

Article

Study on extraction kinetics of α -cyclopentylmandelic acid enantiomers with hydroxyethyl- β -cyclodextrin as chiral selector[☆]Panliang Zhang^{1,2}, Pan Jiang³, Weifeng Xu¹, Yu Liu¹, Biquan Xiong¹, Yunren Qiu^{2,*}, Kewen Tang^{1,*}¹ Department of Chemistry and Chemical Engineering, Hunan Institute of Science and Technology, Yueyang 414006, China² School of Chemistry and Chemical Engineering, Central South University, Changsha 410083, China³ College of Chemical Engineering, Xiangtan University, Xiangtan 411105, China

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ABSTRACT

In this work, the kinetic study on reactive extraction of α -cyclopentylmandelic acid (α -CPMA) enantiomers was performed in a Lewis cell using hydroxyethyl- β -cyclodextrin (HE- β -CD) as chiral selector. The enantioselective complexation equilibrium between HE- β -CD and α -CPMA enantiomers was studied by phase solubility method. The important process parameters affecting the initial extraction rate were separately studied and the reaction rate equations were deduced. The optimal conditions for kinetic study were as follows: stirring speed of $75 \text{ r} \cdot \text{min}^{-1}$, interfacial area of 12.56 cm^2 , pH of 2.5, initial HE- β -CD concentration of $0.05 \text{ mol} \cdot \text{L}^{-1}$, initial α -CPMA concentration of $5 \text{ mmol} \cdot \text{L}^{-1}$, and temperature of 278 K . The reaction has been found to be first order in α -CPMA and second order in HE- β -CD with the forward rate constants of $2.056 \times 10^{-3} \text{ m}^6 \cdot \text{mol}^{-2} \cdot \text{s}^{-1}$ and $1.459 \times 10^{-3} \text{ m}^6 \cdot \text{mol}^{-2} \cdot \text{s}^{-1}$ for (S)- α -CPMA and (R)- α -CPMA, respectively. The complexation equilibrium constants were evaluated as $61 \text{ L} \cdot \text{mol}^{-1}$ and $117 \text{ L} \cdot \text{mol}^{-1}$ for (S)- α -CPMA and (R)- α -CPMA, and the intrinsic enantioselectivity is estimated as 1.92.

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1. Introduction

In pharmaceuticals industry, α -cyclopentylmandelic acid (α -CPMA, Fig. 1) is the key intermediate of soft anticholinergics, e.g., glycopyrrolate which is a well-known antagonist of muscarinic receptors and used for the treatment sialorrhea [1], hyperhydrosis [2], and overactive bladder and for presurgery treatment. Recently, Tóth-Sarudy *et al.* have investigated biological effects of pure stereoisomeric novel soft anticholinergics prepared by (R)-cyclopentylmandelic acid [3]. Generally, the two enantiomers of chiral drug show different interactions with biological receptors or enzymes, hence giving rise to different biological effects. One enantiomer may produce desired pharmaceutical activities, while the other may be inactive or, in the worst cases, produce unwanted effects. Although this is well-known to us, the majority of commercial chiral drugs are racemic mixtures. It is a challenge to find an efficient and economic chiral separation method for obtaining enantiomerically pure compounds.

During the past decades, the methods of enantioselective separation from racemic mixtures are rising rapidly such as kinetic resolutions [4], crystallization [5], chromatographic techniques [6], capillary electrophoresis (CE) [7], liquid membrane [8] and liquid–liquid extraction (LLE) [9–11]. Recently, enantioselective liquid–liquid extraction

(ELLE) with cyclodextrin derivatives as a specific chiral selector [12–14] seems to be an attractive alternative, because of the possibility to operate on all scales from laboratory separations to large-scale processes in the chemical industry. Using cyclodextrin derivatives also has the advantages of owning unique physical properties and nontoxic side effects. Nevertheless, those works mainly focuses on the study of thermodynamics of the corresponding extraction process and seeking for efficient extraction system. Only limited information concerning the kinetic study on chiral solvent extraction is available [15]. Kinetics of the extraction process is very important for a deep understanding of the process, and for the selection, design, operation and reliable scale-up of the reactive extraction equipment.

Therefore, the extraction kinetics should be carefully investigated to realize the industrial application of ELLE. Several technologies are employed to investigate the extraction kinetics, such as single drop technology [16,17], high-speed stirring method [18,19], microfluidic device [20] and constant interfacial area cell [21–25]. Compared to the other techniques, the Lewis cell (or constant interfacial area cell) has a wider range of applications and is easier to be operated. In this work, the Lewis cell was selected as a model reactor and the kinetics of reactive extraction of α -CPMA enantiomers by hydroxyethyl- β -cyclodextrin (HE- β -CD) was studied. Equilibrium study shows that HE- β -CD has good recognition ability towards α -CPMA enantiomers. As is shown in our previous work, the distribution ratios of (S)- α -CPMA and (R)- α -CPMA ($k_S = 2.212$ and $k_R = 1.293$) and the enantioselectivity ($\alpha = 1.711$) indicates that HE- β -CD can be a good

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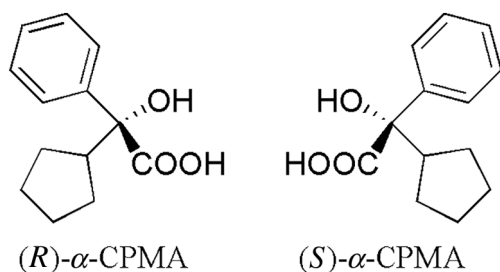


Fig. 1. Molecular structure of α-CPMA.

hydrophilic chiral selector for extractive separation of α-CPMA enantiomers [26]. Additionally, two questions should also be considered. The first one is the intrinsic enantioselectivity, which indicates the upper limit of enantioselectivity that can be reached with HE-β-CD as chiral selector. The second one is the extraction kinetics because a reliable reactive extraction system requires not only the sufficiently high equilibrium selectivity, but also the sufficiently fast extraction kinetics. Hence, the intrinsic enantioselectivity and the process parameters affecting the extraction kinetics were investigated, such as agitation speed and interfacial area and so on to understand the transfer mechanism of the chiral extraction.

2. Theory

When the system for reactive extraction of α-CPMA enantiomers from organic phase to aqueous phase with HE-β-CD reaches its equilibrium, free HE-β-CD and the complex of HE-β-CD with α-CPMA enantiomers remain in the aqueous phase due to the high hydrophilicity of HE-β-CD, while α-CPMA enantiomers can distribute over the organic and aqueous phases. Therefore, the main reactions for enantioselective extraction of α-CPMA enantiomers by HE-β-CD are restricted to the aqueous phase. A homogeneous reaction model is applied as the suitable approach to study the reactive extraction of α-CPMA enantiomers by HE-β-CD in the Lewis cell.

In the homogeneous reaction model, the mass transfer process can be described in various ways. In this paper, the two-film model as a classical mass transfer model was selected [10], and the mass transfer crossing the two phase interface is accompanied by the reactions in aqueous phases.

The organic and aqueous bulk phases are assumed to be perfectly mixed, and physical equilibrium is assumed at the interface. At $t = 0$, the mass transfer resistance in the organic phase film can be ignored. Therefore, the following equation is deduced,

$$C_{R,aq}^* = PC_{R,org}^* = PC_{R,0} \quad (1)$$

where, $C_{R,aq}^*$ and $C_{R,org}^*$ represent the interfacial concentration of (R)-α-CPMA on the aqueous side and on the organic side, respectively; $C_{R,0}$ is the initial concentration of (R)-α-CPMA in organic phase, P the physical partition coefficient.

Depending on the physicochemical and hydrodynamic properties of a reactive extraction system, four limiting regimes can be distinguished to characterize the extraction kinetics [27], which is summarized in Table 1 [21]. The dimensionless Hatta number (Ha) can be accustomed to indicate these regimes. The Hatta number can be expressed as Eq. (2) for the forward part of the rate law $r_R = k_{m,n} C_R^m C_{CD}^n$ taking place in the aqueous phase.

$$Ha_R = \frac{\sqrt{\frac{2}{m+1} \cdot k_{m,n} \cdot C_{R,aq}^{m-1} \cdot [CD]_0^n \cdot D_{aq,R}}}{K_{L,aq,R}} \quad (2)$$

Table 1

The discern condition for regimes: Lewis cell

Regime	Description	Ha_A	Dependency on	
			a	Stirring
1	Very slow reaction	<0.2	None	None
2	Slow reaction	<0.2	α	α
3	Fast reaction	>2	α	None
4	Instantaneous reaction	>2	α	α

Note: a is the specific area (area/volume, m^{-1}). α means linear dependency.

in which, $k_{m,n}$ is rate constant for (m,n) reaction; $[CD]_0$ represents the initial concentration of HE-β-CD in aqueous phase; $D_{aq,R}$ is the diffusivity of (R)-α-CPMA in aqueous phase; $K_{L,aq,R}$ is the physical mass transfer coefficient; m is the order of reaction with respect to (R)-α-CPMA; n is the order of reaction with respect to HE-β-CD.

The expressions of the extraction rate for relevant regimes were given by Doraiswamy and Sharma [27]. For regime 3, namely the extraction accompanied by a fast reaction, the expression for the rate of extraction is given by the following Eq. (3):

$$R_R = \sqrt{\frac{2}{m+1} \cdot k_{m,n} \cdot C_{R,aq}^{m+1} \cdot [CD]_0^n \cdot D_{aq,R}} \quad (3)$$

All of the above equations can be defined for (S)-α-CPMA in the same way.

3. Materials and Methods

3.1. Materials

Hydrophilic extractant hydroxyethyl-β-cyclodextrin (HE-β-CD) was purchased from Zhiyuan Biotechnology Co., Ltd. (Binzhou, China). Racemic α-cyclopentylmandelic acid (α-CPMA, purity $\geq 96.0\%$) was brought from Heowns Biochemical Technology Co., Ltd. (Tianjing, China). 1,2-Dichloroethane (purity $\geq 99.0\%$) was purchased from Huihong Reagent Co. Ltd. (Changsha, China). Acetonitrile (HPLC grade) was supplied by Comio Chemical Reagent Co. Ltd. (Tianjin, China).

3.2. Analytical method

The quantification of α-cyclopentylmandelic acid (α-CPMA) enantiomers in aqueous phase were performed by HPLC (waters, USA), which was equipped with a Diamonsil C18 column (250 mm $\times$ 4.6 mm I.D., 5 μm of particle size; Dikma Technologies). Detailed information about the analytical method is available in the literature [28]. Results showed that the first eluted peak for all the chromatograms was (S)-α-CPMA and the second peak was (R)-α-CPMA.

For pH measurements of the aqueous phase, a pH meter with a pH electrode (Orion, model 720A) was employed.

3.3. Experiment procedure

3.3.1. Determination of intrinsic enantioselectivity

Phase solubility method is employed and detailed information about this method is available in the literature [29]. Excess amounts of racemic α-CPMA were added to aqueous solutions containing increasing amounts of HE-β-CD (0, 0.01, 0.02, 0.04, 0.06, 0.08, and 0.1 mol·L⁻¹). The suspensions were shaken for 24 h in a water bath at 278 K. when the inclusion reaction reach its equilibrium, the suspensions were filtered through 0.45 μm membrane filters, appropriately diluted with the mobile phase and the total concentrations of α-CPMA enantiomers were analyzed by HPLC. The apparent inclusion complexation equilibrium constants are calculated from the phase solubility diagram.

3.3.2. Determination of extraction kinetics

The Lewis cell (Fig. 2) used for the kinetic investigations was modified by Tang [24]. The actual interface is controlled by a Teflon circular disc which is fixed in the middle of the cylindrical glass cell. The total area of the holes in the circular disks is changed to vary the actual interface from 7.07–15.9 cm². The cell, equipped with a jacket, is thermostated with a Scientz DC-1020 water bath (set at 278 K). To carry out an experiment, a fixed volume (110 ml) of phosphate buffer solution (pH value of 2.5) containing HE- β -CD was first introduced into the cell, and equal volume of organic phase was then added carefully without disturbing the interface. In this work, 1,2-dichloroethane was used as organic solvent and the substrate, α -CPMA racemate, was initially dissolved in the organic solvent. The stirrers were rotated at the same speed but in opposite directions. And it was the time to start timing when the blender was started. Then samples were taken out from the aqueous phase by injection syringe at specified time intervals. The concentration of α -CPMA enantiomers was determined by HPLC. The concentration of α -CPMA in the organic phase was calculated by mass balance.

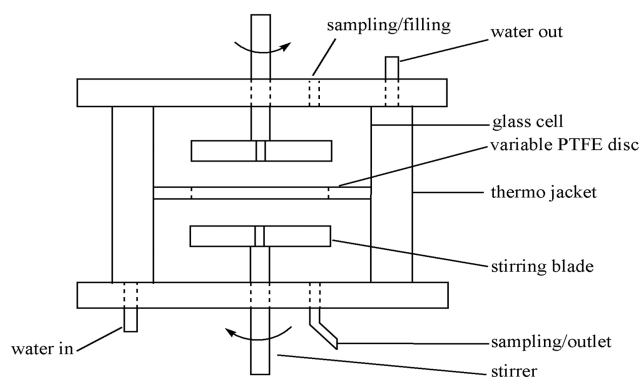


Fig. 2. Diagram of the Lewis cell.

3.4. Data treatment

The initial extraction rate $R_{R,0}$ was obtained by the following equation:

$$R_{R,0} = \frac{V_{aq}}{A} \left(\frac{dC_{R,aq}}{dt} \right)_{t=0} = - \frac{V_{org}}{A} \left(\frac{dC_{R,org}}{dt} \right)_{t=0} \quad (4)$$

where, A is the interfacial contact area taken as the total area of the holes in the circular disks; $C_{R,aq}$ is the concentration of (R)- α -CPMA in aqueous phase at time t ; V_{aq} and V_{org} are the volume of the aqueous and organic phase, respectively. Eq. (4) can be defined for (S)- α -CPMA in the same way.

4. Results and Discussion

4.1. Determination of physical mass transfer coefficient

The value of physical mass transfer coefficient K_L is required for further confirming the regime of reactive extraction. This was obtained by conducting physical extraction (diluent only) of α -CPMA enantiomers from the organic phase. For a batch process, a differential mass balance yields the following equation:

$$R_R = \frac{V_{aq}}{A} \left(\frac{dC_{R,aq}}{dt} \right) = K_{L,aq,R} \cdot (C_{R,aq}^* - C_{R,aq}) \quad (5)$$

According to Eq. (1), Eq. (5) was integrated, the time-dependent concentration of (R)- α -CPMA in aqueous phase is given by:

$$\frac{1}{1+P} \ln \left(\frac{PC_{R,0}}{PC_{R,0} - (1+P)C_{R,aq}} \right) = \frac{K_{L,aq,R} \cdot A}{V_{aq}} \cdot t \quad (6)$$

The plot of $1/(1+P) \ln[PC_{R,0}/(PC_{R,0} - (1+P)C_{R,aq})]$ versus time (t) yielded a straight line, as shown in Fig. 3. The corresponding slope of the line was used to evaluate $K_{L,aq,R}$ as $1.499 \times 10^{-6} \text{ m} \cdot \text{s}^{-1}$. As the two enantiomers have the same physical properties, $K_{L,aq,S}$ is equal to $K_{L,aq,R}$.

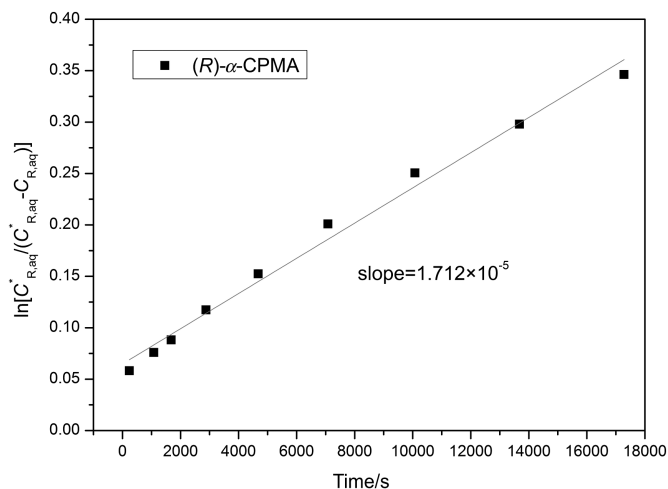


Fig. 3. The plot of $\ln[C_{R,aq}^*/(C_{R,aq}^* - C_{R,aq})]$ versus time (t). Conditions: $[\alpha\text{-CPMA}]_0 = 5 \text{ mmol} \cdot \text{L}^{-1}$, $A = 12.56 \text{ cm}^2$, $N = 75 \text{ r} \cdot \text{min}^{-1}$, $T = 278 \text{ K}$, $R^2 = 0.988$.

4.2. Determination of intrinsic enantioselectivity

The intrinsic enantioselectivity is defined as the ratio of the inclusion complexation equilibrium constants for (R)- and (S)- α -CPMA (K_R and K_S , respectively). The inclusion complexation equilibrium constants are determined by a phase solubility method. Fig. 4 shows the phase distribution diagrams for (R)- and (S)- α -CPMA in an aqueous solution with increasing the concentration of HE- β -CD under temperature of 298 K. It is found that the solubility of (R)- and (S)- α -CPMA increases linearly with the increase of HE- β -CD concentration. Consequently, the diagrams can be classified as A_L type, indicating that a 1:1 inclusion complex is formed between HE- β -CD and α -CPMA enantiomer. According to the method described in the literature [29], K_R and K_S are calculated from the slope and the intercept of the phase solubility diagrams. K_R and K_S were evaluated as $61 \text{ L} \cdot \text{mol}^{-1}$ and $117 \text{ L} \cdot \text{mol}^{-1}$, respectively and the intrinsic enantioselectivity is estimated as 1.92, which shows the upper limit of enantioselectivity that can be reached with HE- β -CD as chiral selector. The K_S is larger than K_R , which indicates that HE- β -CD preferentially form inclusion complex with (S)- α -CPMA. The difference in inclusion complexation equilibrium constants gives the basic driving force for separation of α -CPMA enantiomers in the extraction process. It is very likely that extraction kinetics of (S)- α -CPMA is faster than that of (R)- α -CPMA.

4.3. Determination of the kinetic regime

4.3.1. Influence of agitation speed on the initial rate of extraction

In the reaction–diffusion system, the speed of agitation is a crucial parameter. Fig. 5 shows the initial rate of reactive extraction of α -CPMA enantiomers at the speed of agitation ranging from $30 \text{ r} \cdot \text{min}^{-1}$ to $105 \text{ r} \cdot \text{min}^{-1}$. In the agitating speed range from 30 to $60 \text{ r} \cdot \text{min}^{-1}$, it

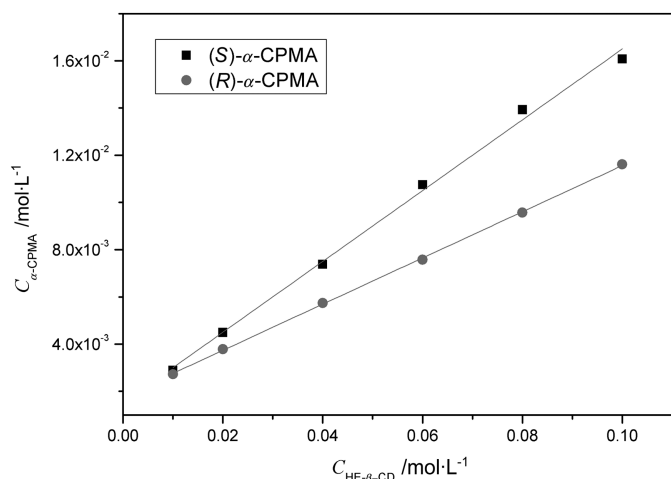


Fig. 4. Phase distribution diagrams of (R)- and (S)-α-CPMA as a function of HE-β-CD concentration. Conditions: concentration of HE-β-CD is set at 0.01, 0.02, 0.04, 0.06, 0.08 and 0.1 mol·L⁻¹; temperature is 278 K.

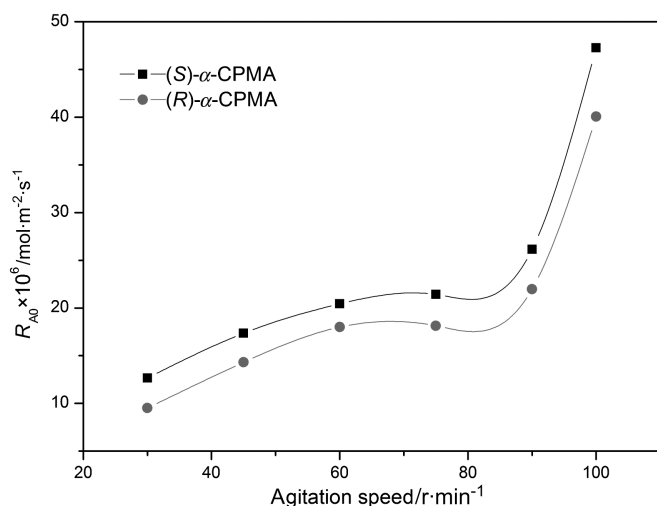


Fig. 5. Influence of agitation speed on the initial rate of extraction. Conditions: [α-CPMA]₀ = 5 mmol·L⁻¹, [CD]₀ = 0.05 mol·L⁻¹, A = 12.56 cm², pH = 2.5, T = 278 K.

is found that the initial extraction rate increases with the stirring speed, indicating that the stagnant interfacial films are very thick in this agitating speed range. The increase of the agitation speed, which reduces the thickness of the stagnant films, can intensify the mass transfer. When the agitating speed further rises from 60 to 85 r·min⁻¹, the initial rate of extraction is independent of the agitation speed, which indicates that the film is stable and thin enough to achieve a fast mass transfer. The reaction between selector and enantiomers are the rate-determining step and the agitation speed has no effect on the overall extraction rate. It can be said that the extraction occurs in a “kinetic regime”. However, when agitation speed is higher than 90 r·min⁻¹, the initial rate of extraction rises straightly with the increase of the agitation speed, and it was observed that the liquid–liquid interface was unstable. The increase in extraction rate may be due to an increase in the actual contacting area. Therefore, an agitation speed of 75 r·min⁻¹ is chosen for most of the experiments unless specified otherwise to ensure that all measurements are performed in the plateau region. In this case, one can study the reaction kinetics in the reactive extraction process by measuring extraction rate. Although any one of the stirring speeds in the range from 60 r·min⁻¹ to 85 r·min⁻¹ could theoretically be selected, 75 r·min⁻¹, the median of the range, was selected to make sure the extraction occurs in a “kinetic regime” and minimize the risk

of disturbing the interface in this paper. When the interface is disturbed, it is difficult to acquire the accurate relation between the reaction rate and other factors. According to the classical limiting regime identification (Table 1), the reaction is deduced to occur either in regime 1 or 3.

4.3.2. Influence of the interfacial area on the initial rate of extraction

To further confirm the kinetic regime, the interfacial area varied at a constant agitation speed (75 r·min⁻¹). As is shown in Fig. 6, the volumetric extraction rate, in terms of the product of R_{A0} with a (a is the specific area, defined as the ratio of interfacial contact area to bulk phase volume), is in proportion to the interfacial area. Therefore, based on the above results, we can come to a conclusion that the reactions between HE-β-CD and α-CPMA enantiomers in a Lewis cell fall in regime 3. As a consequence, the extraction is a fast chemical reaction in the diffusion film.

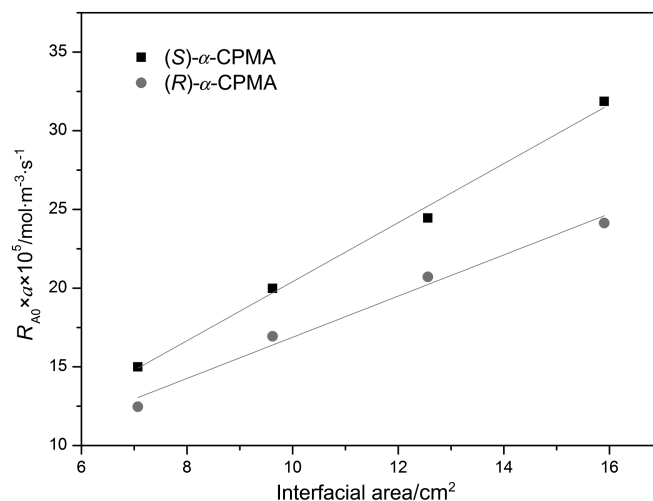


Fig. 6. Influence of the interfacial area on the initial rate of extraction. Conditions: [α-CPMA]₀ = 5 mmol·L⁻¹, [CD]₀ = 0.05 mol·L⁻¹, N = 75 r·min⁻¹, pH = 2.5, T = 278 K.

4.3.3. Influence of pH value on the initial rate of extraction

As is shown in Fig. 7, the initial extraction rate keeps nearly unchanged at pH ≤ 3.0 and then increases rapidly with the pH value. It is also observed that the difference of initial extraction rate between (R)-α-CPMA and (S)-α-CPMA keeps nearly unchanged at pH ≤ 3.0 and then becomes smaller with the further increase of pH. Because α-CPMA is a weak acid and there exists an acid–base dissociation equilibrium for α-CPMA in the aqueous phase, the above observation may be explained by the fact that the existence form of the α-CPMA enantiomers in aqueous phase is changed with the pH of aqueous phase. At pH lower than 3.0, α-CPMA is predominantly in its molecular form. HE-β-CD mainly includes the molecular α-CPMA because the hydrophobic nature of its inner cavity [30]. In this case, most of enantiomers are extracted through the enantioselective complexation and the separation ability is enhanced. However, the molecular α-CPMA is a hydrophobic species, therefore the extraction rate is relatively low. With the increase of pH value, the amount of ionic α-CPMA enantiomers is increased. As HE-β-CD can hardly include ionic α-CPMA enantiomers, the amount of enantiomers that is extracted through the enantioselective complexation is decreased and the separation ability is reduced. Owing to the hydrophilicity of the ionic α-CPMA, the extraction rate is enhanced with the rise of pH value. Hence, except as otherwise specified in this work, all experiments are operated at pH = 2.5.

4.4. Determination of the reaction order

4.4.1. Order with respect to α-CPMA

The concentration of (R)-α-CPMA in the aqueous phase versus time at different initial concentration of α-CPMA in organic phase is

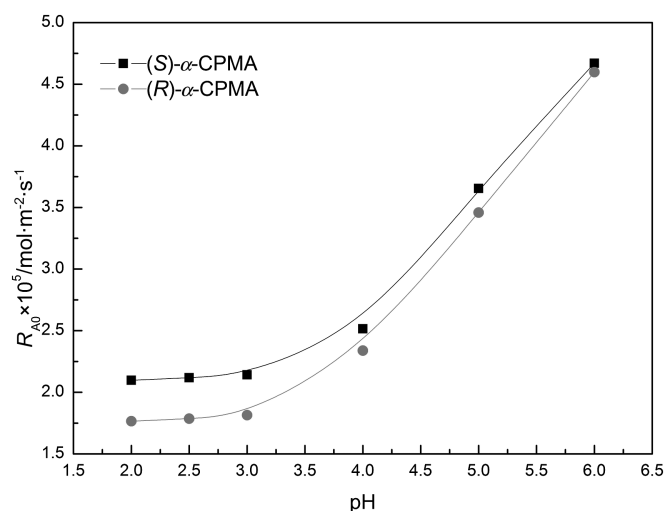


Fig. 7. Influence of pH value on the initial rate of extraction. Conditions: $[\alpha\text{-CPMA}]_0 = 5 \text{ mmol}\cdot\text{L}^{-1}$, $[\text{CD}]_0 = 0.05 \text{ mol}\cdot\text{L}^{-1}$, $A = 12.56 \text{ cm}^2$, $N = 75 \text{ r}\cdot\text{min}^{-1}$, $T = 278 \text{ K}$.

shown in Fig. 8. To determine the reaction order of α -CPMA, the initial extraction rate is plotted as a function of the initial concentration of α -CPMA in the organic phase, which is shown in Fig. 9. It is obvious that the initial extraction rate for (S)- α -CPMA and (R)- α -CPMA is linearly proportional to their initial concentration. Regression analysis of the data yielded $m = 1$ (according to Eq. (3)). Both reactions are first order with respect to (S)- α -CPMA and (R)- α -CPMA.

4.4.2. Order with respect to HE- β -CD

The effect of HE- β -CD concentration in aqueous phase on the initial extraction rates was investigated in the range of 0 to $0.10 \text{ mol}\cdot\text{L}^{-1}$ (Fig. 10). There is clearly a linear relationship between the initial extraction rate and the concentration of HE- β -CD. Second order in HE- β -CD is obtained from regression analysis of the data according to Eq. (3).

4.5. Rate constant

For a (1,2) inclusion reaction in aqueous phase, the initial rate of the extraction can be expressed as:

$$R_{R,0} = (D_{\text{aq},R} \cdot k_{m,n,R})^{1/2} \cdot C_{R,0}^* \cdot [\text{CD}]_0 \quad (7)$$

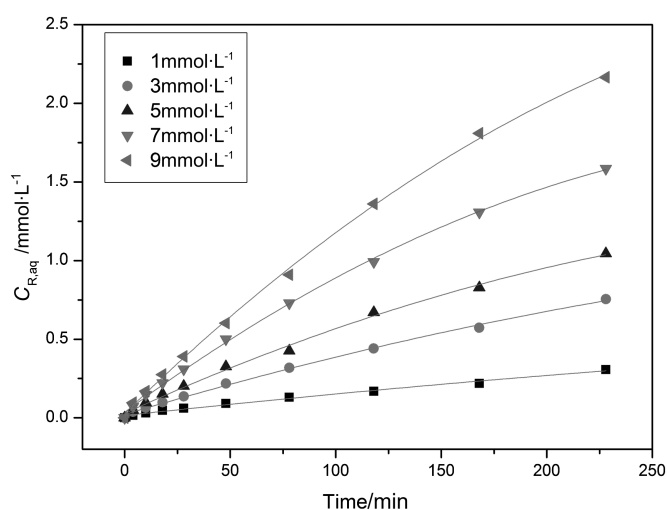


Fig. 8. Variation of the (R)- α -CPMA concentration versus time at different initial concentration of α -CPMA in the organic phase. Conditions: $[\text{CD}]_0 = 0.05 \text{ mol}\cdot\text{L}^{-1}$, $A = 12.56 \text{ cm}^2$, $N = 75 \text{ r}\cdot\text{min}^{-1}$, $\text{pH} = 2.5$, $T = 278 \text{ K}$.

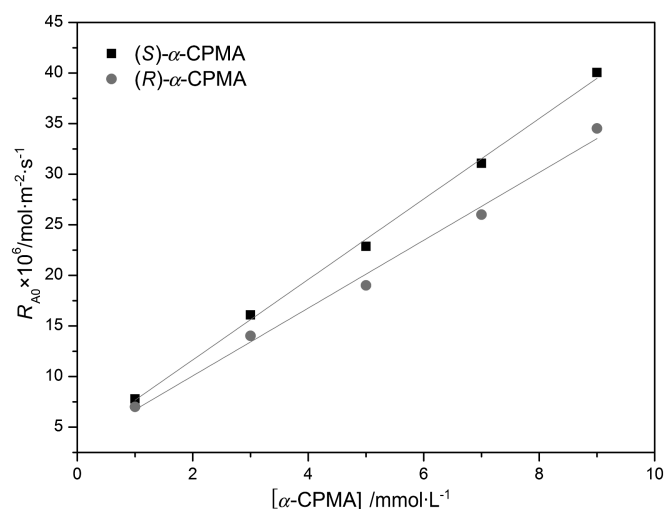


Fig. 9. Influence of α -CPMA concentration on the initial rate of extraction. Conditions: $[\text{CD}]_0 = 0.05 \text{ mol}\cdot\text{L}^{-1}$, $A = 12.56 \text{ cm}^2$, $N = 75 \text{ r}\cdot\text{min}^{-1}$, $\text{pH} = 2.5$, $T = 278 \text{ K}$.

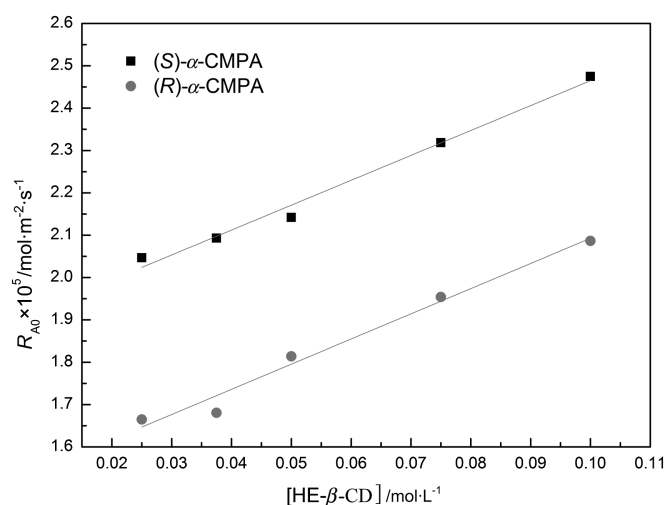


Fig. 10. Influence of HE- β -CD concentration on the initial rate of extraction. Conditions: $[\text{CPMA}]_0 = 5 \text{ mmol}\cdot\text{L}^{-1}$, $A = 12.56 \text{ cm}^2$, $N = 75 \text{ r}\cdot\text{min}^{-1}$, $\text{pH} = 2.5$, $T = 278 \text{ K}$.

$$R_{S,0} = (D_{\text{aq},S} \cdot k_{m,n,S})^{1/2} \cdot C_{S,0}^* \cdot [\text{CD}]_0 \quad (8)$$

The value of $D_{\text{aq},R}$ of $4.158 \times 10^{-10} \text{ m}^2 \cdot \text{s}^{-1}$ was estimated by Wilke–Chang equation. $D_{\text{aq},S}$ is equal to $D_{\text{aq},R}$ because of the similar physico-chemical properties. The value of rate constant $k_{m,n,S}$ and $k_{m,n,R}$ was calculated from Eqs. (7) and (8) as $2.056 \times 10^{-3} \text{ m}^6 \cdot \text{mol}^{-2} \cdot \text{s}^{-1}$ and $1.459 \times 10^{-3} \text{ m}^6 \cdot \text{mol}^{-2} \cdot \text{s}^{-1}$, respectively. The rate constant for (S)- α -CPMA is larger than that for (R)- α -CPMA, the results are consistent with the inclusion complexation equilibrium constants evaluated in this paper. Compared with the results for α -cyclohexyl-mandelic acid (α -CHMA) reported by our coworkers [21], the rate constants in this paper are one order smaller. Because the β -CD selector has a peculiar hydrophobic cave, and the hydrophobic property of α -CPMA is lower than α -CHMA, the inclusion of α -CHMA is easier than inclusion of α -CPMA, which may explain why the rate constants for α -CPMA is smaller than for α -CHMA.

For a (1,2) reaction, the Hatta number can be expressed by following equations:

$$Ha_R = \frac{\sqrt{D_{\text{aq},R} \cdot k_{m,n,R} \cdot [\text{CD}]_0^2}}{K_{L,\text{aq},R}} \quad (9)$$

$$Ha_S = \frac{\sqrt{D_{aq,S} \cdot k_{m,n,S} \cdot [CD]_0^2}}{K_{L,aq,S}} \quad (10)$$

To verify that kinetics of the reactive extraction fall into regime 3, the values of the parameter Ha were evaluated by Eqs. (9) and (10). According to results mentioned above, Ha_S and Ha_R were calculated as 30.84 and 25.97, respectively. The above results reflect the intrinsic kinetics of the extraction process. Because Ha is higher than 2 for both of the enantiomers, conditions for validation of regime 3, this reactive extraction process is accompanied by a fast reaction. Generally, a practical extraction process that is performed for a technological purpose, is usually operated under conditions where the two phases are vigorously mixed, in order to shorten the extraction time as much as possible. Therefore, the practical processes are generally reaction-controlling processes. Thus, the “fast reaction” nature made the reactive extraction of α -CPMA enantiomers by HE- β -CD very promising in industrial application.

5. Conclusions

Kinetic study on liquid–liquid reactive extraction of α -CPMA enantiomers with HE- β -CD was performed in a Lewis cell. The inclusion complexation equilibrium between HE- β -CD and α -CPMA enantiomers was studied by phase solubility method to gain an insight into the nature of extraction process. Results indicated that HE- β -CD preferentially form inclusion complex with (S)- α -CPMA. The intrinsic enantioselectivity is estimated as 1.92. The extraction is enhanced by the “fast chemical reaction” between HE- β -CD and α -CPMA enantiomers. The value of rate constant $k_{m,n,S}$ and $k_{m,n,R}$ was obtained as $2.056 \times 10^{-3} \text{ m}^6 \cdot \text{mol}^{-2} \cdot \text{s}^{-1}$ and $1.459 \times 10^{-3} \text{ m}^6 \cdot \text{mol}^{-2} \cdot \text{s}^{-1}$, respectively. The reactions are of first order dependent on α -CPMA enantiomers and second order with respect to HE- β -CD. The results obtained in this paper will be useful for the design and operation of reactive extraction in large-scale.

Nomenclature

A	the interfacial contact area taken as the area of the disc, m^2
a	specific area (area/volume), m^{-1}
C	concentration, $\text{mol} \cdot \text{m}^{-3}$
D	diffusivity, $\text{m}^2 \cdot \text{s}^{-1}$
Ha	Hatta number
$K_{L,aq}$	physical mass transfer coefficient of α -CPMA in aqueous phase
k	the rate constant of reaction
P	the physical distribution ratio
V	the volume of each phase, m^3
$[]$	concentration, $\text{mol} \cdot \text{m}^{-3}$

Subscripts and Superscripts

aq	aqueous phase
m	order of reaction with respect to α -CPMA
n	order of reaction with respect to HP- β -CD
org	organic phase
ov	over all (both phase)
0	initial value
*	the value on the phase interface

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