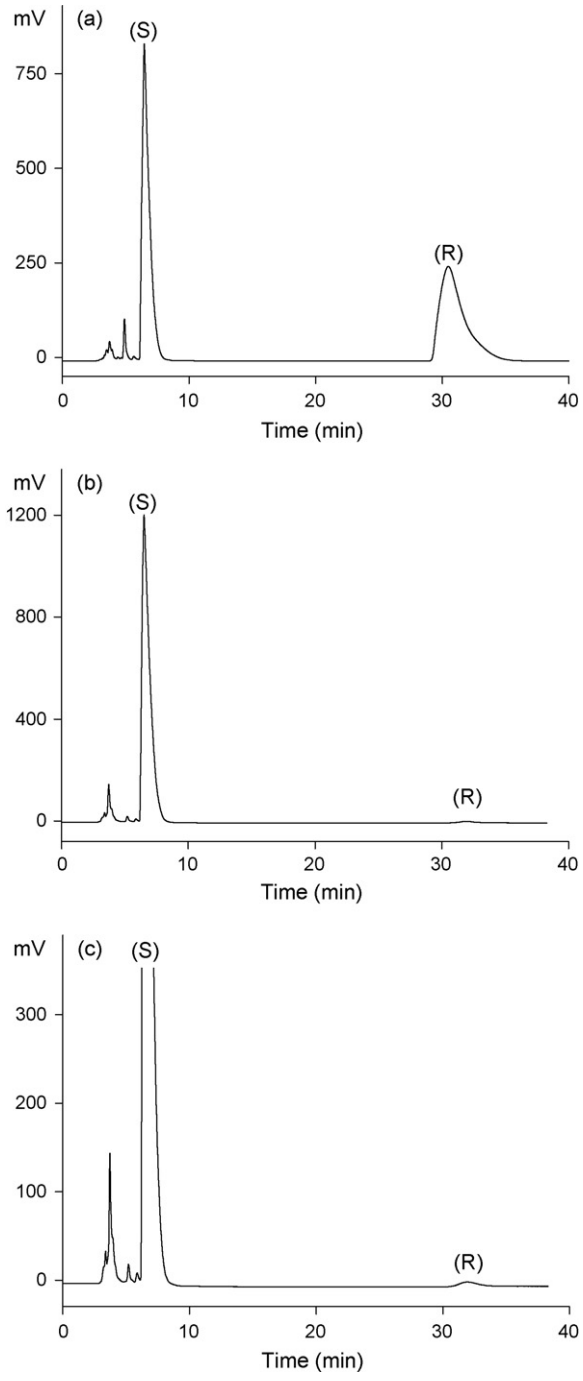

Fig. 3. (a) Chromatogram for the resolution of racemic cathinone (**3**) on CSP **2**. (b) Chromatogram for the resolution of (*S*)-cathinone prepared from (*S*)-alanine on CSP **2**. (c) The expanded chromatogram of (b). Mobile phase: 80% acetonitrile in water + sulfuric acid (10 mM) and ammonium acetate (1 mM); flow rate: 0.5 ml/min; detection: 254 nm UV; column temperature: 20 °C.

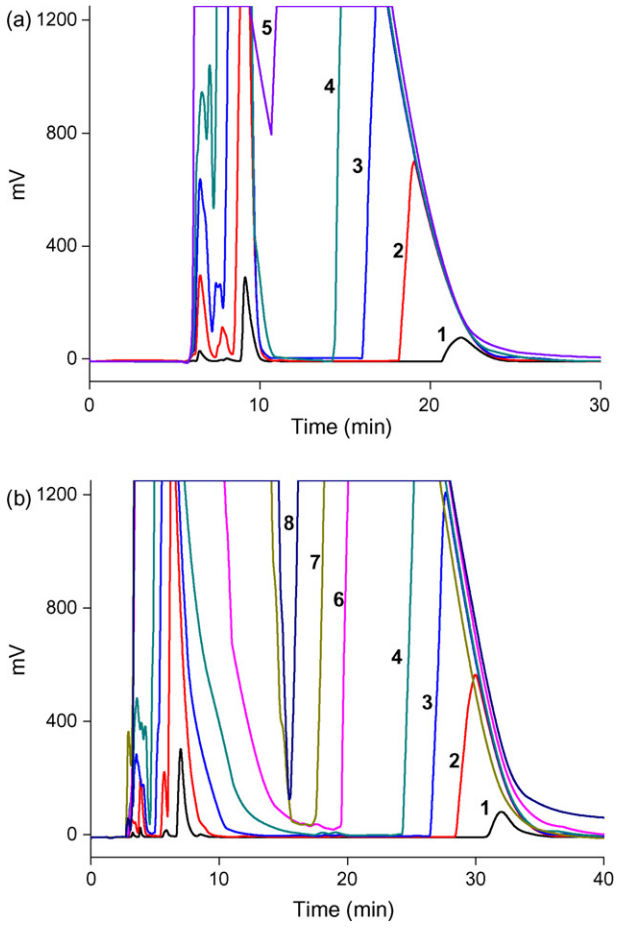

Fig. 4. The loading capacity study for the resolution of racemic cathinone (**3**) (a) on CSP **1** and (b) on CSP **2**. Chiral column size: 150 mm × 4.6 mm i.d.; injected sample amount: (1) 1.0 μl (0.005 mg), (2) 10 μl (0.05 mg), (3) 25 μl (0.125 mg), (4) 50 μl (0.25 mg), (5) 100 μl (0.5 mg), (6) 150 μl (0.75 mg), (7) 200 μl (1.00 mg), (8) 300 μl (1.50 mg); mobile phase: (a) 50% acetonitrile in water containing sulfuric acid (10 mM) and ammonium acetate (1 mM); (b) 80% acetonitrile in water containing sulfuric acid (10 mM) and ammonium acetate (1 mM); detection: 254 nm UV; flow rate: 0.5 ml/min; column temperature: 20 °C.

from 30 to 20 °C and then to 10 °C, the retention factors and the separation factors increase and these trends are exactly consistent with those on CSP **1** [18]. The diastereomeric complex formation of the two enantiomers of racemic analytes with the chiral crown ether selector of the CSP is expected to become more favorable at lower temperature and this is more significant with the more stable diastereomeric complex. In this instance, the retention and the separation factors should increase as the column temperature is decreased. The resolution factors also increase as the column temperature is lowered from 30 to 20 °C, but they decrease as the column temperature is lowered further to 10 °C. When the column temperature was lowered to 10 °C, the chromatographic peaks corresponding to the second eluted enantiomers began to show tailing and the peak tailing of the second eluted enantiomers at lower temperature might be responsible for the diminished resolution factors at 10 °C.

3.3. *Practical application of CSP **2***

The practical usefulness of CSP **1** in the determination of the enantiomeric purity of cathinone was demonstrated in a previous study [18]. Similarly, the practical usefulness of CSP **2** is demonstrated by the chromatograms shown in Fig. 3. The comparison of the chromatogram for the resolution of racemic cathinone (Fig. 3a) with that of the resolution of (*S*)-cathinone prepared from (*S*)-alanine (Fig. 3b or c) shows that (*S*)-cathinone is contaminated with a small amount of (*R*)-cathinone. Based on the peak areas corresponding to the two enantiomers shown in Fig. 3b or c, the enantiomeric purity of (*S*)-cathinone was calculated to be 99.0% ee (*R*:*S* = 99.5:0.5). The enantiomeric purity of (*S*)-cathinone was exactly consistent with that of the starting (*S*)-alanine.

The larger separation factors for the resolution of cathinone and its analogues on CSP **2** compared to those on CSP **1** are expected to make CSP **2** more useful than CSP **1** for the preparative chromatography. As a preliminary test for the practical usefulness of CSP **2** in the preparative scale resolution of racemic cathinone, its loadability was checked. As shown in Fig. 4, the baseline resolution was observed on CSP **2** until 200 μl (1.00 mg) of sample solution was injected. However, the base line resolution was not observed on CSP **1** when only 100 μl (0.50 mg) of sample solution was injected. From these results, the protection of the residual silanol groups of CSP **1** with *n*-octyl groups seems to be quite helpful for the preparative scale resolution of cathinone.

4. Conclusion

CSP **2** was successfully applied to the resolution of cathinone and its analogues. The chiral recognition ability of CSP **2** was much greater than that of CSP **1** in terms of the separation and the resolution factors. From these results, it was concluded that the simple protection of the residual silanol groups of CSP **1** with lipophilic *n*-octyl groups can considerably improve its chiral recognition ability. The chromatographic behaviors for the resolution of cathinone and its analogues on CSP **2** were dependent on the content and the type of the organic and acidic modifiers, the ammonium acetate concentration in aqueous mobile phase and the column temperature. In addition, the loadability of CSP **2** was significantly improved compared to that of CSP **1**. Consequently, we expect that a large chiral column packed with CSP **2** can be successfully utilized in the preparative scale resolution of cathinone or its analogues.

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