Equilibrium Studies on Reactive Extraction of α-Cyclohexyl-mandelic Enantiomers Using Hydrophilic β-Cyclodextrin Derivatives Extractants

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β-Cyclodextrin (*β*-CD) is negligibly soluble in organic liquids and can be modified to achieve a higher solubility in water. In this paper, racemic *α*-cyclohexyl-mandelic acid (*α*-CHMA) was separated by chiral reactive extraction with aqueous *β*-cyclodextrin derivatives. Hydroxypropyl-*β*-cyclodextrin (HP-*β*-CD), hydroxyethyl-*β*-cyclodextrin (HE-*β*-CD), and methyl-*β*-cyclodextrin (Me-*β*-CD) were selected as chiral selectors for reactive extraction of *α*-CHMA enantiomers from organic phase to aqueous phase. Factors affecting the extraction efficiency were investigated, including the types of organic solvents and *β*-CD derivatives, the concentrations of the chiral selector and *α*-CHMA enantiomers, pH and temperature. The experimental results demonstrate that HP-*β*-CD, HE-*β*-CD, and Me-*β*-CD have stronger recognition abilities for *S*-*α*-CHMA than for *R*-*α*-CHMA. Among the three derivatives, HP-*β*-CD shows the strongest separation factor for *α*-CHMA enantiomers. A high enantioseparation efficiency with a maximum separation factor (*α*) of 2.02 is observed at pH 2.5 and 5 ℃.

Keywords chiral resolution, reactive extraction, cyclodextrin, *α*-cyclohexyl-mandelic acid

Introduction

There is an increasing demand for optically pure enantiomers in the chemical industry.[1] Many researchers have attempted the separation of optically active compounds.[2-8] The most used method in industry is diasteriomeric crystallisation. However, crystallisation is generally inflexible and thus its development for each new racemic mixture is quite time consuming.[9] Furthermore, this process is relatively slow, difficult to control and involves solid-phase handling. Asymmetric synthesis and kinetic resolution have been developed as viable alternatives to avoid these problems caused by crystallization.[10] However, these processes require the development of an appropriate path for each product, leading to considerable costs and long development periods. Membrane-based approaches will become very important for continuous operation, but at the moment still suffer from being generally less enantioselective.[11]

Chiral solvent extraction has been of interest and currently appears to be a time-saving and cost-effective process. As a promising large-scale production technique, chiral solvent extraction has attracted a lot of researchers to make great efforts in recent years.[3-5,12,13] Separation factor is the most important parameter for chiral extraction, which directly influences the separation effect. For example, for a 99% pure product (*R*/*S*= 100) about 190 NTU (number of transfer units) are required for an enantioselectivity of 1.05, a number decreasing to approximately 30 when *α* increases to a value of 1.20.[14] Therefore, it is very important to improve the separation factor.

Tartaric acid derivatives are normal chiral selectors used for chiral extraction.[14-16] The separation factors of the selectors are somehow low, and a large number of theoretical stages are required in chiral extraction processes. Therefore, it is necessary to develop new selectors with high separation factor to speed up the application of solvent extraction, and realize large-scale production. More recently, the chiral ligand-exchange concept has been applied to liquid-liquid extraction technology and obtained high separation factors holding advantages over chiral ligand-exchange chromatography for large-scale applications.[4] Steensma *et al.*[17] reported chiral separation of amines, amino acids and amino-alcohols by reactive extraction.

Cyclodextrins (CD) are optically active materials. They interact with guest molecule selectively, and form inclusion complexes depending on various interactions involving Van der Waals, dispersive forces, dipole-

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CHINESE JOURNAL OF CHEMISTRY

dipole interactions, electrostatic forces and hydrogen bonding. By using the selective inclusion property, CDs have recently been used as means of separation for isomers or mixtures normally difficult to separate, for example, in liquid chromatography, fixed membrane, liquid membrane and selective titration methods. Cyclodextrins show negligible solubilities in organic liquids and can be modified to achieve high solubility in water. Aqueous cyclodextrin solutions were selected as extractants for the separation of aromatic compounds from cracker feeds and of toluene oxidation products from toluene.[18] Recently, Meindersma *et al.*[19] reported extraction of toluene, *o*-xylene from heptane and benzyl alcohol from toluene with aqueous cyclodextrins. 7-Desmethyl-ormeloxifene enantiomers were separated by countercurrent chromatography with sulfated β-CD as chiral selector.[20] In our recent work, the optimal separation factor of 2.49 towards α-cyclohexyl-mandelic acid enantiomers was obtained by biphasic recognition chiral extraction,[6] but another step of back-extraction will be added in the recovery of product. At present, there is no other report on separation of enantiomers by reactive extraction with aqueous cyclodextrin derivatives.

This paper presented that α-cyclohexyl-mandelic acid enantiomers were separated by reactive extraction with aqueous cyclodextrins extractants. α-CHMA (Figure 1) is a significant chiral drug precursor used to synthesize some chiral drugs such as oxybutynin, which is a principal drug to cure urinary incontinence and has a wide market. Owing to *S*-enantiomer having better drug effect and lower side-effect than racemic mixture, it is necessary to resolve racemic mixture or esterify chiral precursor *S*-α-CHMA in order to obtain *S*-oxybutynin, but the later can reduce cost greatly.

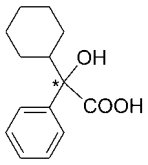

Figure 1 Chemical structure of α-cyclohexyl-mandelic acid.

The chiral reactive extraction is carried out by the formation of two diastereomeric complexes between β-CD derivative and α-CHMA enantiomers (Figure 2). Each of α-cyclohexyl-mandelic acid enantiomers has one carboxylic group and an aromatic group. One dissociation equilibria exists in aqueous solutions:

$$HA \xleftrightarrow{K_a} A^- + H^+ \tag{1}$$

where HA and A^- are neutral molecule and anion of *R*(*S*)-α-CHMA, respectively.

The distribution ratios D_R and D_S for *R*-α-CHMA and *S*-α-CHMA can be calculated by the following formulas:

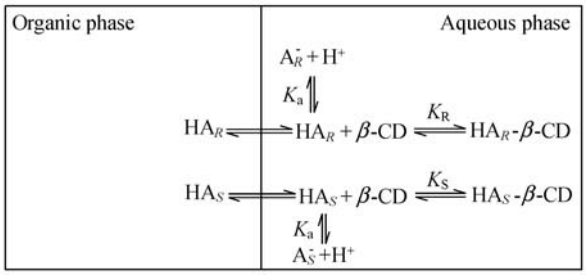

Figure 2 Diagram of distribution of enantiomers in a chiral reactive extraction system.

$$D_R = \frac{C_{W,R}}{C_{O,R}} \tag{2}$$

$$D_S = \frac{C_{W,S}}{C_{O,S}} \tag{3}$$

Among which $C_{O,R}$ and $C_{W,R}$ represent concentrations of *R*-α-CHMA in organic phase and aqueous phase, respectively; $C_{O,S}$ and $C_{W,S}$ represent the concentrations of *S*-α-CHMA in organic phase and aqueous phase, respectively.

Separation factor (α) is defined as

$$\alpha = \frac{D_S}{D_R} \tag{4}$$

Here $D_S > D_R$. The distribution ratios *D* values between 0.2 and 5 are the most accurate because of their low relative error (5%—10%). *D* values which are <0.1 or >10 must be judged with great care, because the relative error easily rises to $>30\%$. As the operational selectivity is calculated from the ratio of the *D* values, a selectivity lower than about 1.1 can not be determined accurately by single extraction experiments.[21]

The yield of an enantiomer is expressed as the fraction of the organic feed that ends up in the aqueous extract phase:

$$Y_S = \frac{[S]_{\text{aq,allforms}}}{[S]_{\text{org,initial}}} \cdot \frac{V_{\text{aq}}}{V_{\text{org}}} \tag{5}$$

$$Y_R = \frac{[R]_{\text{aq,allforms}}}{[R]_{\text{org,initial}}} \cdot \frac{V_{\text{aq}}}{V_{\text{org}}} \tag{6}$$

In chiral separation process, the enantiomers excess (*ee*) is used as a measure of the enantioselectivity of a process, which can be defined as follow:

$$ee_{\text{org}} = \frac{[R]_{\text{org,allforms}} - [S]_{\text{org,allforms}}}{[S]_{\text{org,allforms}} + [R]_{\text{org,allforms}}} \times 100\% \tag{7}$$

$$ee_{\text{aq}} = \frac{[R]_{\text{aq,allforms}} - [S]_{\text{aq,allforms}}}{[S]_{\text{aq,allforms}} + [R]_{\text{aq,allforms}}} \times 100\% \tag{8}$$

Koska and Haynes[22] combined the yield and *ee* in the performance factor (PF). The PF is a very useful tool to optimize an enantioselective extraction process and is defined as

$$PF = ee_{org} Y_S \quad (9)$$

According to the possible mechanism for chiral reactive extraction of α-CHMA enantiomers, the types of organic solvents and β-CD derivatives, the concentrations of the chiral selector and α-CHMA enantiomers, pH and temperature could affect the extraction efficiency. The factors affecting the extraction efficiency were investigated.

Experimental

Materials

Racemic α-CHMA (HA) was purchased from Guangde Keyuan Chemical Co., Ltd., with a purity > 98% and a melting point of 163—164 ℃. β-CD was got from Shanghai Chemical Co., Ltd. Hydrophilic extractants, HP-β-CD (D.S.=5.7), HE-β-CD (D.S.=4.6) and Me-β-CD (D.S.=5.1) were obtained from Shandong Xinda Fine Chemical Co., Ltd. *n*-Octanol was bought from Yili & Co. Inc. (Beijing, China). Solvent for chromatography was of HPLC grade. Unless otherwise stated, all reagents were of analytical grade and bought from different suppliers.

Analytical method

The quantification of α-CHMA enantiomers in aqueous phase was performed by HPLC (Agilent Technologies Corporation, Series 1100, USA) equipped with a UV detector (Merck, Hitachi, Japan). A Lichrospher C18 column (250 mm×4.6 mm i.d., 5 μm) (Hanbon Science & Technology Co. Ltd., China) was utilized. Chromatographic conditions according to Ref. 23 were as follows. The mobile phase was a mixture of 0.075 mol/L KH_2PO_4 aqueous solution, alcohol, and acetonitrile (V∶V∶V=65∶20∶15) 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 a fixed temperature and the detection was monitored at a wavelength of 220 nm. The injection volume was 20 μL. The pH of the aqueous phase was measured with a pH electrode and a pH meter (Orion, model 720A, USA). The retention time of *S*-enantiomer is less than that of *R*-enantiomer.

Extraction experiments

In the extraction system, the aqueous phase was prepared by dissolving β-CD derivatives (HP-β-CD, HE-β-CD, Me-β-CD) as the chiral selectors in a 0.1 mol/L phosphate salt buffer solution. Racemic α-cyclohexyl-mandelic acid was dissolved in organic solvent to prepare the organic phase. All liquid-liquid reactive extraction experiments were carried out in 25 mL glass-stoppered tube in a thermostat bath. Equal volume (each 2 mL) of the aqueous and the organic phase were placed together and shaken sufficiently (5 h) before being kept in a water bath at a fixed temperature until the distribution behavior achieved equilibrium. The mixing time was sufficient to reach the equilibrium. After phase separation, the concentration of α-CHMA enantiomers in the aqueous phase was analyzed by HPLC. The concentrations of α-CHMA enantiomers in organic phase were calculated from the mass balance by substractive method.

Results and discussion

The chromatogram of racemic α-CHMA before and after extraction was shown in Figures 3(a) and 3(b), respectively. It can be calculated from Figure 3(a) that the chromatographic peak area of *S*-α-CHMA is equal to that of *R*-α-CHMA, which indicates that the content of *S*-α-CHMA is the same as that of *R*-α-CHMA. Racemic α-CHMA were separated by reactive extraction with 0.1 mol/L HP-β-CD in 0.1mol/L phosphate salt buffer solution, and α-CHMA in the aqueous phase at equilibrium was analyzed by HPLC [Figure 3(b)].

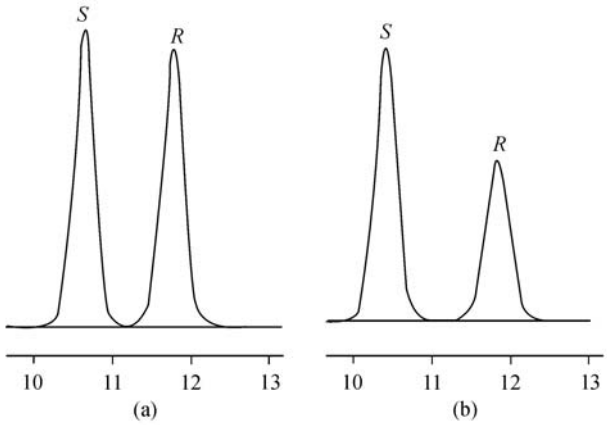

Figure 3 Chromatograms of α-CHMA enantiomers before (a) and after (b) extraction. [HP-β-CD]=0.1 mol/L, pH=2.5, temperature 5 ℃.

Influence of organic solvents

Solvent molecules play an important role in the complexation process, for instance by desolvation of the enantiomers and extractant, solvation of the complex and possibly by acting as a ligand.[24] The influence of organic solvent on distribution behavior was investigated in various extraction systems containing 0.1 mol/L HP-β-CD in aqueous phase and α-CHMA enantiomers in different organic solvents at 5 ℃. It was observed from Table 1 that the solvent has a clear influence on the distribution ratios and enantioselectivity. When *n*-heptane is used as solvent, big distribution ratios are obtained, although low separation factor is found. While *n*-octanol is used as solvents, HP-β-CD shows separation factors towards α-CHMA enantiomers but with very small distribution ratios. The high viscosity of *n*-octanol and the associated slow phase settling is a drawback of this solvent. Separation factors and distribution ratios for α-CHMA enantiomers are relatively high with 1,2-dichloroethane and methylene chloride as

solvents. Highest separation factor and performance factor are achieved with 1,2-dichloroethane as solvent. So 1,2-dichloroethane is a suitable solvent for extraction of α-CHMA enantiomers.

Table 1 Influence of organic solvent[a]

Organic solvent	D_S	D_R	a	ee_{org}/%	PF
n-Octanol	0.08	0.04	2.00	1.89	0.0014
n-Heptane	7.55	7.14	1.06	2.56	0.0226
Methylene chloride	3.33	2.19	1.52	15.15	0.1165
1,2-Dichloroethane	4.77	2.36	2.02	26.37	0.2180

[a] Aqueous phase: [HP-β-CD] = 0.1 mol/L, [α-CHMA] = 1.0 mmol/L, pH = 2.5.

Screening of chiral selectors

Whether and to what extent a complex is formed, can be predicted on the basis of size, shape and polarity of the guest molecule and various interactions involving Van der Waals, dispersive forces, dipole-dipole interactions, electrostatic forces and hydrogen bonding. The size of the guest determines whether it fits into the cavity, shape and polarity influence the possible stabilizing effects by interactions within the cavity or with side groups on the cavity rim. The size of the guest of α-CHMA enantiomers fits into the cavity of β-CD derivatives, so β-CD derivatives can form complexes with α-CHMA enantiomers. But to what extent a complex is formed depends on the shape and polarity of β-CD derivatives. Therefore, three types of β-CD derivatives show different separation factors towards α-CHMA enantiomers.

Separation factors and distribution ratios for α-CHMA enantiomers were investigated in several extraction systems containing different β-CD derivatives (Me-β-CD or HE-β-CD or HP-β-CD) at 5 ℃ (Table 2). From Table 2, it is clearly seen that the separation factors of the three β-CD derivatives are always above 1, which indicates that they have stronger recognition abilities for *S*-α-CHMA than for *R*-α-CHMA. Among the three β-CD derivatives, HP-β-CD has the highest separation factor.

Table 2 Chiral recognition ability of different β-CD derivatives[a]

Extractant	D_S	D_R	α	ee_{org}/%
Me-β-CD	13.11	11.92	1.10	4.41
HE-β-CD	4.80	3.58	1.34	11.73
HP-β-CD	4.77	2.36	2.02	26.37

[a] Aqueous phase: [Me-β-CD] = 0.1 mol/L, [HE-β-CD] = 0.1 mol/L, [HP-β-CD] = 0.1 mol/L, pH = 2.5, [α-CHMA] = 1.0 mmol/L.

Influence of pH

In aqueous solution, α-CHMA molecules exist in two states of molecule (HA) and anion (A^-). δ_1 and δ_0 represent the percentage distributions of α-CHMA species of HA and A^-, respectively.

$$\delta_1 = \frac{[H^+]}{[H^+]+K_a} \tag{10}$$

$$\delta_0 = \frac{K_a}{[H^+]+K_a} \tag{11}$$

The relationship between the relative concentrations of all HA species and the pH values of the solution at 5 ℃ can be determined by Matlab (Figure 4). From Figure 4, it was found that both molecule HA and anion A^- exist in aqueous solution round the pH of pK_a (3.53), anion A^- is the main species of HA when pH > 4.5, and α-CHMA enantiomers mainly exist in the form of neutral molecule HA when pH ≤ 2.5. It can be predicted that there is obvious influence of pH on the distribution behavior of α-CHMA enantiomers in the reactive extraction systems containing HP-β-CD.

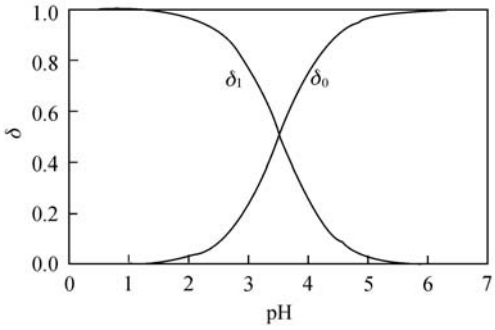

Figure 4 Percentage distribution of α-cyclohexyl-mandelic acid species as a function of pH.

To better understand the effect of pH on the distribution behavior, partition ratios and separation factor were investigated in the extraction systems containing 0.1 mol/L HP-β-CD in 0.1 mol/L KH_2PO_4/H_3PO_4 buffer solution at different pH values (Figure 5). It is shown from Figure 5 that the influence of pH on distribution behavior is notable. This new organization of the results, as a function of pH, shows clearly that all the distribution ratios increase when increasing the pH, while the separation factors follow opposite tendency.

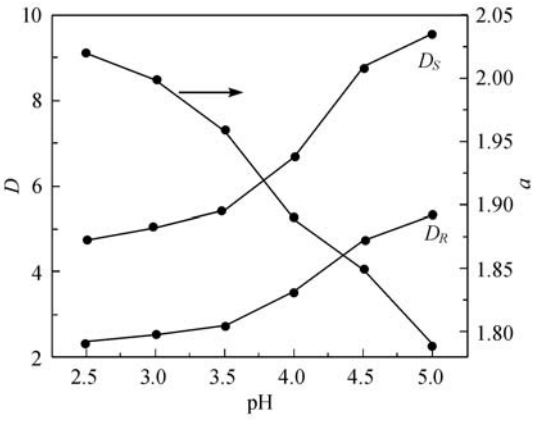

Figure 5 Influence of pH on *D* and *α*. [HP-β-CD] = 0.1 mol/L, [α-CHMA] = 1.0 mmol/L, temperature 5 ℃.

The possible reasons for these may be that the neutral molecule of α-CHMA enantiomers can react with HP-β-CD to form diastereomeric complexes, while the ionic forms of α-CHMA enantiomers can not. The amount of ionic α-CHMA (A^-) increases with the rise of the pH, but the amount of molecular α-CHMA decreases. With the rise of the pH value, more molecular α-CHMA in organic phase is transferred to aqueous phase and changed into ionic α-CHMA, which leads to the results that the non-selective physical partitioning of α-CHMA in organic phase and HP-β-CD complexation decrease with pH. As a result, distribution ratios increase with the rise of the pH, but separation factors obviously decrease with the rise of the pH. Therefore, it should be kept at low pH to perform the extraction process.

Influence of HP-β-CD concentration

HP-β-CD and α-CHMA enantiomers can form two diastereomeric complexes, which not only enhances the solubility of the enantiomers in a buffer solution, but also improves the separation factors for α-CHMA enantiomers. As a result the concentration of HP-β-CD has a great influence on distribution ratios and separation factors.

Figure 6 shows the influence of HP-β-CD concentration on distribution behavior of α-CHMA enantiomers by varying the concentration from 0 to 0.12 mol/L, at pH 2.5 and 5 ℃. It can be seen from Figure 6 that distribution ratios and separation factors all increase with the rise of the concentration of HP-β-CD, which can be explained by a larger amount of complexes formed in aqueous phase. When the concentration of HP-β-CD is 0, both distribution ratios of 0.02 are very low and no separation factor is found which indicates that the physical partitioning of CHMA hardly occurs in the aqueous phase in the absence of HP-β-CD. The fact that α-CHMA enantiomers hardly partition into the aqueous phase in the absence of HP-β-CD also shows that α-CHMA enantiomers partitioning behaviour in the presence of β-CD is carried out through enantioselective complexation between enantiomers and selector. Therefore, the model approach on the reactive extraction of α-CHMA enantiomers may be interfacial reactive model to describe mass transfer and reaction kinetics in the system.

Influence of α-CHMA enantiomers concentration

The influence of α-CHMA enantiomers concentration on extraction efficiency is shown in Figure 7. All distribution ratios and separation factors reduce with the increase of the initial concentration of α-CHMA enantiomers, which indicates a better enantioseparation efficiency at low initial concentrations. This can be due to the fact that the non-selective physical partitioning of α-CHMA in organic phase is enhanced upon the increase of the initial concentration of α-CHMA enantiomers, but the percent of α-CHMA which form complexes with HP-β-CD, decreases with the increase of initial concentration. It is concluded that at low concentrations most extraction is through enantioselective complexation and at higher concentrations more non-selective partitioning is occurring in organic phase.

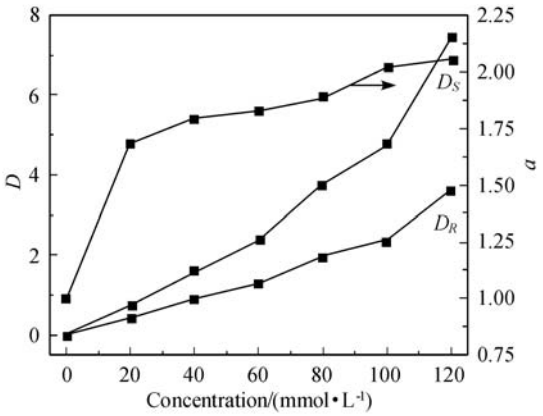

Figure 6 Influence of concentration of HP-β-CD on D and α. [α-CHMA]=1.0 mmol/L, pH=2.5, and temperature 5 ℃.

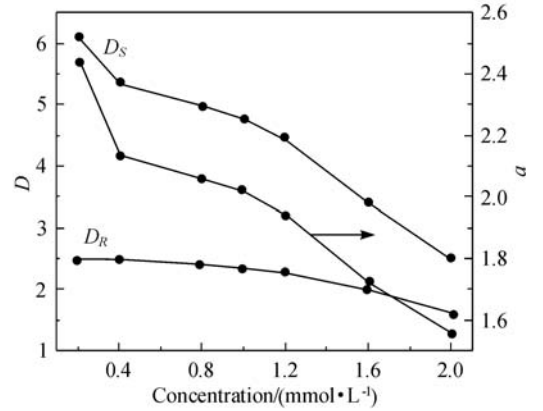

Figure 7 Effect of initial concentration of α-CHMA on D and α. [HP-β-CD]=0.1 mol/L, pH=2.5, and temperature 5 ℃.

Influence of temperature

The influence of temperature on the distribution behavior was investigated in the range of 5—30 ℃ with racemic α-CHMA as the solute in the organic phase. It was observed from Table 3 that higher temperature leads to a decrease in distribution ratios and separation factors. The fact that the decreasing distribution ratios is obtained indicates that with the rise of temperature, the non-selective physical partitioning of α-CHMA in organic phase is increasing and β-CD complexation decreases. A decrease in separation factors can be explained that the selector-enantiomer interaction weakens with temperature and the discrimination ability of the selector for α-CHMA enantiomers weakens as well.

The variations of ln k and ln α versus $1/T$ are shown in Figure 8. The results can be described as fitting very well with the Van't Hoff model, indicating that the complexes do not change in conformation and that enantioselective interactions remain unchanged in the temperature range studied.

CHINESE JOURNAL OF CHEMISTRY

Table 3 Influence of the temperature on the enantioseparation of α-CHMA enantiomers[a]

T/K	D_S	D_R	α	ee_{org}/%
278	4.77	2.36	2.02	26.37
283	3.08	1.67	1.84	20.80
288	2.36	1.37	1.72	17.23
293	1.80	1.11	1.62	14.02
298	1.26	0.82	1.54	10.85
303	1.01	0.69	1.46	8.58

[a] Aqueous phase: [HP-β-CD] = 0.1 mol/L, [α-CHMA] = 1.0 mmol/ L, pH=2.5.

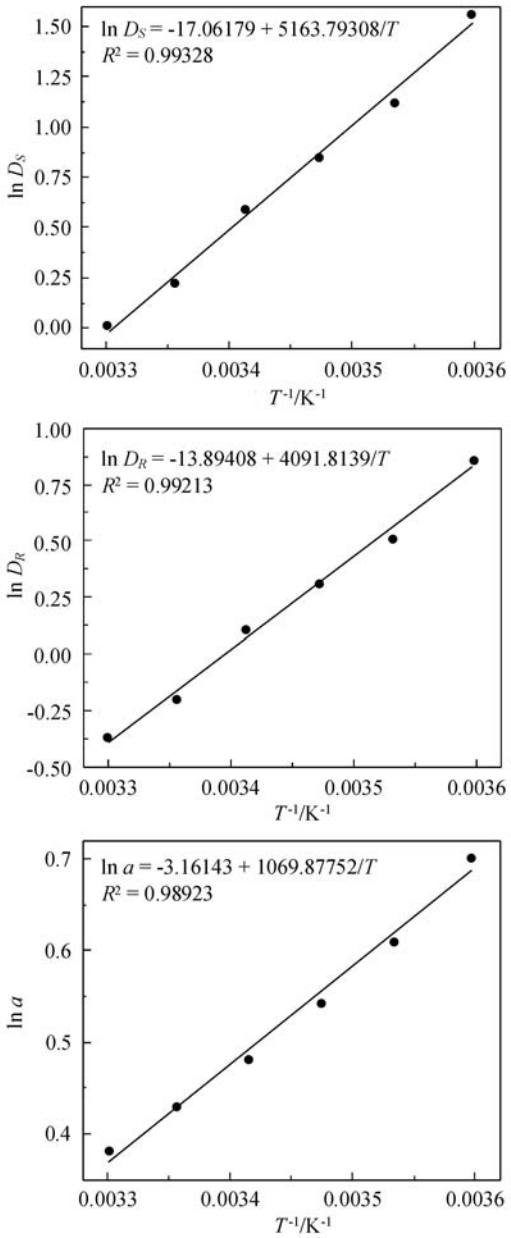

Figure 8 Influence of temperature on the enantioseparation of α-CHMA. [HP-β-CD] = 0.1 mol/L, [α-CHMA] = 1.0 mmol/L, pH=2.5.

Conclusion

In this paper, liquid-liquid reactive extraction has been proposed and evaluated as alternative industrial technique for separation of α-CHMA enantiomers. It was found that aqueous hydroxypropyl-β-cyclodextrin solution is a sufficient reactive extractant for α-CHMA enantiomers. The efficiency of extraction depends on several factors including the types of organic solvents and β-CD derivatives, the concentrations of the chiral selector and α-CHMA enantiomers, pH and temperature, and the optimum extraction conditions are achieved to improve the separation factors. A better enantioseparation efficiency can be obtained at low initial concentration. Higher temperature leads to a decrease in distribution ratios and separation factors. A good enantioseparation efficiency with a maximum separation factor of 2.02 is obtained at pH 2.5 and 5 ℃, and the *ee* in the organic phase reaches 26.37% after one stage extraction. α-CHMA enantiomers hardly partition into the aqueous phase in the absence of HP-β-CD, which shows the model approach on the reactive extraction of α-CHMA enantiomers may be interfacial reactive model to describe mass transfer and reaction kinetics in the system. It can be envisioned that liquid-liquid reactive extraction will allow enantioselective separation of various aromatic acid enantiomers with aqueous β-cyclodextrin. Full separation of α-CHMA can be carried out by multistage extraction.

References

1 Ward, T. J.; Bake, B. A. *Anal. Chem.* **2008**, *80*, 4363.
2 Tang, K. W.; Chen, Y. Y.; Liu, J. J. *Sep. Purif. Technol.* **2008**, *62*, 681.
3 Tang, L.; Ga, H.; Kim, J.; Choi, S.; Nandhakumar, R.; Kim, K. M. *Tetrahedron Lett.* **2008**, *49*, 6914.
4 Koska, J.; Haynes, C. A. *Chem. Eng. Sci.* **2001**, *56*, 5853.
5 Colera, M.; Costero, A. M.; Gaviña, P.; Gil, S. *Tetrahedron: Asymmetry* **2005**, *16*, 2673.
6 Tang, K. W.; Chen, Y. Y.; Huang, K. L.; Liu, J. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2399.
7 Lee, S. B.; Mitchell, D. T.; Trofin, L.; Nevanen, T. K.; Söderlun, H.; Matin, C. R. *Science* **2002**, *296*, 2198.
8 Makino, K.; Goto, T.; Hiroki, Y.; Hamada, Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 882.
9 Babic, K.; Driessen, G. H. M.; van der Ham, A. G. J.; de Haan, A. B. *J. Chromatogr., A* **2007**, *42*, 84.
10 Viegas, R. M. C.; Carlos, A. M. A.; João, G. C.; Coelhoso, I. M. *J. Membr. Sci.* **2007**, *305*, 203.
11 Carlos, A. M. A.; João, G. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 5293.
12 Lacour, J.; Goujon-Ginglinger, C.; Torche-Haldimann, S.; Jodry, J. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3695.
13 Viegas, R. M. C.; Afonso, C. A. M.; Crespo, J. G. G.; Coelhoso, I. M. *Sep. Purif. Technol.* **2007**, *53*, 224.
14 Keurentjes, J. T. F.; Nabuurs, L. W. M.; Vegter, E. A. *J. Membr. Sci.* **1996**, *113*, 354.
15 Tan, B.; Luo, G. S.; Wang, J. D. *Sep. Purif. Technol.* **2007**,

53, 330.
16 Vladimir, P.; Miće, K.; Martin, E. *Chem*. *Int*. *Ed*. **1989**, *28*, 1147.
17 Steensma, M.; Kuipers, N. J. M.; de Haan, A. B.; Kwant, G. *Chem*. *Eng*. *Sci*. **2007**, *62*, 1395.
18 Uemasu, I.; Kushiyama, S. *Fuel Process*. *Technol*. **2004**, *85*, 1519.
19 Meindersma, G. W.; van Schoonhoven, T.; Kuzmanovic, B.; de Haan, A. B. *Chem*. *Eng*. *Process*. **2006**, *45*, 175.
20 Foucault, A. P. *J*. *Chromatogr*., *A* **2001**, *906*, 365.
21 Steensma, M.; Kuipers, N. J. M.; de Haan, A. B.; Kwant, G. *Chirality* **2006**, *18*, 314.
22 Koska, J.; Haynes, C. A. *Chem*. *Eng*. *Sci*. **2001**, *56*, 5853.
23 Hu, S. S.; Wu, Y. Z.; Shi, M. R. *Fine Chem.* **2004**, *21*, 730 (in Chinese).
24 Steensma, M.; Kuipers, N. J. M.; de Haan, A. B.; Kwant, G. *Chem*. *Technol*. *Biotechnol*. **2006**, *81*, 588.

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