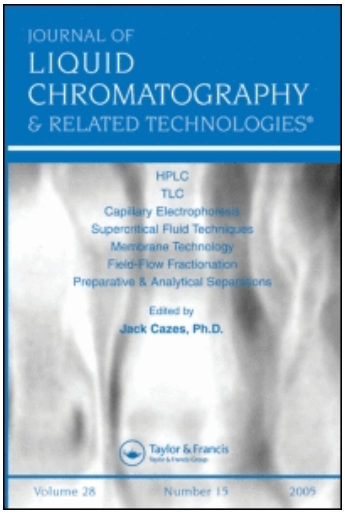

Journal of Liquid Chromatography & Related Technologies
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597273

Enantioseparation of Paroxetine Precursors by HPLC on Amylose and Tartardiamide-Based Chiral Stationary Phases

Zongbi Bao[a]; Baogen Su[a]; Yiwen Yang[a]; Qilong Ren[a]
[a] Department of Chemical and Biochemical Engineering, National Laboratory of Secondary Resources Chemical Engineering, Zhejiang University, Hangzhou, P. R. China

To cite this Article Bao, Zongbi , Su, Baogen , Yang, Yiwen and Ren, Qilong(2008) 'Enantioseparation of Paroxetine Precursors by HPLC on Amylose and Tartardiamide-Based Chiral Stationary Phases', Journal of Liquid Chromatography & Related Technologies, 31: 8, 1147 — 1161
To link to this Article: DOI: 10.1080/10826070802000665
URL: http://dx.doi.org/10.1080/10826070802000665

Journal of Liquid Chromatography & Related Technologies®, 31: 1147–1161, 2008

ISSN 1082-6076 print/1520-572X online
DOI: 10.1080/10826070802000665

Enantioseparation of Paroxetine Precursors by HPLC on Amylose and Tartardiamide-Based Chiral Stationary Phases

Zongbi Bao, Baogen Su, Yiwen Yang, and Qilong Ren

Department of Chemical and Biochemical Engineering, National Laboratory of Secondary Resources Chemical Engineering, Zhejiang University, Hangzhou, P. R. China

Abstract: Two important precursors of antidepressant *trans*-(−)-paroxetine, i.e., *trans*-4-(4′-fluorophenyl)-3-hydroxymethyl-1-methylpiperidine and *trans*-3- ethoxycarbonyl-4-(4′-fluorophenyl)-1-methylpiperidine-2,6-dione have been directly separated by HPLC on Chiralpak AD-H and Kromasil CHI-TBB columns. All the experiments were conducted in the normal phase mode. The mobile phases were mixtures of *n*-hexane and alcohol modifiers including ethanol, 2-propanol, and 1-propanol, with or without addition of diethylamine. Excellent separation was obtained for both enantiomers. Effects of the type and content of polar alcohol modifiers on enantioseparation was investigated. An unusual retention behavior was observed, i.e., the retention of enantiomers increased when the alcohol modifier was changed from 2-propanol to ethanol. The elution orders of the enantiomers on both columns were examined. The thermodynamic parameters obtained from van't Hoff plots were all negative, which indicated that the chiral separation were enthalpically driven.

Keywords: Enantioseparation, Chiral stationary phase, Chiralpak AD-H, Kromasil CHI-TBB, Paroxetine precursors, HPLC

INTRODUCTION

Trans-(−)-paroxetine (**1**), (3S,4R)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4′-fluorophenyl)piperidine, is a selective 5-hydroxytryptamine (5-HT)

Correspondence: Zongbi Bao, Department of Chemical and Biochemical Engineering, National Laboratory of Secondary Resources Chemical Engineering, Zhejiang University, Hangzhou 310027, P. R. China. E-mail: renql@zju.edu.cn

reuptake inhibitor currently used as an antidepressant,[1] which is used in the treatment of social anxiety disorder, obsessive compulsive disorder, panic disorder, and generalized anxiety disorder.[2] Clinical studies show that the drug is as effective as tricyclic antidepressants, but has much less side effects.[3,4] The molecular structure of paroxetine contains two chiral centers in the piperidine ring, resulting in two pairs of enantiomers, i.e., the *cis* and *trans* forms.

Most of the manufacturing routes developed towards the preparation of this compound, marketed as a single enantiomer, involve the key intermediate, racemic mixtures of *trans*-4-(4′-fluorophenyl)-3-hydroxymethyl -1-methylpiperidine (**2**), which can be obtained from *trans*-3- ethoxycarbonyl-4-(4′-fluorophenyl)-1-methylpiperidine-2,6-dione (**3**) by a reduction step. (Figure 1). The optically pure enantiomers of **2** and **3** can be obtained by chiral resolution using a biocatalytic method[5] or diastereoisomeric crystallization of salts with chiral acids such as (−)-di-p-toluoyltartaric acid and L-tartaric acid.[6,7]

The resolution of chiral compounds by high performance liquid chromatography (HPLC) has rapidly advanced in the past decade with the development of a variety of chiral stationary phases (CSPs).[8–10] Separation of enantiomers by HPLC can well be established with nearly 100 different CSPs commercially available.

To the best of our knowledge, the direct enantiomeric separation of both precursors of *trans*-(−)-paroxetine by chiral HPLC has not previously been demonstrated and published. Zukowski et al.[2] and Ferretti et al.[11] tried a number of chiral columns and mobile phases and established a chiral HPLC method suitable to separate paroxetine racemates on the Chiralpak AD column. Vivekanand et al.[12] reported that an excellent separation of another important intermediate of paroxetine was achieved using Chiralpak AD with a mobile phase consisting of hexane, ethanol, and trifluoroacetic acid in the ratio 93:7:0.3 (*v*/*v*/*v*). In this paper, we resolved the racemic compounds **2** and **3** by HPLC using Chiralpak AD-H and Kromasil CHI-TBB columns. The mobile phases employed were mainly mixtures containing *n*-hexane and different alcohol modifiers including ethanol, 2-propanol, and 1-propanol. The effects of the mobile phases, particularly the type and

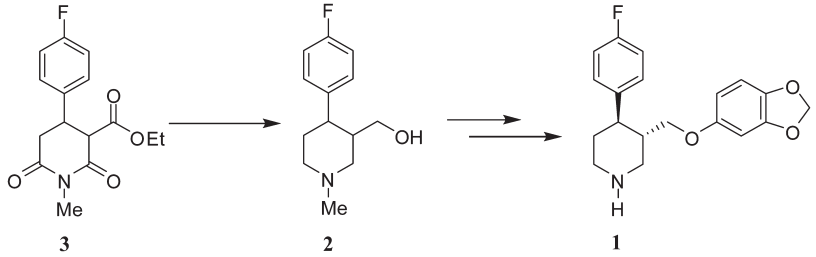

Figure 1. A synthetic pathway of *trans*-(−)-paroxetine (**1**).

content of polar modifiers on the enantioseparation, were investigated. Thermodynamic parameters of enantioseparation of compound **3** were determined and the elution order of both enantiomers was examined.

EXPERIMENTAL

Chemicals and Reagents

All reagents were analytical grade or better. *n*-Hexane, methyl *tert*-butyl ether (MTBE), 2-propanol, and 1-propanol were all of HPLC grade, and provided from Tedia (USA). Anhydrous ethanol (Sinopharm Chemical Reagent Co., Shanghai, China) was an analytical reagent. Analytical grade diethylamine (DEA) and triethylamine (TEA) were obtained from Wulian Reagents Co. (Shanghai, China). The individual *trans*-(−)-**2** and racemates **2** and **3** were kindly supplied by Zhejiang Chiral Medicine Chemicals Co. (Hangzhou, China). The purity of both racemates was more than 98%, and used without further purification. The structures of the studied compounds are shown in Figure 1.

Instrumentation

A Waters (Milford, MA, USA) HPLC system equipped with 1525 binary pump, 717 plus autosampler, 2695 column oven, and 2487 dual λ absorbance detector was used. A polarimeter detector supplied by PDR-Chiral (USA) was used in series with the UV detector. The chromatographic data were acquired and processed with Breeze software (Version 3.3). The Chiralpak AD-H column (250 mm × 4.6 mm, 5 μm) was packed with amylose tris(3,5-dimethylphenylcarbamate) coated on a silica gel support, and obtained from Daicel Chemical Industries (Tokyo, Japan). A Kromasil CHI-TBB column (250 mm × 4.6 mm, 5 m) was packed with Kromasil silica, which was chemically bonded with O,O′-bis(4-tert-butylbenzoyl)-N,N′-diallyl-L-tartardiamide, and purchased from Eka-Nobel (Sweden).

Sample Preparation

The racemic sample solutions were prepared in the mixture of *n*-hexane-2-propanol 90:10 (*v*/*v*) with a final concentration of about 0.5 mg mL^{-1}, and degassed in an ultrasonic bath before use. Samples of individual enantiomers of *trans*-(−)-(3S,4R)-**3** and *trans*-(+)-(3R,4S)-**3** were obtained from a racemic mixture by semi-preparative HPLC with a Chiralpak AD-H column (250 mm × 4.6 mm) using a mobile phase of *n*-hexane-2-propanol (80:20,

v/v), at a flow rate of 1.0 mL min^{-1}. The fractions were collected and the solvent was evaporated to desired volume under reduced pressure.

Chromatographic Conditions

The mobile phase consisted of *n*-hexane and polar alcohol modifiers with or without addition of DEA. Unless otherwise mentioned, the flow rate was 1.0 mL min^{-1}. All experiments were conducted at 30°C, except those used for the study of the effect of temperature on enantioseparation. The detection wavelengths were set at 265 and 220 nm for compounds **2** and **3**, respectively. The injection volume was 5 μL. The dead time (t_0) was determined by the first significant baseline disturbance. Retention times (t_R) of enantiomers were the mean values of two replicate determinations.

RESULTS AND DISCUSSION

Effect of the Mobile Phase Composition on Separation

For the Chiralpak AD-H column, the mobile phases consisting of *n*-hexane and polar alcohol modifiers were recommended by the manufacturer. The alcohol modifiers can not only compete with the solute for hydrogen bonding to the carbamate of CSP, but also cause changes of the steric environments of the chiral cavity by adsorbing to the chiral cavities or achiral polar function groups, affecting the retention and selectivity of enantiomers.[13] As for the Kromasil CHI-TBB column, the retention and selectivity is mainly dependent on the hydrogen bonding ability of the solute with CSP, which can be regulated by mobile phase modifiers such as esters, ethers, ketones, and alcohols. In addition to hydrogen bonding there are also π-π interactions and steric interactions.[14]

In the present work, *n*-hexane was used as the major constituent of the mobile phase. The alcohols (2-propanol, 1-propanoal, and ethanol) were added to *n*-hexane to study the effect of polarity of mobile phases on the enantioseparation. A variety of mobile phase compositions were investigated by changing the type and content of polar alcohol modifiers. When racemate **2** was separated on a Chiralpak AD-H column, a small amount of DEA (0.1%) was added to mobile phase to prevent interaction of solute with residual active sites of silica, and improve peak shape and enhance enantioselectivity.

The effects of the concentration of polar modifiers on the separation of racemates **2** and **3** on the Chiralpak AD-H column are listed in Tables 1 and 2, respectively. As shown in Tables 1 and 2, excellent separations of both compounds were obtained with the Chiralpak AD-H column and

Table 1. The chromatographic parameters, retention factor (k), enantioselectivity (α), and resolution factor (R_s) of compound **2** on Chiralpak AD-H

Mobile phase	k_1	k_2	α	R_s
n-Hexane-2-propanol-DEA (97:3:0.1, *v*/*v*)	5.18	6.18	1.19	4.14
n-Hexane-2-propanol-DEA (95:5:0.1, *v*/*v*)	2.72	3.26	1.19	3.61
n-Hexane-2-propanol-DEA (90:10:0.1, *v*/*v*)	1.12	1.33	1.19	2.27
n-Hexane-1-propanol-DEA (95:5:0.1, *v*/*v*)	2.62	3.26	1.24	4.40
n-Hexane-1-propanol-DEA (90:10:0.1, *v*/*v*)	1.12	1.38	1.24	3.26
n-Hexane-1-propanol-DEA (85:15:0.1, *v*/*v*)	0.67	0.82	1.22	2.24
n-Hexane-ethanol-DEA (95:5:0.1, *v*/*v*)	2.54	2.84	1.11	2.45
n-Hexane-ethanol-DEA (93:7:0.1, *v*/*v*)	1.69	1.88	1.11	2.15
n-Hexane-ethanol-DEA (90:10:0.1, *v*/*v*)	1.18	1.32	1.12	1.91

mobile phases investigated. The retention factors (k) of each enantiomer decreased as the concentration of alcohols in mobile phase increased, as expected from the increase of polarity of the mobile phase and solute solubility. However, enantioselectivity (α) has hardly been affected by the concentration of polar modifiers, even though the strength and the number of hydrogen bonds between solute and stationary phase decreased as the mobile phase polarity increased. This implied that hydrogen bonding seemed to take place mainly at achiral sites on the CSP, or that the chiral discrimination mechanism did not lie in hydrogen bonding, although the -OH and C═O available on the solutes could interact with carbamate groups on the

Table 2. The chromatographic parameters, retention factor (k), enantioselectivity (α), and resolution factor (R_s) of compound **3** on Chiralpak AD-H

Modifier	k_1	k_2	α	R_s
2-Propanol (%, *v*/*v*)				
10	6.83	11.47	1.68	11.85
15	4.19	6.99	1.67	11.25
20	3.22	5.30	1.65	10.34
25	2.49	4.08	1.64	9.69
30	2.06	3.32	1.61	8.66
1-Propanol (%, *v*/*v*)				
10	9.40	13.95	1.48	9.32
20	4.35	6.28	1.44	7.84
30[a]	2.88	4.11	1.42	7.30
Ethanol (%, *v*/*v*)				
10	21.18	25.54	1.20	4.88
20	10.58	12.21	1.15	3.51
30	6.95	8.01	1.15	3.21

[a]Flow-rate 0.8 mL min^{-1}.

CSP.[15] It was more reasonable that enantioselectivity on the Chiralpak AD-H column was achieved by insertion of the fluorophenyl portion of the solute into the chiral cavities and π-π interaction between the solute and CSP. Compared to the enantiomers of compound **2**, greater retention factors of enantiomers of **3** were observed when the concentration of modifier was identical, since there were two >C═O groups at 2 and 6 position around the nitrogen atom and subject to much stronger interactions with achiral and chiral sites. The enantioselectivity might be enhanced due to potential dipole-dipole interaction ethoxycarbonyl moiety of the solute with carbamate of CSP.

As illustrated in Figure 2, the retention factors for **3** increased significantly and the enantioselectivity was greatly deteriorated when ethanol instead of

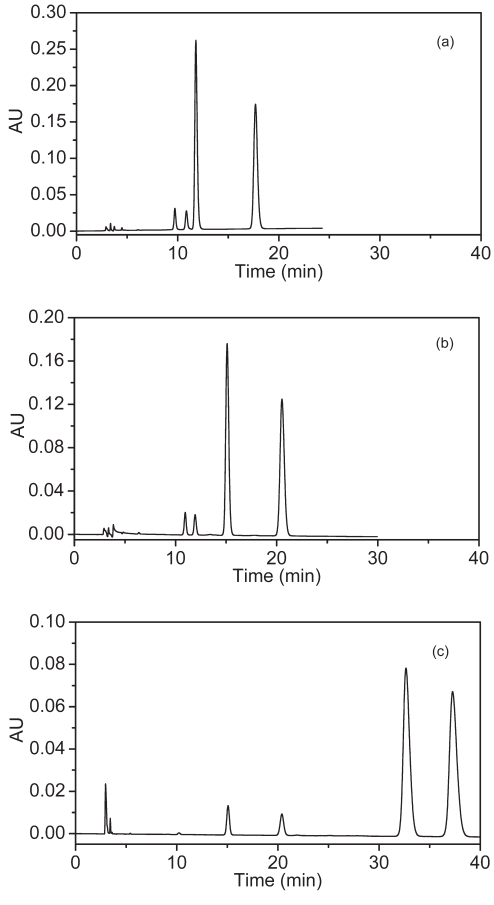

Figure 2. Chromatograms for the chiral separations of compound **3** on Chiralpak AD-H. Mobile phase: (a) *n*-hexane-2-propanol 80:20 (*v*/*v*); (b) *n*-hexane-1-propanol 80:20 (*v*/*v*); (c) *n*-hexane-ethanol 80:20 (*v*/*v*); flow rate: 1.0 mL min^{-1}; λ: 220 nm.

2-propanol (or 1-propanol) was used as the modifier, despite the fact that polarity had increased. For **2**, a similar but not obvious trend was also observed if we used the same molar ratio of ethanol instead of 1-propanol in *n*-hexane. This uncommon behavior might indicate that different alcohol modifiers significantly affected the conformation of the chiral cavities on the CSP, as well as the conformational flexibility of the solute. Wang et al.[16,17] utilized solid state NMR to identify structural differences in amylose tris(3,5-dimethylphenylcarbamate) chiral stationary phase when alcohol modifiers with varying size and bulkiness were used in the mobile phase. 2-Propanol is the most bulky molecule compared to ethanol and 1-propanol, while 1-propanol has larger bulkiness than ethanol. The alcohol molecules can be adsorbed to the chiral cavities of CSP through hydrogen bonding. The increasing size of alcohol molecules leads to a decrease of the residual space of chiral cavities. Consequently, enantiomers that fit into the chiral cavities well will be more retained. In addition, the solvate of alcohol modifiers and solute may affect the partition of the solute between the mobile phase and the stationary phase, thus affecting the retention of the solute.

With the Kromasil CHI-TBB column, attempts to separate racemate **2** using different mobile phases with addition of DEA or TEA did not succeed, and **3** was only baseline resolved when the percentage of 2-propanol in mobile phase was not more than 1%, as shown in Table 3. As expected, increasing the amount of 2-propanol in mobile phase reduced the retention and efficiency of resolution due to an increase of hydrogen bonding between the -OH of alcohols and the hydrogen of the amide group in the CSP, and weakened the interaction C═O of solute with the NH group in the CSP. Furthermore, it was of interest to note that the enantioselectivity increased when MTBE was added to the mobile phase, when the

Table 3. The chromatographic parameters, retention factor (k), enantioselectivity (α), and resolution factor (R_s) of compound **3** on Kromasil CHI-TBB

	Mobile phase (v/v)	k_1	k_2	α	R_s
n-Hexane-2-propanol	90:10	1.44	1.51	1.05	0.58
	95:5	3.25	3.45	1.06	1.31
	98:2	4.11	4.36	1.06	1.24
	99:1	6.18	6.73	1.09	1.51
n-Hexane-1-propanol	90:10	1.19	1.25	1.05	0.48
	98:2	3.64	3.89	1.07	1.46
n-Hexane-ethanol	90:10	1.33	1.39	1.04	0.43
n-Hexane-MTBE	80:20	6.99	8.20	1.17	—
n-Hexane-MTBE-2-propanol	60:40:1	1.94	2.19	1.13	1.67
	80:20:1[a]	3.53	3.95	1.12	1.69
	95:5:2	4.18	4.48	1.07	1.16

[a]Flow-rate 2.0 mL min^{-1}; "—": deteriorated peak shape.

concentration of 2-propanol was maintained under 1%. This indicated that use of MTBE as a modifier favored the hydrophobic interaction and enhanced the chiral recognition between the CSP and the solute.

Stability and Elution Order

During the experiments, we found that compound **3** was not stable enough when it was dissolved in the alcohol modifiers. The impurity peak had not been observed after a complete chromatographic run when a freshly prepared solution was injected into the column (Figure 3a). However, if the sample solution was stored overnight at $0 \sim 5^{\circ}$C, a repeat injection was carried out at the same chromatographic conditions and another chromatogram was obtained as shown in Figure 3b. It can obviously be found that compound **3** has partly been decomposed and the optical active impurities have come into being. This can be confirmed by Figure 4, which was established on the Chiralpak AD-H column and detected by a polarimeter detector. It can also be observed that (−)-impurity was eluted before the (+) one. The structures of the impurities would await further study.

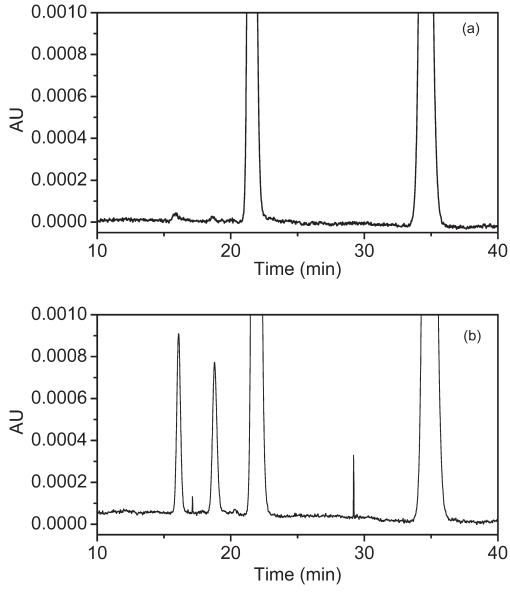

Figure 3. Chromatograms for compound **3** freshly prepared (a) and stored overnight (b) on Chiralpak AD-H. Mobile phase: *n*-hexnae-2-propanol 90:10 (*v*/*v*); flow rate: 1.0 mL min^{-1}; λ: 220 nm.

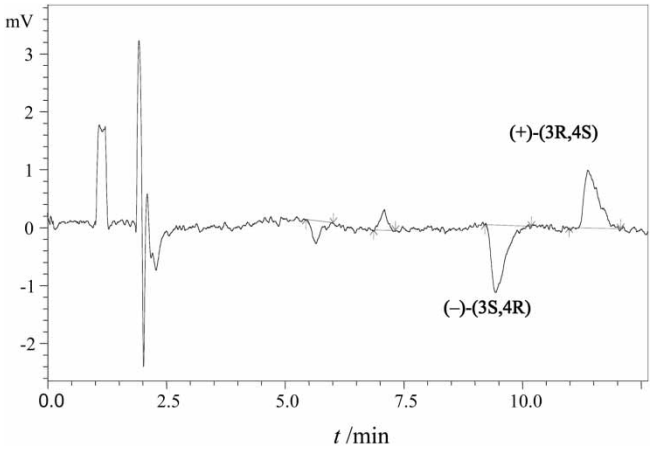

Figure 4. The elution order for impurities and trans enantiomers of compound **3**; mobile phase: *n*-hexane-ethanol 70:30 (v/v); stationary phase: Chiralpak AD-H (150 × 4.6 mm); flow rate: 1.0 mL min^{-1}.

For **2**, the absolute configuration and the sign of optical rotation of the enantiomer was confirmed by injecting an individual enantiomer with a known configuration. As seen in Figure 5, the first eluted enantiomer of **2** on Chiralpak AD-H column was *trans*-(+)-(3R,4S). This was opposite to the elution order of another intermediate of paroxetine reported by Vivekanand et al.[12] In all experiments performed on the Chiralpak AD-H column, *trans*-(−)-**3** was eluted before the *trans*-(+)-**3** while its order was inversed on the Chromasil CHI-TBB column (Figure 6). We also found that elution order inversion was not observed in all cases for both compounds and CSPs in this study.

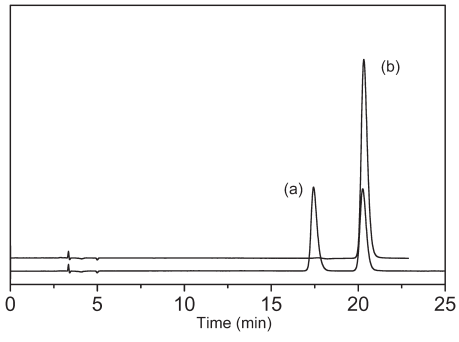

Figure 5. Chromatograms for racemate **2** (a) and *trans*-(−)-(3S,4R)-**2** (b) on Chiralpak AD-H. Mobile phase: *n*-hexnae-2-propanol-DEA 95:5:0.1 (*v*/*v*); flow rate: 1.0 mL min^{-1}; λ: 265 nm.

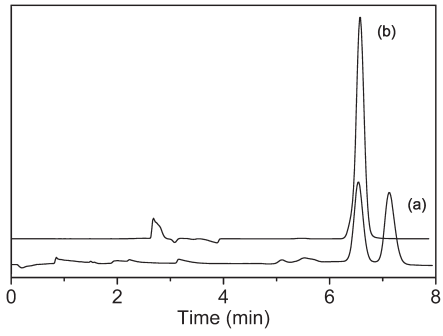

Figure 6. Chromatograms for racemate **3** (a) and *trans*-(+)-(3R,4S)-**3** (b) on Kromasil CHI-TBB. Mobile phase: *n*-hexnae-MTBE-2-propanol 80:20:1 (*v*/*v*); flow rate: 2.0 mL min^{-1}; λ: 220 nm.

Effect of Temperature: Thermodynamic Parameters for Enantiomeric Separation

Usually, thermodynamic studies are considered as an important tool to have an insight on the chiral recognition mechanism.[18,19] In this study, the effect of temperature on the separation was investigated and the thermodynamic parameters were determined by changing the temperature of the chiral column. Chromatographic experiments were carried out at 5°C intervals from 25 to 40°C. The column was equilibrated for at least 30 min at set temperature prior to each injection. Table 4 shows the effects of the column temperature on the retention, selectivity, and resolution of **2** and **3**. It was expected that, in most cases, the retention factors, selectivity, and resolution decreased as column temperature increased. However, only a small variation of the first eluted enantiomer of **2** was observed within the range of temperature studied. For **3**, the retention and selectivity significantly decreased as column temperature increased.

Table 4. Effect of temperature on chiral separation of compounds **2** and **3**

Temperature	*Trans*-**2**				*Trans*-**3**			
°C	k_1	k_2	α	R_s	k_1	k_2	α	R_s
25	2.74	3.32	1.21	3.61	3.67	6.22	1.69	10.57
30	2.72	3.26	1.20	3.44	3.22	5.30	1.65	10.34
35	2.72	3.22	1.18	3.18	2.85	4.57	1.60	10.03
40	2.72	3.19	1.17	2.85	2.54	3.96	1.56	9.55

Mobile phase: *n*-hexane-2-propanol-DEA 95:5:0.1 (*v*/*v*) for **2**; *n*-hexane-2-propanol 80:20 (*v*/*v*) for **3**.

Enantiomeric separation is generally based on the transitory and reversible diastereomeric complexes between the enantiomers and the chiral selector of the CSP. The diastereomers formation process for the enantiomers can be characterized by the thermodynamic parameters ΔH^0 and ΔS^0. The retention factor k can be described by the van't Hoff equation as follows:

$$\ln k = -\frac{\Delta H^0}{RT} + \frac{\Delta S^0}{R} + \ln \varphi \tag{1}$$

where ΔH^0 and ΔS^0 are the enthalpy and entropy of the solute transfer (mobile to CSP), respectively, T is the absolute temperature, R is the gas constant, and φ is the phase ratio.

In addition, the enantioseparation process is generally governed by differences in the adsorption free energy $\Delta\Delta G^0$ of the enantiomers. This difference can be calculated from the retention differences associated with the selectivity, and mathematically described by Equation (2):

$$\Delta\Delta G^0 = \Delta\Delta H^0 - T\Delta\Delta S^0 = -RT \ln \alpha = -RT \ln \frac{k_2}{k_1} \tag{2}$$

where the values of $\Delta\Delta H^0$ and $\Delta\Delta S^0$ represent the differences of ΔH^0 and ΔS^0 for a given pair of enantiomers.

If the plots of ln$k$ versus $1/T$ are linear within a temperature range, the temperature independent thermodynamic parameters can be derived from the slope $(-\Delta H^0/R)$ and the intercept $(\Delta S^0/R + \ln\varphi)$ of the straight line. The obtained van't Hoff plots were linear in all instances. The corresponding linear correlation coefficient r^2 was above 0.999 in all cases. Figure 7 demonstrated the results for **3** when using 2-propanol as polar modifier of mobile phase. The linearity of ln$k$ versus $1/T$ suggests that the conformation of the CSP does not change within the range of experimental temperature. Table 5 reveals that the change in content of 2-propanol from 10% to 15% leads to a decrease in ΔH_1^0 and ΔH_2^0, indicating an increase in interaction between

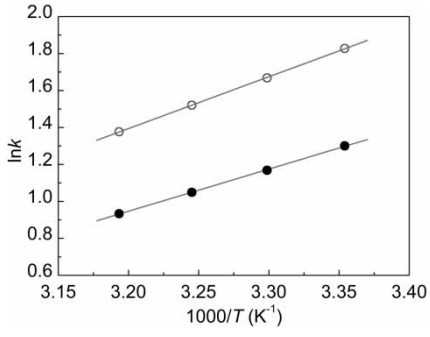

Figure 7. Plots of ln$k$ versus $1000/T$ (K^{-1}) for enantiomers of **3**. (●) *trans*-(−)-(3S,4R) and (○) *trans*-(+)-(3R,4S); Mobile phase: *n*-hexnae-2-propanol 80:20 (v/v).

Table 5. The thermodynamic parameters for the separation of compound **3** on Chiralpak AD-H

Mobile phase (v/v) (n-Hexane: 2-propanol)	ΔH_1^0 ($J \cdot mol^{-1}$)	ΔH_2^0 ($J \cdot mol^{-1}$)	$\Delta S_1^0 + R\ln\varphi$ ($J \cdot mol^{-1} \cdot K^{-1}$)	$\Delta S_2^0 + R\ln\varphi$ ($J \cdot mol^{-1} \cdot K^{-1}$)	$\Delta\Delta H^0$ ($J \cdot mol^{-1}$)	$\Delta\Delta S^0$ ($J \cdot mol^{-1} \cdot K^{-1}$)
90:10	−16456	−21198	−38.6	−49.9	−4742	−11.3
85:15	−19595	−23992	−52.7	−62.9	−4397	−10.3
80:20	−18961	−23310	−52.8	−63.0	−4349	−10.2
75:25	−19888	−24104	−58.1	−67.9	−4216	− 9.8

the enantiomer and Chirapak AD CSP. However, a slight variation in ΔH_1^0 and ΔH_2^0 was observed when the concentration of 2-propanol in mobile phase was changed from 15% to 25%. This can be explained by the fact that the steric structure of the CSP remained unchanged when the alcohol concentration in the mobile phase was above 10%.[17] While $\Delta\Delta H^0$ increased with 2-propanol concentration, the $\Delta\Delta S^0$ proportionally increased. The change in the two parameters essentially canceled each other out, resulting in small changes in $\Delta\Delta G^0$. Such phenomena are often described as entropy enthalpy compensation effect, which occurs universally in host guest chemistry.[20] As seen in Figure 8, a linear relationship between $\Delta\Delta H^0$ and $\Delta\Delta S^0$ for different alcohol concentrations is illustrated graphically with linear correlation coefficient r^2 above 0.999.

From Tables 5 and 6, we can find that the absolute magnitudes of ΔH_2^0 of the second eluted enantiomer obtained on Chiralpak AD-H column is clearly larger than that of ΔH_2^0 obtained on Kromaisl CHI-TBB column, resulting in larger $\Delta\Delta H^0$ related to the selectivity. It is conceivable that the supermolecular structure of the Chiralpak AD-H phase with chiral cavities provides more

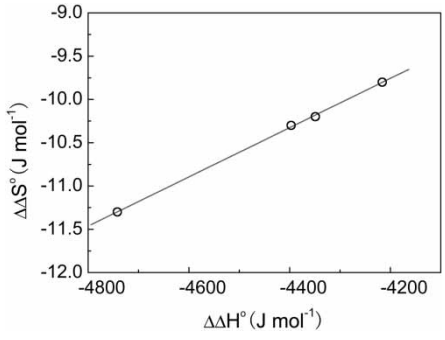

Figure 8. Plots of $\Delta\Delta S^0$ versus $\Delta\Delta H^0$ for compound **3** on Chiralpak AD-H. Mobile phase: different percentage of 2-propanol in n-hexane.

Table 6. The thermodynamic parameters for the separation of compound **3** on Kromasil CHI-TBB.

	Mobile phase (v/v)	ΔH_1^0 ($J \cdot mol^{-1}$)	ΔH_2^0 ($J \cdot mol^{-1}$)	$\Delta S_1^0 + R\ln\varphi$ ($J \cdot mol^{-1} \cdot K^{-1}$)	$\Delta S_2^0 + R\ln\varphi$ ($J \cdot mol^{-1} \cdot K^{-1}$)	$\Delta\Delta H^0$ ($J \cdot mol^{-1}$)	$\Delta\Delta S^0$ ($J \cdot mol^{-1} \cdot K^{-1}$)
n-Hexane-2-propanol	95:5	−18587	−19215	−53.7	−55.3	−628	−1.6
n-Hexane-MTBE-2-propanol	80:20:1	−13269	−14219	−32.9	−35.0	−950	−2.1

versatile functions and environments to give stronger interactions and better chiral recognition in comparison with the network structure of the Kromasil CHI-TBB phase. Moreover, the calculated $\Delta\Delta H^0$ and $\Delta\Delta S^0$ are negative in all cases, which indicate that the transfer of the solute from the mobile phase to the stationary phase and the separation are enthalpically driven

CONCLUSIONS

Excellent separation of the two important precursors of *trans*-(−)-paroxetine were achieved by HPLC with Chiralpak AD-H and Kromasil CH-TBB columns. For **2**, it was successfully resolved only on the Chiralpak AD-H column and the interaction of *trans*-(−) enantiomer with CSP was stronger than that of *trans*-(+). For **3**, it was found that *trans*-(−)-(3S,4R)-**3** eluted prior to *trans*-(+) on the Chiralpak AD-H column and that was inversed on the Kromasil CHI-TBB column. The type and composition of the mobile phase significantly affected the retention and resolution of the enantiomers. Retention factors increased when the alcohol modifier was changed from 2-propanol to 1-propanol and ethanol. The thermodynamic study of the chromatographic process indicated that the enantioseparations in this study were all enthalpically driven.

ACKNOWLEDGMENT

The authors thank Specialized Research Fund for the Doctoral Program of Higher Education of China under Grant No. 20030335070 for financial support.

REFERENCES

1. Dechant, K.L.; Clissold, S.P. Paroxetine: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in depressive illness. Drugs **1991**, *41*, 225–253.
2. Zukowski, J.; Brightwell, M.; De Biasi, V. Chiral HPLC method for chiral purity determination of paroxetine drug substance. Chirality **2003**, *15*, 600–604.
3. Cohn, J.B.; Wilcox, C.S. Paroxetine in major depression: a double-blind trial with imipramine and placebo. J. Clin. Psych. **1992**, *53*, 52–56.
4. Boyer, W.F.; Blumhardt, C.L. The safety profile of paroxetine. J. Clin. Psych. **1992**, *53*, 61–66.
5. Zepp, C.M.; Gao, Y.; Heefner, D.L. Biocatalytic method of preparing optically pure precursors of paroxetine. Chem. Abstr. **1994**, *120*, 217289.
6. Brook, C.S.; Curzons, A.D.; Grady, C.W.; O'Connor, A.J. Novel optical resolution processes for (-)trans-piperidine carbinol. Chem. Abstr. **2001**, *135*, 78530.
7. Yamazaki, S.; Ishibashi, T.; Kawada, Y.; Yumoto, H.; Yoshikawa, T.; Igi, M. Preparation of trans-(-)-4-(4-fluorophenyl)-3-hydroxy-methyl-piperidine L-tartrates. Chem. Abstr. **2001**, *132*, 64174.
8. Subramanian, G. *A Practical Approach to Chiral Separations by Liquid Chromatography*; Subramanian, G., Ed.; VCH Publishers: Weinheim, Germany, 1994.
9. Beesley, T.E.; Scott, R.P.W. *Chiral Chromatography*; John Wiley and Sons: Chichester, 1998.
10. Okamoto, Y.; Yashima, E. Polysaccharide drivatives for chromatographic separation of enantiomers. Angew. Chem. Int. Ed. **1998**, *37*, 1020–1043.
11. Ferretti, R.; Gallinella, B.; La Torre, F.; Turchetto, L. Validated chiral high-performance liquid chromatographic method for the determination of trans-(−)-paroxetine and its enantiomer in bulk and pharmaceutical formulations. J. Chromatogr. B **1998**, *710*, 157–164.
12. Vivekanand, V.V.; Ravi Kumar, V.; Mohakhud, P.K.; Reddy, G.O. Enantiomeric separation of the key intermediate of paroxetine using chiral chromatography. J. Pharm. Biomed. Anal. **2003**, *33*, 803–809.
13. Kang, G.W.; Ko, J.H.; Cheong, W.J. Thermodynamic study of enantioseparation of arylpropionic acids with a Chiralcel OJ-H stationary phase. J. Liq. Chromatogr. & Rel. Technol. **2005**, *28*, 513–526.
14. Aboul-Enein, H.Y. Chiral separation of some non-steroidal anti-inflammatory drugs on tartardiamide DMB chiral stationary phase by HPLC. J. Sep. Sci. **2003**, *26*, 521–524.
15. Danel, C.; Foulon, C.; Park, C.; Yous, S.; Bonte, J.P.; Vaccher, C. Chiral resolution of the enantiomers of new aromatase inhibitors by liquid chromatography on amylose stationary phases. Chromatographia **2004**, *59*, 181–188.
16. Wenslow, R.M.; Wang, T. Solid-state NMR characterization of amylose tris(3,5-dimethylphenylcarbamate) chiral stationary-phase structure as a function of mobile-phase composition. Anal. Chem. **2001**, *73*, 4190–4195.
17. Wang, T.; Wenslow, R.M. Effects of alcohol mobile-phase modifiers on the structure and chiral selectivity of amylose tris(3,5-dimethyl-phenylcarbamate) chiral stationary phase. J. Chromatogr. A **2003**, *1015*, 99–110.
18. Weng, W.; Zeng, Q.; Yao, B.; Wang, Q.; Li, S. Influence of mobile phase composition on the apparent thermodynamic characteristics in liquid chromatographic enantioseparation on a tartardiamide-based stationary phase. Chromatographia **2005**, *61*, 561–566.

19. Rojkovičová, T.; Lehotay, J.; Armstrong, D.W.; Čižmárik, J. Study of the mechanism of enantioseparation. Part XII. Comparison study of thermodynamic parameters on separation of phenylcarbamic acid derivatives by HPLC using macrocyclic glycopeptide chiral stationary phases. J. Liq. Chromatogr. & Rel. Technol. **2006**, *29*, 2615–2624.
20. Rekharsky, M.; Inoue, Y. Chiral recognition thermodynamics of β-cyclodextrin: The thermodynamic origin of enantioselectivity and the enthalpy-entropy compensation effect. J. Am. Chem. Soc. **2000**, *122*, 4418–4435.

Received August 30, 2007
Accepted December 17, 2007
Manuscript 6195