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Chromatographic Resolution of α-Amino Acids by (*R*)-(3,3'-Halogen Substituted-1,1'-binaphthyl)-20-crown-6 Stationary Phase in HPLC

Peng Wu,[a,#] Yuping Wu,[a,#] Junhui Zhang,[a] Zhenyu Lu,[a] Mei Zhang,[b] Xuexian Chen,[a] and Liming Yuan*,[a]

[a] *Department of Chemistry, Yunnan Normal University, Kunming, Yunnan 650500, China*
[b] *Department of Traditional Chinese Medicine, Yunnan University of Traditional Chinese Medicine, Kunming, Yunnan 650500, China*

Three new chiral stationary phases (CSPs) for high-performance liquid chromatography were prepared from *R*-(3,3'-halogen substituted-1,1'-binaphthyl)-20-crown-6 (halogen＝Cl, Br and I). The experimental results showed that *R*-(3,3'-dibromo-1,1'-binaphthyl)-20-crown-6 (**CSP-1**) possesses more prominent enantioselectivity than the two other halogen-substituted crown ether derivatives. All twenty-one α-amino acids have different degrees of separation on *R*-(3,3'-dibromo-1,1'-binaphthyl)-20-crown-6-based **CSP-1** at room temperature. The enantioselectivity of **CSP-1** is also better than those of some commercial *R*-(1,1'-binaphthyl)-20-crown-6 derivatives. Both the separation factors (α) and the resolution (R_s) are better than those of commercial crown ether-based CSPs [CROWNPAK CR(＋) from Daicel] under the same conditions for asparagine, threonine, proline, arginine, serine, histidine and valine, which cannot be separated by commercial CR(＋). This study proves the commercial usefulness of the *R*-(3,3'-dibromo-1,1'-binaphthyl)-20-crown-6 chiral stationary phase.

Keywords α-amino acid, chiral crown ethers, stationary phase, high-performance liquid chromatography

Introduction

Chiral stationary phases (CSPs) have been established as the most accurate and convenient means for the exact determination of the enantiomeric composition of chiral compounds in high-performance liquid chromatography (HPLC). Various CSPs have been developed.[1,2] The crown ether CSPs have attracted the most attention since they were developed by Sogah and Cram in the 1970s.[3] (3,3'-Diphenyl-1,1-binaphthyl)-20-crown-6,[4-8] (＋)-(18-crown-6)-2,3,11,12-tetracarboxylic acid,[9,10] and phenolic pseudo chiral crown ethers[11,12] are the most effective CSPs of the crown ether type.[13] A series of CSPs based on immobilized chiral crown ethers [(＋)-18-crown-6 tetracarboxylic acid] and (3,3-diphenyl-1,1-binaphthyl)-20-crown-6 on polystyrene or silica gel showed good resolution ability for α-amino acids and their derivatives.[14-21] The related commercialized CSP known as CROWNPAK CR(＋) (Daicel Chemical Industries) has proven to be useful for the chromatographic resolution of chiral compounds that contain a primary amino group.[22-24] However, the enantioseparation of some α-amino acids on commercialized CSPs is inconvenient because a lower temperature (5－10 ℃) is needed. To develop new and effective crown ether-based CSPs is really a challenge task. In the present study, we report a series of stationary phases of *R*-(3,3'-halogen substituted-1,1'-binaphthyl)-20-crown-6 coated on silica gel. The preparation of three novel chiral crown ether stationary phases, *R*-(3,3'-dibromo-1,1'-binaphthyl)-20-crown-6 (**CSP-1**), *R*-(3,3'-dichloro-1,1'-binaphthyl)-20-crown-6 (**CSP-2**), and *R*-(3,3'-diiodo-1,1'-binaphthyl)-20-crown-6 (**CSP-3**) (Figure 1) was initiated from binaphthol. The chiral recognition ability of **CSP-1** was greater than that of the commercial CROWNPAK CR(＋) column for the resolution of α-amino acids.

Experimental

Apparatus

The HPLC system consisted of a Shimadzu LC-15C HPLC pump and an SPD-15C UV/V detector (Japan) operating at 210 nm. Data acquisition and processing were performed with an N2000 chromatography data system. An Auto science AT-330 column heater (±0.1 ℃) was used to control the column temperature during the HPLC separations. ^{1}H NMR and ^{13}C NMR

* E-mail: yuan_limingpd@126.com; Tel: 0086-0871-65941088, Fax: 0086-0871-65941088; #These Authors equally contributed to the work.
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spectra were obtained with a Varian Mercury Plus 300 and a Unity-Inova 500 spectrometer. Scanning electron microscopy (SEM) images were recorded on an FEI Quanta FEG 650 scanning electron microscope (USA).

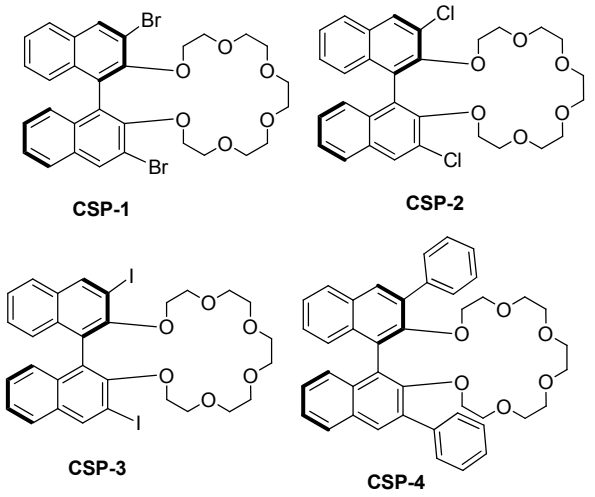


Figure 1 The structure of the crown ether chiral stationary phases (CSPs).

A stainless steel empty column (250 mm long×4.6 mm i.d.) and a 1/3 HP liquid pump were purchased from Alltech (USA). A CROWNPAK CR (+) chiral crown ether column (150 mm long×4.0 mm i.d.) was purchased from Daicel (Japan).

Materials

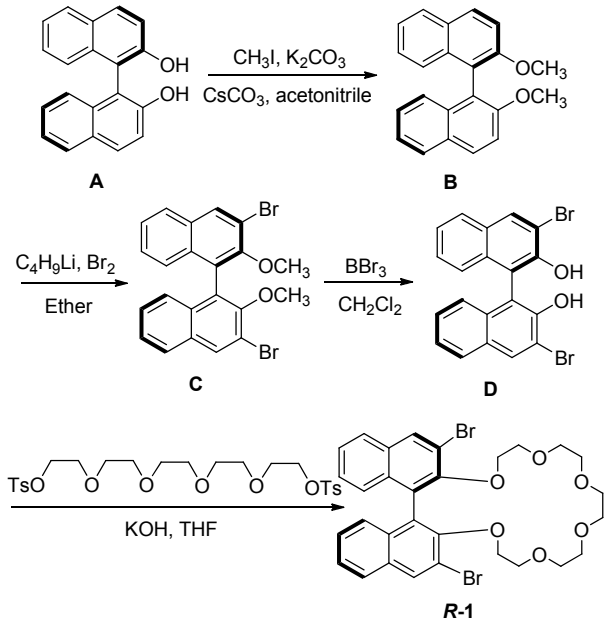
All chemicals were at least analytical grade, including (*R*)-(+)-1,1'-bi-2-naphthol ($C_{20}H_{14}O_2$, 99%, Daicel, China), methyl iodide (CH_3I, 99%, Xiya Reagent, China), *n*-butyllithium (*n*-C_4H_9Li, 1.6 mol/L in hexanes, Adamas-beta, China), hexachloroethane (C_2Cl_6, 98%, Adamas-beta, China), iodine (I_2, 96%, Adamas-beta, China), phenylboronic acid ($C_6H_7BO_2$, 98%, Adamas-beta, China), pentaethylene glycol ditosylate ($C_{24}H_{34}O_{10}S_2$, 95%, Alfa Aesar, USA), boron tribromide (BBr_3, 95%, Adamas-beta, China), and C_{18} silica gel (average particle size: 5 μm, average pore diameter: 12 nm) from the Sepax of America. All reactions were performed in purified and dried solvents and glass dried under nitrogen gas.

Synthesis of *R*-(3,3'-dibromo-1,1'-binaphthyl)-20-crown-6 (*R*-1)

R-(3,3'-Dibromo-1,1'-binaphthyl)-20-crown-6 (***R*-1**) was synthesized using (*R*)-(+)-1,1'-bi-2-naphthol as the starting material. The synthetic route is shown in Scheme 1.

K_2CO_3 (20.0 g, 145 mmol) and $CsCO_3$ (0.50 g, 1.5 mmol) were added to a solution of (*R*)-(+)-1,1'-bi-2-naphthol (10.0 g, 35 mmol) in 250 mL of acetonitrile, and the solution was stirred under nitrogen at 70 ℃. After 10 min, methyl iodide (6.5 mL, 0.1 mol) was added dropwise over a period of 15 min. Then, the mixture was refluxed for 4 h. The reaction mixture was extracted by dichloromethane. The organic phase was washed, dried and evaporated at 50 ℃ to afford **(*R*)-B** (10.51 g, 95.4% yield). (NMR in Supplementary Information S1)

Scheme 1 Synthetic route of *R*-(3,3'-dibromo-1,1'-binaphthyl)-20-crown-6



n-Butyllithium (23.5 mL, 37.6 mmol) was added dropwise to a stirred solution of tetramethylethylenediamine (3.8 mL, 26.6 mmol) in dry diethyl ether (150 mL). After the mixture was stirred for 15 min at 25 ℃, **(*R*)-B** (5.0 g, 16 mmol) was added, and the suspension was stirred for 3 h. The mixture was cooled to −75 ℃, and 3 mL of bromine (9.6 g, 60 mmol) in 10 mL of pentane was added over a 10 min period. The mixture was warmed to 25 ℃ and stirred for 3 h. Then, 300 mL of a saturated solution of Na_2SO_3 was added, and the mixture was stirred for an additional 2 h. The mixture was then extracted with dichloromethane, and the organic layer was dried and evaporated. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 20∶1) to give **(*R*)-C** (3.8 g, 50.3% yield). (NMR in Supplementary Information S2)

BBr_3 (2 mL, 32.3 mmol) was added to a solution of **(*R*)-C** (3.0 g, 6.36 mmol) in dry dichloromethane (150 mL) at 0 ℃, and the mixture was stirred for 24 h at 25 ℃. The reaction was quenched by the slow addition of water. The organic layer was washed with water, dried, evaporated, and chromatographed on silica gel (silica gel, petroleum ether/acetone, 30∶1, *V*/*V*) to obtain **(*R*)-D** (2.31 g, 81.2% yield). (NMR in Supplementary Information S3)

(*R*)-D (2.0 g, 4.46 mmol) and pentaethylene glycol ditosylate (2.5 g, 4.5 mmol) in 250 mL dry tetrahydrofuran were stirred under nitrogen, and KOH (0.24 g, 4.3 mmol) was added. The mixture was refluxed for 72 h at 60 ℃. The mixture was extracted with 300 mL dichloromethane/water (1∶1, *V*/*V*), and the organic layer

was dried and evaporated. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 10∶1, *V*/*V*) to obtain a viscous yellow oil of the desired compound ***R*-1** (2.38 g, 83.1% yield) (NMR in Supplementary Information S4 and Figures S1 and S2)

Synthesis of *R*-(3,3'-dichloro-1,1'-binaphthyl)-20-crown-6 (*R*-2) and R-(3,3'-diiodo-1,1'-binaphthyl)-20-crown-6 (*R*-3)

The synthesis of the other two halogen substituted crown ethers (***R*-2**, ***R*-3**) was similar to that of ***R*-1**. The details are described in the Supplementary Information (Scheme S1 and Scheme S2).

Preparation of CSPs and column packing

The preparation of ***R*-1**-coated **CSP-1** followed the traditional coating method: compound ***R*-1** (0.40 g, 0.71 mmol) was dissolved in 10 mL of dichloromethane. Then, the solution was added slowly to the C_{18} silica gel (3.60 g) through a dropper. When the dichloromethane was removed, the residue of ***R*-1** was coated on the C_{18} silica gel. The stationary phase was through a sieve and the **CSP-1** was prepared. **CSP-2** and **CSP-3** were prepared using the same method.

A 4.0 g mass of the prepared **CSPs** was dispersed in a mixture of methanol/water (1∶10, *V*/*V*). Then, the suspension was packed into a stainless steel column using the conventional slurry packing method with an Alltech slurry packer at 40−50 MPa. The water was used as the pressuring solvent to avoid the dissolution of crown ethers (Supplementary Information Figure S10). The column was conditioned for 20−30 min using the perchloric acid solution (10 mmol/L, pH=2) before use. The t_0 was estimated using sodium nitrate salt in HPLC**.**

Results and Discussion

Characterization of CSPs

The prepared **CSP-1**, CSP-**2**, and **CSP-3** were characterized by elemental analysis (Supplementary Information Table S1). As shown in Table S1, the carbon, nitrogen and hydrogen contents of the C_{18} silica gel were 16.84%, <0.5%, and 19%, respectively. The carbon and hydrogen contents of the coated CSPs increased, indicating the crown ethers were successfully coated on the C_{18} silica gel. To further investigate the coating properties of the surface wall of the C_{18} silica, SEM was performed. The surface of the C_{18} silica spheres was smooth, and the hybrid particles had a uniform spherical morphology (Figures 2a, b and c). In addition, the coating composition of **CSP-1** was studied by energy-dispersive spectrometry (EDS) analysis. The spatial distribution of the Si, C, O and Br of the **CSP-1** was examined by elemental mapping analysis (Figure 2d). Br was distributed homogeneously throughout the C_{18} silica. Therefore, ***R*-1** was successfully coated on the C_{18} silica gel.

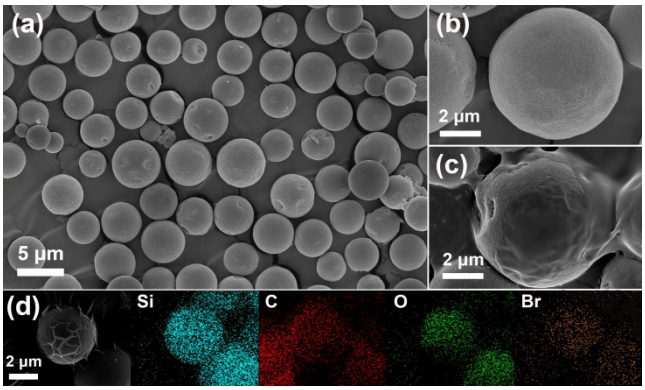


Figure 2 (a) SEM image of silica spheres; (b) SEM image of the C_{18} silica before coating its surface; (c) SEM image of the coated surface; (d) a close view of the detailed features of the **CSP-1** electrode, along with the (Si, C, O, Br) corresponding EDS element mapping of the silica composite.

Comparison of CSP-1 with structurally similar CSPs for the separation of α-amino acids

To investigate the effect of different CSP structures on the recognition of racemic amino acids, we prepared a series of new **CSPs**, **CSP-1**, **CSP-2** and **CSP-3**. Their structures are shown in Figure 1, and the synthetic methods are provided in the supporting information (Scheme S1 and Scheme S2). The CSPs were evaluated for the separation of various α-amino acid enantiomers, and the resolution results are summarized in Table 1. The experimental results indicate that all twenty-one α-amino acids have different degrees of separation on **CSP-1** at room temperature. The chromatograms are shown in Figure 3 and Figure S7 (Supplementary Information). Consequently, **CSP-1** possesses prominent enantioselectivity. Most α-amino acids could be separated on **CSP-2**, except tryptophan, glutamine, aspartic acid, alanine, proline, threonine and histidine (Table 1). However, **CSP-3** only separated three amino acids, leucine, cysteine, and alanine. As shown in Table 1, the enantioselectivity of the three crown ether-based CSPs is ranked as **CSP-1**>**CSP-2**>**CSP-3** under the same conditions.

Comparison of a CSP-1 column with a commercial CROWNPAK CR(+) column for the separation of α-amino acids

The resolution of 21 α-amino acids on **CSP-1** and commercial CSP CR(+) using perchloric acid solution (pH=2) as a mobile phase with a flow rate of 0.5 mL•min^{-1} at 25 ℃ is summarized in Table 1. The results showed that the chiral recognition ability of **CSP-1** was excellent; all the α-amino acids could have different degrees of separation on the **CSP-1** packed column, whereas only 15 analytes were separated on commercial **CSP** CR(+). Proline, histidine, valine, asparagine, threonine, arginine, and serine were not separated on the CR(+) column, which is basically consistent with the

Table 1 Comparison of the resolutions of *α*-amino acids on **CSP-1**, **CSP-2** and **CSP-3** based columns

Racemates	CR(+)			**CSP-1**			**CSP-2**			**CSP-3**		
	k_1	α	R_s	k_1	α	R_s	k_1	α	R_s	k_1	α	R_s
Phenylglycine	1.62	4.01	7.52	5.20	1.48	6.82	7.15	1.70	5.52	2.91	1.00	—
4-Hydroxyphenylglycine	1.08	6.14	11.5	4.73	1.57	8.28	6.46	1.45	4.33	1.33	1.00	—
Methionine	1.25	1.98	2.56	2.85	1.34	2.64	4.19	1.23	1.38	2.47	1.00	—
Tyrosine	5.04	1.58	4.32	8.83	1.26	2.25	8.85	1.25	2.86	2.92	1.00	—
Phenylalanine	3.84	1.36	0.90	12.8	1.26	1.35	3.31	2.12	1.80	3.11	1.00	—
Arginine	0.37	1.00	—	0.51	1.38	1.75	0.94	1.15	0.67	0.52	1.00	—
Tryptophan	21.8	1.25	1.23	4.86	2.39	1.83	7.58	1.00	—	3.78	1.00	—
Lysine	2.62	1.30	1.61	0.54	1.26	1.48	1.06	1.12	0.64	0.33	1.00	—
Leucine	1.58	1.68	0.88	3.81	1.39	1.83	4.84	1.28	1.51	1.38	2.25	0.92
Isoleucine	1.23	1.25	0.50	3.86	1.24	1.03	4.28	1.25	1.17	3.34	1.00	—
Glutamic acid	0.32	3.03	1.69	0.65	1.53	2.52	0.96	1.30	1.61	0.65	1.00	—
Glutamine	0.25	2.19	1.28	0.34	1.55	2.61	0.47	1.00	—	0.51	1.00	—
Aspartic acid	0.27	1.53	0.66	0.45	1.10	0.73	0.54	1.00	—	0.49	1.00	—
Cysteine	0.39	2.34	2.77	0.46	1.26	2.12	1.34	1.09	0.54	0.49	1.17	0.31
Alanine	0.22	2.21	0.62	0.33	1.43	1.92	0.47	1.00	—	0.40	1.32	0.41
Proline	0.20	1.00	—	0.19	1.81	0.80	0.49	1.00	—	0.73	1.00	—
Serine	0.23	1.00	—	0.38	1.42	0.92	2.53	2.55	1.89	0.46	1.00	—
Threonine	0.21	1.00	—	0.22	2.11	1.67	0.53	1.00	—	0.52	1.00	—
Asparagine	0.23	1.00	—	0.43	1.30	0.86	0.54	1.35	0.75	0.54	1.00	—
Histidine	0.26	1.00	—	1.71	1.26	2.95	0.62	1.00	—	0.48	1.00	—
Valine	0.61	1.00	—	2.55	1.15	1.30	1.61	1.20	0.92	1.34	1.00	—

Chromatographic conditions: **CSP-1** (250 mm long×4.6 mm i.d.), **CSP-2** (250 mm long×4.6 mm i.d.), **CSP-3** (250 mm long×4.6 mm i.d.). Mobile phase: perchloric acid (10 mmol/L, pH=2). Flow rate: 0.5 mL•min^{-1}. Detection: 210 nm UV. Temperature: 25 ℃. k_1: retention factor of the first eluted enantiomer. α: separation factor. R_S: resolution. —: could not be separated.

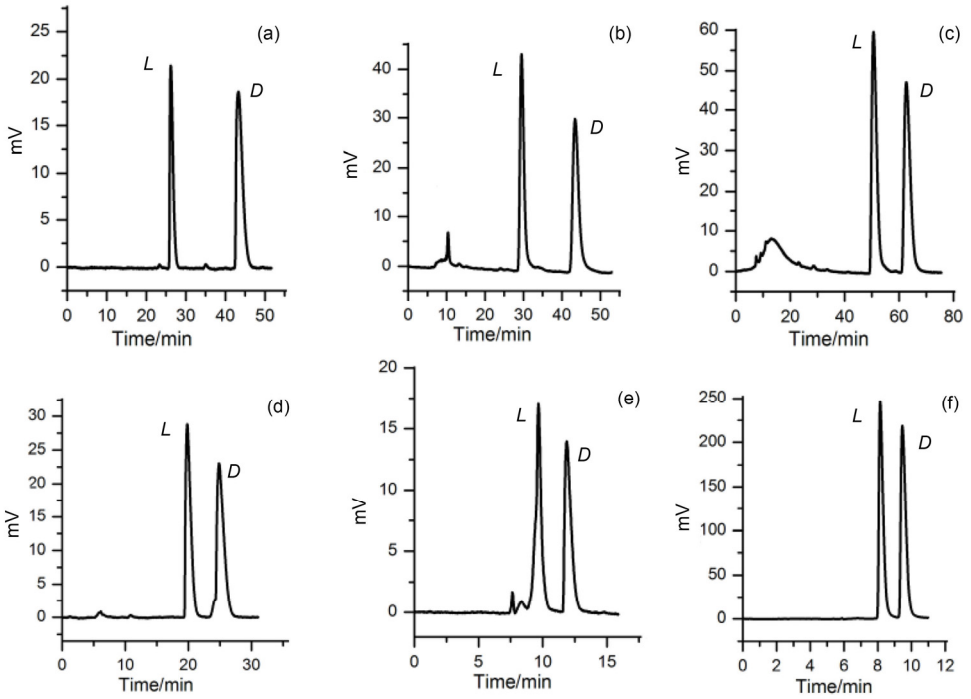


Figure 3 Representative chromatograms of *α*-amino acids on the **CSP-1** (250 mm long×4.6 mm i.d.): (a) phenylglycine, (b) 4-hydroxyphenylglycine, (c) tyrosine, (d) methionine, (e) glutamic acid, and (f) histidine using a perchloric acid solution (10 mmol/L, pH =2) as the mobile phase at a flow rate of 0.5 mL•min^{-1} at 25 ℃. The signals were monitored with a UV detector at 210 nm.

released application notes of commercial CROWNPAK CR(+) column. The representative chromatograms for comparison are shown in Supplementary Information Figure S8. In addition, the Crownpak CR-I(+) has been reported[25] which has the similar stationary phase with CROWNPAK CR(+) or CR(−). However, the synthesis of Crownpak CR-I is very complicated than that of the CROWNPAK CR(+) or CR(−),[26] especially more complicated than that of **CSP-1**. On the other hand, the proline is really resolved on **CSP-1**, which is not resolved on Crownpak CR-I column.

The ring of crown ethers can form complexes with $R\text{-}NH_3^+$ guests, and the direction and extent of configurational bias in the crown ether are important for enantioseparation. Under acidic conditions at pH=2, amino acids are protonated and converted into RNH_3^+ cations. When the 3,3'-position of *R*-(1,1'-binaphthyl)-20-crown-6 was disubstituted with bromine, chlorine, iodine and phenyl, different directions and extents of configurational bias for the crown ether were observed. The substituent identification ability followed the order Br>Ph>Cl>I; these selectivity trends can be explained by both position and species of the substituent. Considering that binaphthyl crown ether skeleton prefers to adopt a twisted conformation, the conformational complementarity between binaphthyl crown ethers and substituent is related to the Br and phenyl selectivity. The 3,3'-dibromo substituents exhibit stronger basicity than other substituents and have the proper size for the binding cleft. The reason for this selectivity towards dibromo is a result of steric hindrance. Because the 1,1'-binaphthyl group of the crown ether and the α-amino acid possess chirality, chiral recognition is obtained on the crown ether column. However, the influence of the chiral microenvironment on the chiral properties of chromatographic systems is complicated; it is difficult to completely understand the chiral recognition mechanism of enantioseparation. To determine the mechanism of chiral recognition, including the exact role of the two bromine groups of **CSP-1**, further studies are needed and are currently underway in our laboratory.

Effect of temperature on the HPLC separation

Cram and co-workers[27,28] observed differences in the stability of two diastereomeric (host-guest) complexes formed between a chiral crown ether and two enantiomers of an amino acid, which increases with decreasing temperature. To investigate the effect of temperature on the enantioselectivity of **CSP-1**, histidine and serine were chosen for a more detailed study. When other chromatogram conditions did not change, we tried to find out the optimum temperature phase for the resolution of a broad spectrum of α-amino acids on **CSP-1** by varying the temperature phase, as shown in Table 2 and Figure 4. When the temperature of the column decreased from 24 to 8 ℃, all three chromatographic parameters, *i.e.*, the retention factors (*k*), separation factors (α), and resolution (R_S), increased. The results shown in Table 2 are consistent with Cram and co-workers' observations.

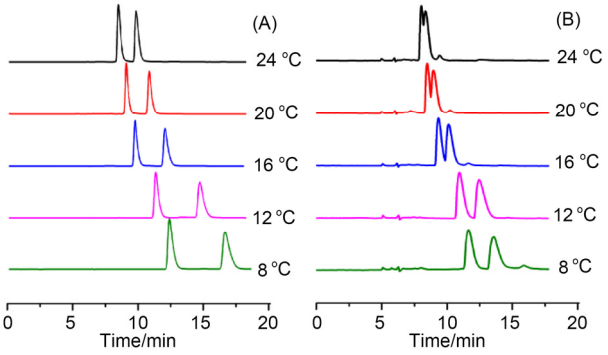


Figure 4 Chromatograms on the **CSP-1** packed column for the separation of (A) histidine and (B) serine at 8−24 ℃. Perchloric acid solution (10 mmol/L, pH=2) as the mobile phase, flow rate of 0.5 mL•min^{-1} and with UV detection at 210 nm.

The van't Hoff plots for the separation of all analytes show good linearity (Supplementary Information Figure S9), suggesting no changes in the interaction mechanism in relation to temperature in the studied temperature range. The thermodynamic parameters for the transfer of all analytes from the mobile phase to the stationary phase of **CSP-1** are summarized in Table 3. The negative values of Δ*G* indicate that the transfer of all analytes from the mobile phase to the stationary phase of **CSP-1** was a thermodynamically spontaneous process that was controlled by Δ*H* and Δ*S*. More negative values of Δ*G* were more favourable for the transfer of the solute from the mobile phase to the stationary phase, resulting in stronger retention for the solute on the stationary phase.

Conclusions

In summary, we have synthesized three chiral crown ethers for HPLC. The *R*-(3,3'-dibromo-1,1'-binaphthyl)-20-crown-6-coated **CSP-1** exhibits excellent enantioselectivity; all 21 α-amino acids have different degrees of separation at room temperature. The resolution ability of **CSP-1** is better than those of two other CSPs. Compared with commercial CROWNPAK CR(+) column, the **CSP-1** based column had stronger chiral recognition ability. The resolution of most α-amino acids on **CSP-1** was higher than that of the commercial crown ether-based CSPs (CROWNPAK CR(+) from Daicel). Proline, histidine, valine, asparagine, threonine, arginine and serine were not separated by the commercial CROWNPAK CR (+) under the same conditions. In addition, the synthetic steps and preparation procedure of chiral crown ether **CSP-1** are less complicated than those of commercial CR(+), which will make **CSP-1** more widely used in practice. This work suggests that chiral crown ether **CSP-1** will become a useful chiral selector for α-amino acids in the near future.

Table 2 Effect of column temperature on retention and enantionselectivity of histidine and serine on **CSP-1**[a]

Temperature/℃	Histidine				Serine			
	k_1'	k_2'	α	R_s	k_1'	k_2'	α	R_s
8	1.39	2.37	1.72	4.42	1.33	1.71	1.29	1.90
12	1.19	1.84	1.56	2.25	1.19	1.49	1.25	1.54
16	0.87	1.33	1.51	2.22	0.87	1.03	1.18	1.05
20	0.77	1.10	1.43	2.18	0.69	0.79	1.13	0.62
24	0.62	0.89	1.42	2.06	0.61	0.65	1.09	0.50

[a] The chromatographic condition was same as that in Table 1 except temperature.

Table 3 Values of ΔH, ΔS, ΔG and r^2 (r refers to the linear correlation coefficient of ln k'–1/T plot) for histidine and serine

Analyte	ΔH/(kJ•mol^{-1})	ΔS/(J•mol^{-1}•K^{-1})	ΔG/(kJ•mol^{-1})	r^2
L-Histidine	–27.94±0.65	–85.74±10.44	–2.45±0.65	0.9973
D-Histidine	–37.51±0.94	–115.09±11.86	–3.31±0.94	0.9963
L-Serine	–28.19±0.78	–87.65±10.77	–2.14±0.78	0.9924
D-Serine	–35.17±1.32	–109.23±11.45	–2.71±1.32	0.9908

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(Zhao, X.)

