Tetrahedron: *Asymmetry* 23 (2012) 1227–1233

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Enantioseparation of α-cyclohexylmandelic acid by solvent sublation

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ARTICLE INFO

Article history:
Received 17 May 2012
Accepted 29 July 2012
Available online 14 September 2012

ABSTRACT

Herein we focused on using a novel separation technology, solvent sublation, for the enantioseparation of α-cyclohexylmandelic acid (CHMA). The experiment was carried out in a conventional bubble column using D-*iso*-butyl tartrate (D-IBTA) and sodium dodecyl sulfate (SDS) as a chiral selector and surfactant, respectively (Fig. 7). Several important parameters influencing the separation performance, such as the type of organic phase, the pH in the aqueous phase, and the concentrations of CHMA, D-IBTA, and SDS were investigated. Under the optimal operating conditions, the enantiomeric excess and separation factor were 54.85% and 4.5, respectively. The yields of D-enantiomer and L-enantiomer were 82.20% and 38.94%, respectively. Finally, the thermodynamic properties of the separation were investigated, which indicated an enthalpy-controlled process. This technique is an efficient chiral separation method, with many advantages, such as low amounts of organic solvent and chiral selector required and easier realization of the multi-stage operation.

1. Introduction

Life is based on biomolecules, such as enzymes, proteins, and DNA that are all of a single handedness. As a consequence, the left- and right-handed enantiomers of chiral, bioactive compounds exhibit different physiological effects on pharmacological activity, metabolism processes, and toxicity when ingested by living organisms. Recently there have been more than 50% of clinical drugs with chiral elements, of which more than 85% exist as racemic mixtures.[1–3] As a result, there is an increasing demand for enantiomerically pure compounds in the chemical industry. Many researchers have attempted to separate optically active compounds using methods such as crystallization, chromatography, kinetic resolution, chiral extraction, membrane separation, and so on, but there still exists some problems for most racemic compounds.[4–23]

The solvent sublation technique is a type of bubble separation process, in which the hydrophobic compounds in water are adsorbed on the bubble surfaces of an ascending gas stream and then collected in an immiscible liquid layer (usually an organic solvent lighter than water) placed on the top of the bulk aqueous phase of the column. This technique has many advantages, such as simultaneous separation and purification, high concentration efficiency, and low expenditure of organic solvent. Solvent sublation has attracted much attention in the fields of environmental analysis, waste water treatment, and the extraction of active constituents.[24–27]

α-Cyclohexylmandelic acid (CHMA, Fig. 1) is a significant chiral drug precursor, which can be used to synthesize chiral drugs such as oxybutynin, which is the principal drug for curing urinary incontinence and which has a wide market. The D-enantiomer has a better drug effect and lower side effects than the racemic (*rac*) mixture.[2] Herein we report a new chiral separation technology—solvent sublation for the separation of *rac*-CHMA as a model of our research. The work was carried out in a conventional bubble column, while using D-*iso*-butyl tartrate (D-IBTA) as the chiral selector and SDS as the surfactant. Compared with the traditional methods of chiral extraction and membrane separation, our aim was to provide a simple and efficient approach to chiral separation.[28] To the best of our knowledge, there have been only a few literature reports regarding enantioseparation by solvent sublation.

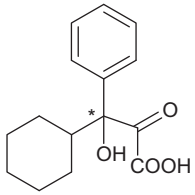

Figure 1. The chemical structure of α-cyclohexylmandelic acid.

2. Results and discussion

In the separation process of solvent sublation, the distribution coefficients (*D*), the values of enantioselectivities including

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http://dx.doi.org/10.1016/j.tetasy.2012.07.017

enantiomeric excess (ee%) and separation factor (β) at equilibrium as the evaluated parameters are defined by:

$$D_{D(L)} = \frac{\text{initial [D] or initial [L]}}{\text{[D] or [L]}} - 1 \quad (1)$$

$$\beta = \frac{\text{distribution ratio of the D-enantiomer}}{\text{distribution ratio of the L-enantiomer}} \quad (2)$$

$$\text{ee } \% = \frac{[L](\text{or}[D]) - [D](\text{or}[L])}{[L] + [D]} \quad (3)$$

among which, [ ] was the concentration (mg/mL) of the enantiomonomer in the aqueous phase.

2.1. Effect of organic solvent

The influence of the organic solvent on the distribution behavior was investigated. From Table 1, we can see that the separation

Table 1
Influence of the organic solvent on the distribution behavior

Organic solvent	D_L	D_D	ee (%)	β
Ethyl acetate	2.47	2.54	1.14	1.02
n-Heptane	2.71	3.02	1.78	1.12
Chloroform	2.92	3.68	4.08	1.25
1,2-Dichloroethane	3.28	4.63	6.83	1.41
n-Pentanol	3.91	5.61	7.89	1.43
n-Hexanol	4.19	6.96	11.97	1.66
n-Heptanol	4.60	9.91	20.05	2.15
n-Octanol	5.29	15.36	30.86	2.91

Initial concentration of *rac*-CHMA, D-IBTA, and SDS: 0.30 mg/mL, 0.20 mol/L, and 0.50 mg/mL, reflux time 4 h, pH 3.2, and temperature 20 °C.

performances for the four types of organic solvents were different, that is, alcohol > 1,2-dichloroethane > chloroform > heptane > ethyl acetate, which might be related to the polarity and interactions of the different organic solvents with the solute. The distribution coefficients and enantioselectivities generally increased with an increase of the length of the alkyl chain of the alcohol. Enantioselectivities and distribution coefficients were relatively higher with *n*-octanol as the organic solvent; therefore *n*-octanol is a suitable organic solvent in this system.

2.2. Effect of the initial concentration of CHMA

Figure 2 shows the influence of CHMA concentration on the distribution behavior. The distribution coefficients and enantioselectivities were enhanced with an increase of the initial solute concentration, and then decreased with a further increase of the CHMA concentration. The rather abrupt leveling-off of D_D and D_L at a certain concentration might suggest that the CHMA-D-IBTA complexes formed in the organic-phase are stronger chiral extractants for CHMA than the initial chiral selectors. If this is so, then it appears that the CHMA complexes in the organic phase are inferior chiral selectors.[18] Furthermore, the solvation ability of *n*-octanol causes the enantioselectivities to decrease at the higher solute concentrations.[3] Therefore, 0.30 mg/mL might be the optimal CHMA concentration in this system.

2.3. Effect of pH in the aqueous phase

In order to investigate the influence of pH on the distribution behavior, the distribution coefficients and enantioselectivities were studied at different pH values.[2,29,30] The results are shown in Figure 3. It can be seen that the distribution coefficients and enantioselectivities increased when increasing the pH in the aqueous phase; the highest separation efficiency was at pH 3.8 and then decreased. A possible reason for this might be that CHMA exists

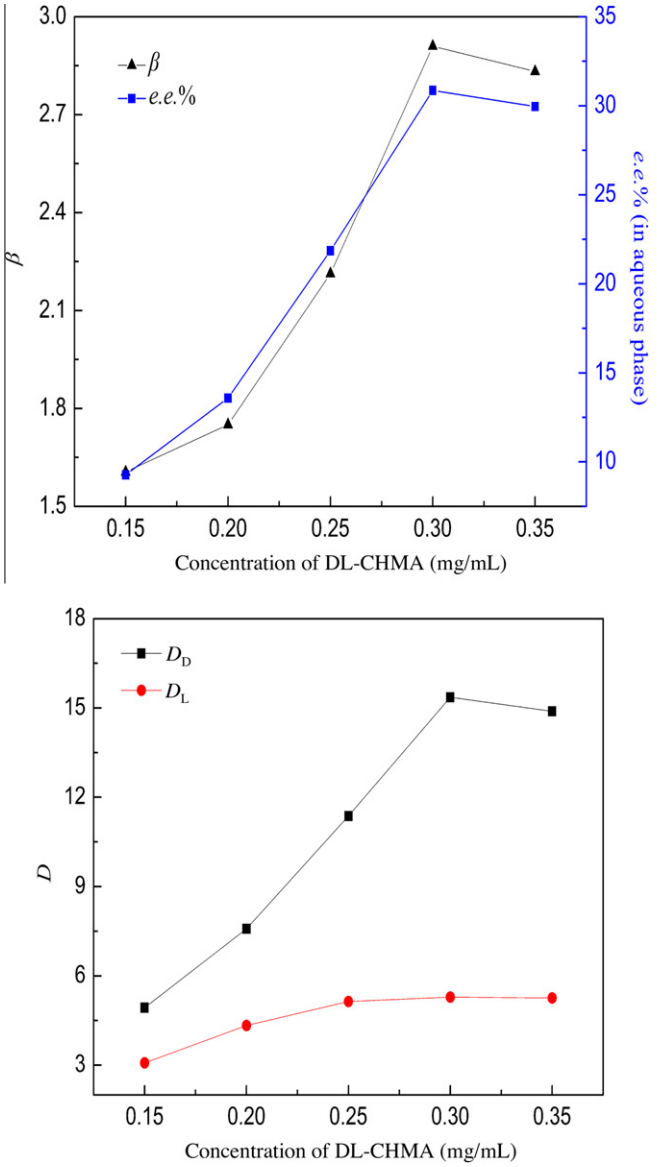

Figure 2. Influence of the initial concentration of *rac*-CHMA on the distribution behavior. Initial concentration of D-IBTA and SDS: 0.20 mol/L and 0.50 mg/mL, pH 3.2, reflux time 4 h and temperature 20 °C.

mainly in molecular form at pH 3.8 and any deviation of this pH leads to an increase of ionic CHMA. D-IBTA mainly has a chiral recognition ability and affinity for molecular CHMA, but not for ionic CHMA; ionic CHMA only exists in the aqueous phase.[2,30] The concentration of complexes formed by D-IBTA and CHMA enantiomers decreased as the pH >3.8. The foaming effect of SDS also decreased with an increase of pH. Therefore, it should be kept at lower pH to carry out the separation process.

2.4. Effect of the initial concentration of D-IBTA

The effect of the concentration of D-IBTA in the organic phase on the enantioseparation efficiency is summarized in Figure 4, which depends on the various molecular interactions during the process of solvent sublation. Increasing the D-IBTA concentration up to 0.3 mol/L, caused the distribution coefficients, especially D_D, to increase. This was because a larger amount of the complexes for the CHMA enantiomers was formed in the organic phase, which would enhance both the distribution coefficients and enantioselectivities.

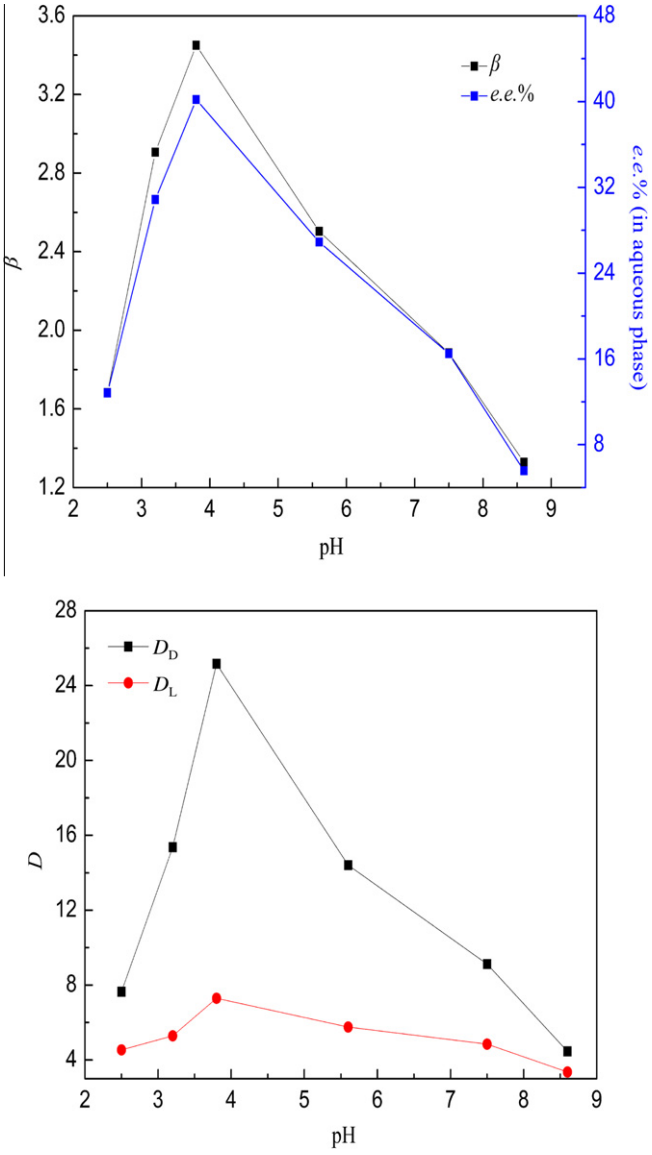

Figure 3. Influence of the pH on the distribution behavior. Initial concentration of *rac*-CHMA, D-IBTA, and SDS: 0.30 mg/mL, 0.20 mol/L, and 0.50 mg/mL, reflux time 4 h and temperature 20 °C.

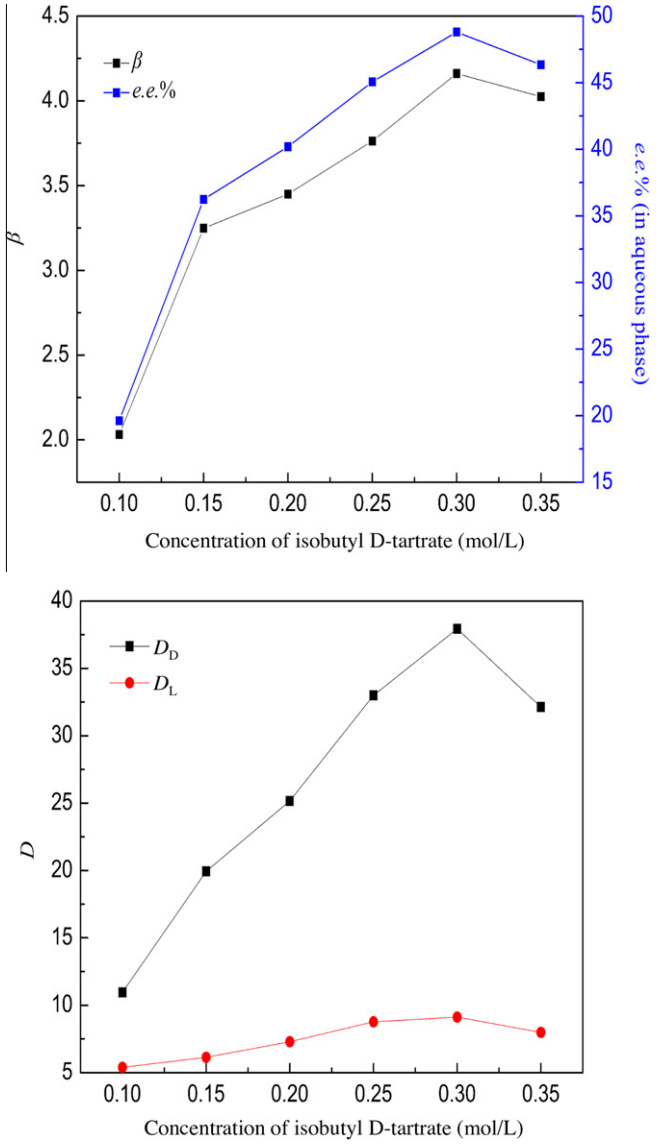

Figure 4. Influence of the initial concentration of D-IBTA on the distribution behavior. Initial concentration of *rac*-CHMA and SDS: 0.30 mg/mL and 0.50 mg/mL, pH 3.8, reflux time 4 h, and temperature 20 °C.

The value of D_D is always larger than that of D_L, which suggests that D-CHMA is preferentially recognized by the D-IBTA. When the concentration of D-IBTA was increased further, the distribution coefficients and enantioselectivities decreased at a moderate extent because of the micelles formed by the excess D-IBTA, which could make the unexpected enantiomonomer be adsorbed. We concluded that the maximum distribution coefficients and enantioselectivities were achieved at a 0.3 mol/L concentration of D-IBTA in this system.

2.5. Effect of the initial concentration of SDS

The effect of SDS concentration in the aqueous phase is shown in Figure 5, which suggested that the distribution coefficients and enantioselectivities became larger with an increase of SDS concentration, and then reached a maximum at the SDS concentration of 0.65 mg/mL. However, increasing the SDS concentration further caused the distribution coefficients and enantioselectivities to decrease. Furthermore, when the SDS concentration increases continuously, some white flocculent precipitates could be found in the sample cell, which in turn affected the results. Therefore, 0.65 mg/mL was found to be the optimal SDS concentration in this system.

2.6. Effect of the reflux time

The effect of the reflux time on the enantioseparation is listed in Table 2. The results suggested that the distribution coefficients and enantioselectivities increased when extending the reflux time up to 4 h, after which it decreased. This is because that the interphase force and the contact area of the interphase increase when extending the reflux time, in which case the distribution coefficients and enantioselectivities showed an increase. However with continuous refluxing, the foam layer becomes thicker, which could lead to the larger resistance to the transfer process and a decrease in the separation efficiency, therefore causing the enantioselectivities to decrease with a further increase of reflux time.[29] As a result the reflux time was fixed at 4 h.

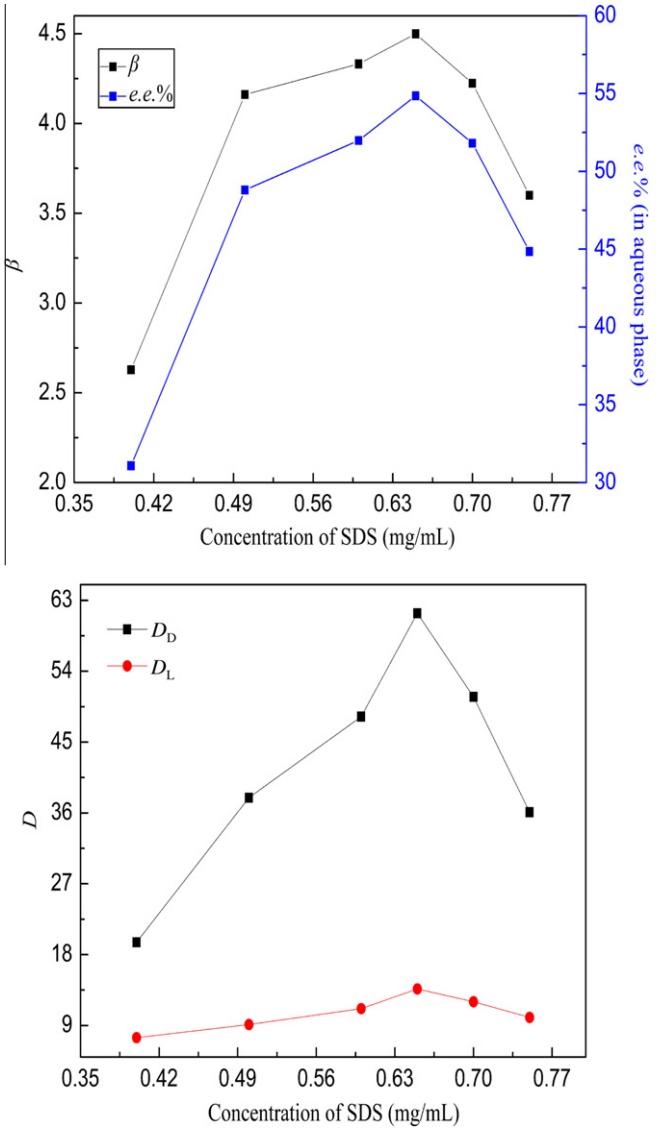

Figure 5. Influence of the concentration of SDS on the distribution behavior. Initial concentration of *rac*-CHMA and D-IBTA: 0.30 mg/mL and 0.30 mol/L, pH 3.8, reflux time 4 h, and temperature 20 °C.

Table 2
Influence of the reflux time on the enantioseparation

Reflux time (h)	D_L	D_D	ee (%)	β
1	9.07	16.68	20.15	1.83
2	11.24	28.41	33.24	2.53
3	12.62	46.02	47.29	3.65
4	13.64	61.37	54.85	4.50
5	11.37	50.79	53.15	4.47
6	10.27	43.12	51.52	4.44

Initial concentration of *rac*-CHMA, D-IBTA, and SDS: 0.30 mg/mL, 0.30 mol/L, and 0.65 mg/mL, pH 3.8, and temperature 20 °C.

2.7. Effect of temperature

The effect of temperature on the distribution behavior was investigated in the range of 283–313 K. Table 3 shows that an increase in temperature at first led to an increase and then a decrease in the distribution coefficients and enantioselectivities. As at the lower temperatures, the activity of the surfactant was low, it could influence the formation of a stable foam layer, moreover, the organic solvent was easier to condense, which also influences the chiral recognition ability of D-IBTA. However, the interaction between the D-IBTA and CHMA enantiomers might be destroyed at higher temperatures. Therefore, 20 °C might be the optimal operational temperature for this system. Figure 6 shows the variations of ln$D$ and lnβ versus 1/T. The results could be described as fitting very well with the Van't Hoff model.

Table 3
Influence of temperature on the enantioseparation

T (°C)	D_L	D_D	ee (%)	β
10	7.56	20.16	31.42	2.67
15	9.61	32.92	42.76	3.43
20	13.64	61.37	54.85	4.50
25	10.81	42.83	48.78	4.02
30	9.88	38.27	47.20	3.87
35	8.87	31.72	43.42	3.57
40	6.69	21.30	36.53	3.18

Initial concentration of *rac*-CHMA, D-IBTA and SDS: 0.30 mg/mL, 0.30 mol/L, and 0.65 mg/mL, pH 3.8, reflux time 4 h.

$$\ln D = -\frac{\Delta H^\circ}{RT} + \frac{\Delta S^\circ}{R} + \ln\varphi \quad (4)$$

$$\ln\beta = -\frac{\Delta_{D,L}\Delta H^\circ}{RT} + \frac{\Delta_{D,L}\Delta S^\circ}{R} \quad (5)$$

In Eq. 4, ΔH° and ΔS° are the entropy change and enthalpy change of the distribution between the organic phase and aqueous phase, respectively. Moreover, φ is the phase ratio (volume ratio of the organic phase to aqueous phase). According to Figure 6, the values of ΔH° and $\Delta S + R\cdot\ln\varphi$ could be found with the slope and intercept of the Van't Hoff curve (Table 4). As the thermodynamic parameter, ΔH° shows the thermo effect of the solute transferred from the aqueous phase to organic phase. The value is negative, which means the process is an exothermic process. In Eq. 5, $\Delta_{D,L}\Delta H^\circ$ and $\Delta_{D,L}\Delta S^\circ$ are the enthalpy change and entropy change of the separation process, respectively. According to the slope and intercept of the Van't Hoff curve in the table, it is obvious that in the range of 283–313 K, there always keeps $|\Delta_{D,L}\Delta H^\circ| > |T\Delta_{D,L}\Delta S^\circ|$, which indicates an enthalpy-controlled process. The CHMA enantiomers form a pair of diastereomeric complexes with the chiral selector, between which the thermodynamic stability differences lead to the enantioseparation.

2.8. Yields of enantiomers under the optimal conditions

By investigating the factors which influence the enantioseparation process of solvent sublation, the optimal operational conditions can be easily found. In this situation, the enantioselectivities were 54.85% and 4.50. The yields of D-enatiomer and L-enantiomer herein are defined as

$$\text{D}\% = \frac{\text{initial [D]} - \text{[D]}}{\text{initial [D]}} \times 100\% \quad (6)$$

$$\text{L}\% = \frac{\text{initial [L]} - \text{[L]}}{\text{initial [L]}} \times 100\% \quad (7)$$

According to the [D] and [L] under the optimal operational conditions, D% and L% were calculated to be 82.20% and 38.94%, respectively. Although the yields were not the highest possible, the solvent sublation still has some advantages when used for the enantioseparation purpose such as easier operation, low amount of organic solvent, little consumption of the chiral selector, and so on.[24–27] It should be noted that the aqueous phase after enantioseparation by solvent sublation can be very easily reused in the next stage by using this method, meaning that all of the enantiomers can in theory be separated.

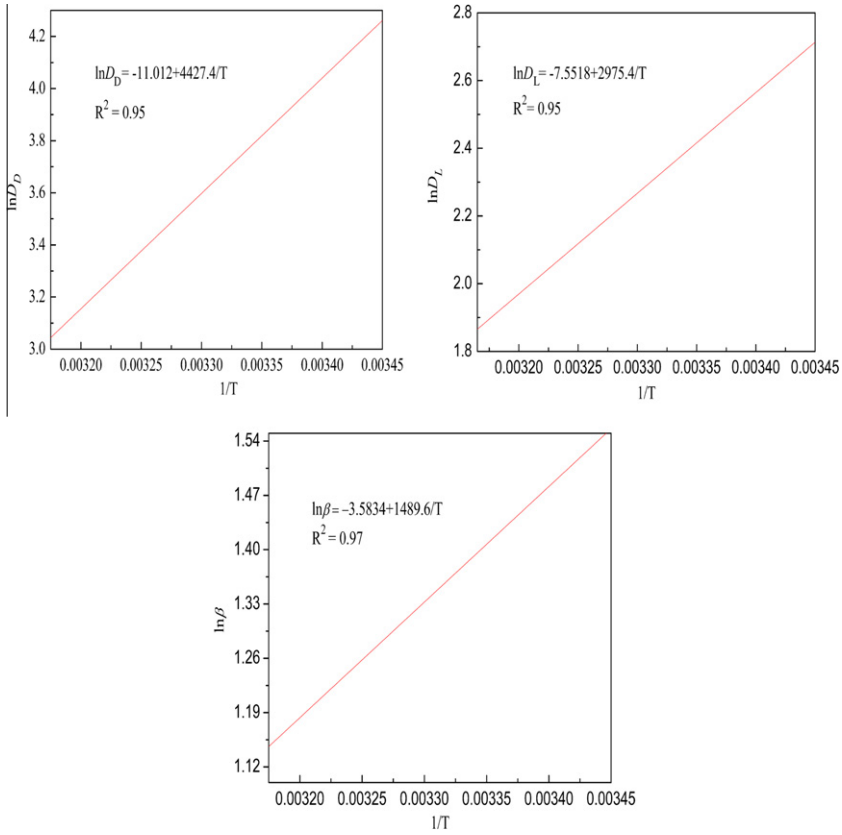

Figure 6. Influence of the temperature on the distribution behavior. Initial concentration of *rac*-CHMA, D-IBTA, and SDS: 0.30 mg/mL, 0.30 mol/L, and 0.65 mg/mL, pH 3.8, reflux time 4 h.

Table 4
The thermodynamic parameters on the enantioseparation

Enantio-monomer	$\Delta H°$/ (KJ mol^{-1})	$\Delta S + R\cdot\ln\varphi$/ (J mol^{-1} K)	$\Delta_{D,L}\Delta H°$/ (kJ mol^{-1})	$\Delta_{D,L}\Delta S°$/ (J mol^{-1} K^{-1})
D-α-CHMA	−12.38	−62.78	−12.38	−29.79
L-α-CHMA	−24.74	−91.55		

3. Conclusion

We have found an effective method using solvent sublation for the separation of *rac*-CHMA. Both the distribution coefficients and enantioselectivities were greatly improved upon with this technology. Several factors including the reflux time, the pH of the aqueous phase, the initial concentration of *rac*-CHMA, D-IBTA, and SDS, which influence the results of enantioseparation, were investigated. Under the optimal operational conditions, the enantiomeric excess and separation factor were 54.85% and 4.50. The yields of the D-enatiomer and L-enantiomer were 82.20% and 38.94%, respectively. Furthermore, this technique, with advantages of low expenditure of organic solvent and chiral selector and easier realization of multi-stage operations, could have a considerable number of potential applications in chiral separation. The thermodynamic properties of the separation were also investigated, which indicated an enthalpy-controlled process.

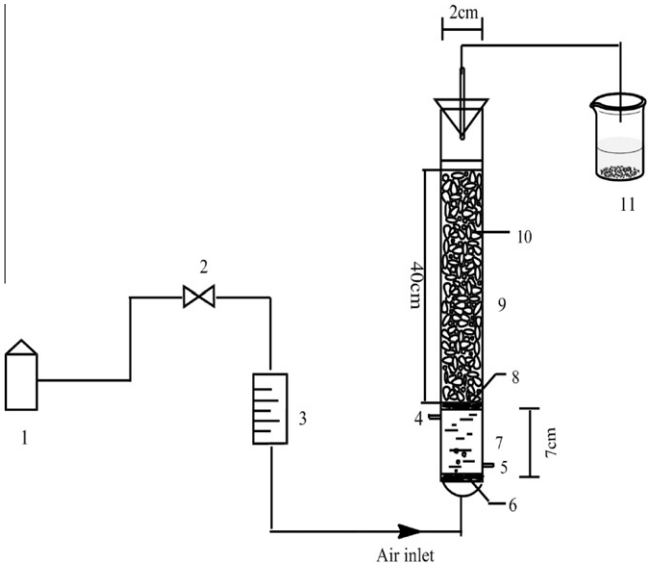

Figure 7. Schematic showing the apparatus used in this work. (1) Air pump, (2) control valve, (3) rotameter, (4) inlet for solution, (5) outlet for solution, (6) gas distributor, (7) sample pool, (8) microporous plate, (9) glass column, (10) ceramic ring and (11) bubble receiver.

4. Experimental

4.1. Materials

D-Tartaric acid with a purity of >99.85% was purchased from Shanghai Xinpu Chemical Factory (Shanghai, China). The hydrophobic chiral selector D-IBTA was prepared as described in the literature from D-tartaric acid. *rac*-CHMA was purchased from Guangde Keyuan Chemical Co., Ltd (Guangde, China), with a purity >98% and a melting point of 163–164 °C. *n*-Octanol (analytically pure) was purchased from Hengxing Chemical Material Co.

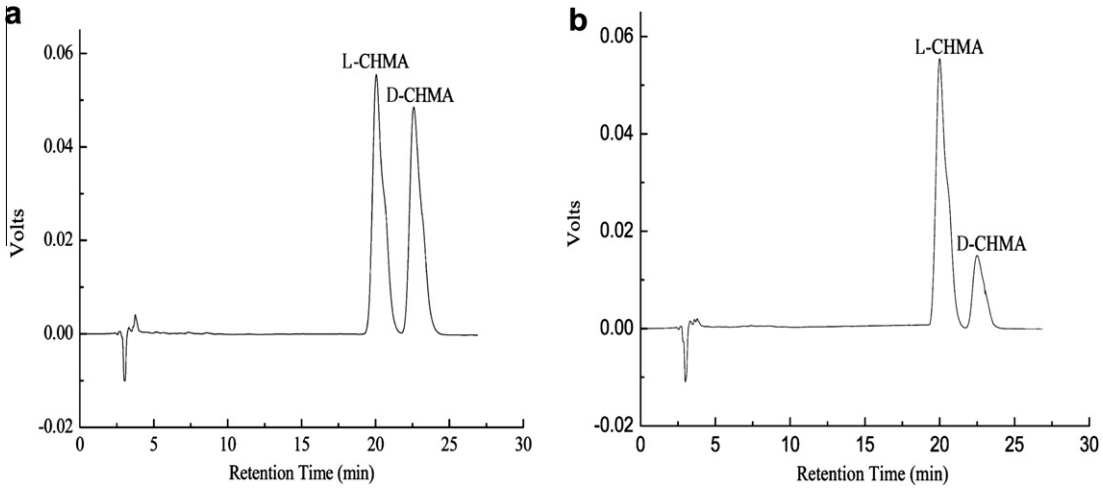

Figure 8. HPLC chromatograms of D,L-CHMA: (a) before and (b) after solvent sublation.

(Tianjin, China). All other chemicals were of analytical-regent grade, and water was deionized and bidistilled.

4.2. Apparatus

The apparatus of the solvent sublation was designed in our laboratory (Fig. 7, assembled by Hunan University Instrument Plant, China). It consists of four basic parts: (1) a sample cell (7 cm × 6 cm i.d.), which is used as the storage for sample solution; (2) an air introduction section with a rotameter to control the air flow rate, which is separated from the sample cell and used to generate air into the column; (3) a glass column (40 cm × 2 cm i.d.) with ceramic raschig rings (1.5 cm × 1.5 cm i.d.) as packing material, which is used for the adsorption and interaction; and (4) a collection device, which is used to make bubbles flow into the container, where the aqueous phase can be collected and the organic phase can be left.

4.3. Analytical method

The quantification of *rac*-CHMA in the aqueous phase was performed by HPLC using a UV detector (Shimadzu, Japan) at a wavelength of 221 nm.[31] The column was Kromail C_{18}, 5 μm particle size of the Packing Material, 250 mm × 4.6 mm I.D. (Hanbon Sci. Technol. Co. Ltd, China). The mobile phase was a mixture of 0.075 mol/L KH_2PO_4 aqueous solution, alcohol, and methyl cyanide (65:20:15, v/v/v) containing 9.5 mmol/L β-CD. The flow rate of the mobile phase was 1.0 mL/min. The column temperature was maintained at 30 °C. The injection volume was 20 μL. The chromatograms are shown in Figure 8. The retention time of L-CHMA was approximately 20.05 min while it was approximately 22.59 min for D-CHMA. It can be calculated from Figure 8(a) that the chromatographic peak area of D-CHMA is equal to that of L-CHMA, which indicates that the content of D-CHMA is the same as that of L-CHMA before solvent sublation.

4.4. Chiral separation of solvent sublation system

The aqueous phase was prepared by dissolving *rac*-CHMA and surfactant SDS in water. The pH value was adjusted with a phosphate salt buffer solution, and measured using a pH meter before separation for each experiment. D-IBTA was used as the chiral selector. We placed 140 mL of the organic and aqueous phases (1:6, v/v) into the sample pool at room temperature. Next, air was introduced into the aqueous phase to form bubbles and refluxed for several hours. The bubbles were collected under a certain gas velocity. After static defoaming and phase separation, the concentrations of the enantiomer in the aqueous phase were analyzed using HPLC. Each experiment was duplicated under identical conditions, and the standard deviation was in the range of ±2%. Since the change in volume was very small, it could be seen as negligible. All experiments were performed at a certain packing height and a steady air flow rate.

Acknowledgements

We wish to acknowledge the support given to this work by the China National Natural Science Foundation (Nos. 21176263 and 20776162).

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