JOURNAL OF CHEMICAL & ENGINEERING DATA

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# Experimental and Modeling Studies on the Enantioselective Extraction of Hydrophobic Pranoprofen Enantiomers with Hydrophilic β-Cyclodextrin as Selectors

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**ABSTRACT:** The enantioselective extraction of hydrophobic pranoprofen (PRA) enantiomers by hydrophilic β-cyclodextrin (β-CD) selectors was studied in a batch system. The influence of process variables, including types of organic solvents and β-CD derivatives, the concentration of the selector, pH, and temperature, on the extraction efficiency was studied. A reactive extraction model with a homogeneous aqueous phase reaction of *R*,*S*-PRA with Me-β-CD (methyl-β-cyclodextrin) was established to describe the experimental data, and important parameters of this model were determined experimentally. The physical distribution coefficients for molecular and ionic PRA were 0.031 and 25.304, respectively. The equilibrium constants of the complexation reactions were (367 and 269) $L \cdot mol^{-1}$ for *R*- and *S*-PRA, respectively. With the experimental and modeled data, the optimum conditions were obtained at a pH of 3.5 and a Me-β-CD concentration of 0.1 $mol \cdot kg^{-1}$ with an optimum performance factor (pf) of 0.039. The model was verified experimentally with excellent results.

## INTRODUCTION

There is an urgent need for data of the enantiomeric purities of chiral species in the pharmaceutical industry, because different enantiomers often show large differences in terms of their bioavailability, distribution, metabolic, and excretion behavior.[1−3] To obtain and identify enantiopure compounds, various methods including asymmetric synthesis, biotransformation, and chiral separation have been developed. Chiral separations continue to increase in their importance because the method is relatively inexpensive, simple to carry out, and has reasonably low time demands.[4,5]

On the basis of the urgent need for efficient techniques to separate the racemates, several chiral separation techniques are developed. Large advances have been achieved in chromatography techniques, but for example, with the development of simulated moving bed (SMB) chromatography, the method is very expensive with low capacity.[6] A considerable amount of research has also been done on crystallization, which is considered to be a very useful technique for the chiral separation of acidic and basic substances.[3,7,8] For the chiral separation of a wide range of substances, chiral solvent extraction is considered to be a very promising technique, which is expected to be cheaper and easier to scale up to commercial scale and has a large application range. Many researchers have made efforts in the field of chiral solvent extraction and have significantly contributed to the development of the field.[9−22] Although ample literature is available for enantioselective extraction, only a few studies provide fundamental insights in the reaction engineering mechanism by combining experimental investigation and mathematical modeling to predict and optimize the extraction performance.[21,22]

Enantioselectivity ($\alpha$) is the most important parameter for chiral extraction. For example, for a 99 % pure product ($R/S$ = 100) about 190 theoretical stages are required for an enantioselectivity of 1.05, a number decreasing to approximately 30 when $\alpha$ increases to a value of 1.20.[10] The chiral extraction process requires an enantioselective extractant dissolved in the extract phase which reacts with the solutes of enantiomers in the feed and plays a key role in the extraction process. There are several normal chiral extractants, such as tartaric acid derivatives,[9−13] crown ethers,[14,15] cinchona alkaloids,[16,17,20,22] and so on.[18,19,21] However, there still exist some drawbacks for the current extractant: First their enantioselectivities are somewhat low, and a large number of theoretical stages are required. Second they are mainly hydrophobic species, and the available works most often deal with the enantioselective extraction toward organic phases. However, reports on the enantioselective extraction of hydrophobic species toward aqueous phase are extremely rare. As most chiral drugs are hydrophobic species, the usual chiral extraction methods have not met the separation of most chiral drugs.

Hydrophilic β-cyclodextrins (β-CDs) can form host−guest complexes with a very wide range of guest molecules. The guest molecule is held within the cavity of the host β-CD molecules when the complexes form. The hydrophobic cavity is in favor of inclusion or partial inclusion of hydrophobic molecules in aqueous solution.[23−25] Chiral recognition of β-CDs toward enantiomers is carried out by the selective complexation of the enantiomers with themselves.[26] Therefore, hydrophilic β-CDs are promising to be used as ideal hydrophilic selectors for the extraction of hydrophobic drug enantiomers from organic phase to aqueous phases. Hydrophilic β-CDs have been used for chiral separation in electrophoresis[27,28] and liquid chromatography[29] and used for the extraction of toluene, *o*-xylene from heptane, and benzyl alcohol from toluene.[30] Enantioselectivities for the extraction of some aromatic acid enantiomers have been

**Received:** June 26, 2011
**Accepted:** September 8, 2011
**Published:** September 28, 2011





dx.doi.org/10.1021/je200638z | *J. Chem. Eng. Data* 2011, 56, 3902–3909

improved greatly by the use of hydrophilic $\beta$-CDs in our recent work.[11,12]

Pranoprofen (PRA) is widely used as an anti-inflammatory drug. Although the difference of metabolic and pharmacokinetic characteristics is observed between PRA enantiomers,[31,32] PRA is usually prescribed in the racemate form. Many researchers have reported analytical methods for the separation of PRA enantiomers,[33,34] but there is no feasible method for the large-scale production of optically pure PRA enantiomers. In this paper, we deal with enantioselective extraction of PRA enantiomers to an aqueous phase of hydrophilic $\beta$-CD solution and propose the reactive extraction as the potential method for large-scale production of optically pure PRA enantiomers. The effects of process variables such as types of organic solvents and $\beta$-CD derivatives, the concentration of the selector, pH, and temperature on extraction efficiency were investigated. Process studies combining experimental investigation and mathematical modeling to predict and optimize the extraction performance of *R*,*S*-PRA with Me-$\beta$-CD have been reported.

## EXPERIMENTAL SECTION

**Materials.** Methyl-$\beta$-cyclodextrin (Me-$\beta$-CD), hydroxyethyl-$\beta$-cyclodextrin (HE-$\beta$-CD), 2-hydroxyethyl-$\beta$-cyclodextrin (2-HE-$\beta$-CD), hydroxypropyl-$\beta$-cyclodextrin (HP-$\beta$-CD), and sulfobutylether-$\beta$-cyclodextrin (SBE-$\beta$-CD) were bought from Qianhui Fine Chemical & Co., Inc. (Shandong, China). Pranoprofen (PRA, 2-(5*H*-[1]-benzopyrano[2,3*b*]-pyridin-7-yl)propionic acid, racemate) was purchased from Hezhong Technology Development Co., Ltd. (Wuhan, China), and the purity was higher than 0.995 (mass fraction). The solvent for chromatography was of high-performance liquid chromatography (HPLC) grade. All other chemicals were of analytical-reagent grade and bought from different suppliers.

**Determination of Physical Distribution Coefficients $P_0$ and $P_i$.** Experiments to determine physical distribution coefficients $P_0$ and $P_i$ of molecular and ionic PRA over the aqueous and 1,2-dichloroethane phases were carried out in a water batch at 10 °C. The organic phase was prepared by dissolving $7.96 \cdot 10^{-4}$ mol·kg$^{-1}$ PRA in 1,2-dichloroethane. The aqueous phases were 0.1 mol·kg$^{-1}$ $Na_2HPO_4/H_3PO_4$ buffer solutions with a series of pH values in the range (3.5 to 7). Equal volumes of the two phases were placed together and shaken sufficiently (5 h) before being kept in a water bath at 10 °C to reach equilibrium. The concentration of PRA in the aqueous phase was analyzed by HPLC. The concentration of PRA in organic phase was determined from a mass balance.

**Determination of Complexation Equilibrium Constants $K_R$ and $K_S$.** Solubility measurements were carried out according to the method of Higuchi and Connors.[35] Excess amounts of racemic PRA, exceeding its solubility, were added to aqueous solutions containing increasing amounts of Me-$\beta$-CD [(0, 0.005, 0.01, 0.015 0.02, 0.025, 0.03, and 0.035) mol·kg$^{-1}$]. The suspensions were shaken for 24 h in a water bath at 10 °C. After equilibration, the suspensions were filtered through 0.45 $\mu$m membrane filters, appropriately diluted with the mobile phase, and the total concentrations of PRA enantiomers were analyzed by HPLC. The apparent stability constants of the complexes are calculated from the straight lines of the phase solubility diagram.

**Extraction Experiments.** The aqueous phase was prepared by dissolving (Me-, HE-, 2-HE, HP-, or SBE-) $\beta$-CD in 0.1 mol·kg$^{-1}$ $Na_2HPO_4/H_3PO_4$ buffer solution, and the organic phase was prepared by dissolving racemic PRA in organic solvent. The extraction experiment was performed in a 10 mL flask tube. Equal volumes (each 2 mL) of the aqueous and the organic phases were placed together and shaken sufficiently (5 h) before being kept in a water bath at a fixed temperature to reach equilibrium. After phase separation, the concentrations of PRA enantiomers in the aqueous phase were analyzed by HPLC. The total amounts of *R*,*S*-enantiomer in the organic and aqueous phases after extracting were consistent with their initial amounts included in organic phase. The concentrations of *R*- and *S*-PRA in the organic phase were calculated from a mass balance.

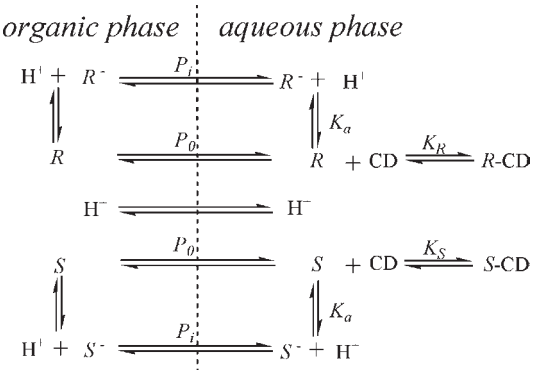


**Figure 1.** Diagram of the mechanism of reactive extraction of PRA enantiomers by Me-$\beta$-CD. R = *R*-PRA, S = *S*-PRA, CD = Me-$\beta$-CD.

**Analytical Method.** The quantification of PRA eantiomers in the aqueous phase was performed by HPLC using an Agilent LC 1200 series apparatus (Agilent Technologies Co. Ltd., USA). An UV detector operated at 230 nm was applied. The column was CHIRALCEL OJ-RH column (Daicel Chemical Industries Ltd., Japan). The mobile phase was a mixture of methanol and 0.5 mol·kg$^{-1}$ $NaClO_4/HClO_4$ buffer solution (pH = 2.0), and the mass fraction of methanol was 0.243. The flow rate was set at 30 mL·h$^{-1}$, and the column temperature was set at 28 °C.

## MECHANISM AND MODEL

**Mechanism of Reactive Extraction.** Knowledge of the reaction mechanism is very useful for optimization of a reactive extraction process. In reactive extraction systems, the reactions may take place in either the organic phase, the aqueous phase, or at the interface. In the reactive extraction of *R*- and *S*-PRA with Me-$\beta$-CD as chiral selector, the extractant, Me-$\beta$-CD, is highly hydrophilic, which excludes the possibility that the reaction takes place in the organic phase. Depending on the solubility of the solutes of *R*- and *S*-PRA in the aqueous phase, the complexation reactions will either be limited to the interface or may take place in the aqueous phase. It is found that the solutes of *R*- and *S*-PRA distribute over the organic and aqueous phases. Therefore, we have applied the homogeneous aqueous phase reaction mechanism here. Further in this paper we will validate this mechanism for the system under study.

The homogeneous aqueous phase reaction mechanism is depicted in Figure 1, and a three-step mechanism is assumed. The first step is a physical process of mass transfer of PRA enantiomers. In this step, molecular PRA enantiomers transfer from the organic phase to the aqueous phase. In the second step, two diastereomeric complexes between Me-$\beta$-CD and (*R*,*S*)-PRA enantiomers form due to such molecular interactions as


dx.doi.org/10.1021/je200638z |*J. Chem. Eng. Data* 2011, 56, 3902–3909

dipole−dipole, hydrophobic, van de Waals, electrostatic, and hydrogen bonding interaction, and two acid−base dissociation equilibria exist in the aqueous phase. In the third step, the ionic solutes of *R*- and *S*-PRA in the aqueous phase partition into the organic phase.

**Model Equations.** The reaction extraction system depicted in Figure 1 may be modeled by a series of coupled equilibrium relations and mass balance equations.

The physical partition coefficient of molecular *R*- and *S*-PRA, $P_0$, can be written as follows:

$$P_0 = \frac{[\mathrm{R}]_w}{[\mathrm{R}]_o} = \frac{[\mathrm{S}]_w}{[\mathrm{S}]_o} \tag{1}$$

where $[\mathrm{R}]_o$ and $[\mathrm{S}]_o$ are the concentrations of the free *R*- and *S*-PRA in the organic phase at equilibrium, respectively; $[\mathrm{R}]_w$ and $[\mathrm{S}]_w$ are the concentrations of the free *R*- and *S*-PRA in the aqueous phase at equilibrium, respectively.

The physical partition coefficient of ionic *R*- and *S*-PRA, $P_i$, can be calculated by the following equation:

$$P_i = \frac{[\mathrm{S}^-]_w}{[\mathrm{S}^-]_o} = \frac{[\mathrm{R}^-]_w}{[\mathrm{R}^-]_o} \tag{2}$$

where $[\mathrm{R}^-]_o$ and $[\mathrm{S}^-]_o$ are the concentrations of the ionic *R*- and *S*-PRA in the organic phase at equilibrium, respectively; $[\mathrm{R}^-]_w$ and $[\mathrm{S}^-]_w$ are the concentrations of the ionic *R*- and *S*-PRA in the aqueous phase at equilibrium, respectively.

The dissociation constant of *R*- and *S*-PRA is

$$K_a = \frac{[\mathrm{S}^-]_w[\mathrm{H}^+]}{[\mathrm{S}]_w} = \frac{[\mathrm{R}^-]_w[\mathrm{H}^+]}{[\mathrm{R}]_w} \tag{3}$$

The complexation equilibrium constants of Me-$\beta$-CD with PRA enantiomoers in aqueous phase can be written as follows:

$$K_S = \frac{[S\text{-CD}]_w}{[\mathrm{S}]_w[\mathrm{CD}]_w} \tag{4}$$

$$K_R = \frac{[R\text{-CD}]_w}{[\mathrm{R}]_w[\mathrm{CD}]_w} \tag{5}$$

where $[S\text{-CD}]_w$ and $[R\text{-CD}]_w$ represent the concentrations of complexes of *R*- and *S*-PRA with Me-$\beta$-CD in the aqueous phase at equilibrium, respectively; $[\mathrm{CD}]_w$ represents the concentration of free Me-$\beta$-CD in the aqueous phase at equilibrium.

Due to $V_w = V_o$, the following equations represent mass balances for *R*- and *S*-PRA over the organic and aqueous phases:

$$C_R = [\mathrm{R}]_o + [\mathrm{R}^-]_o + [\mathrm{R}]_w + [\mathrm{R}^-]_w + [R\text{-CD}]_w \tag{6}$$

$$C_S = [\mathrm{S}]_o + [\mathrm{S}^-]_o + [\mathrm{S}]_w + [\mathrm{S}^-]_w + [S\text{-CD}]_w \tag{7}$$

where $C_R$ and $C_S$ are the initial concentrations of *R*- and *S*-PRA in the organic phase, respectively.

The mass balance for Me-$\beta$-CD over the organic and aqueous phases can be written as:

$$C_{CD} = [\mathrm{CD}]_w + [R\text{-CD}]_w + [S\text{-CD}]_w \tag{8}$$

where $C_{CD}$ represents the initial concentration of Me-$\beta$-CD added to the aqueous phase.

By combining the equilibrium equations above, the distribution ratios and enantioselectivity for PRA enantiomers are calculated based on the mechanism as a complex function of a series of important equilibrium constants and process variables as follows:

$$k_R = \frac{P_0P_i[\mathrm{H}^+]\left(1 + K_a/[\mathrm{H}^+] + K_R[\mathrm{CD}]\right)}{P_i[\mathrm{H}^+] + P_0K_a} \tag{9}$$

$$k_S = \frac{P_0P_i[\mathrm{H}^+]\left(1 + K_a/[\mathrm{H}^+] + K_S[\mathrm{CD}]\right)}{P_i[\mathrm{H}^+] + P_0K_a} \tag{10}$$

$$\alpha = \frac{1 + K_a/[\mathrm{H}^+] + K_S[\mathrm{CD}]}{1 + K_a/[\mathrm{H}^+] + K_R[\mathrm{CD}]} \tag{11}$$

where $k_R$ and $k_S$ represent the distribution ratios of *R*- and *S*-PRA, respectively; $\alpha$ represents enantioselectivity; $[\mathrm{H}^+]$ is obtained by determining the pH value, and $[\mathrm{CD}]$ can be calculated from the following equation:

$$K_RK_S[\mathrm{CD}]^3 + (AK_R + AK_S + K_SK_RC_R + K_SK_RC_SK_RK_SC_{CD})[\mathrm{CD}]^2 + (A^2 + AK_RC_R + AK_SC_SAK_SC_{CD}AK_RC_{CD})[\mathrm{CD}]A^2C_{CD} = 0 \tag{12}$$

where $A$ is a variable defined as:

$$A = 1 + \frac{1}{P_0} + \frac{[\mathrm{H}^+]}{K_a} + \frac{[\mathrm{H}^+]}{P_iK_a} \tag{13}$$

The extraction efficiency of the reactive extraction system is further evaluated by enantiomeric excess in the aqueous phases (ee), fractions of the solutes ($\phi_R$ and $\phi_S$) extracted into the aqueous phase, and the performance factor (pf). They can be expressed in terms of distribution ratios as the following equations:

$$\mathrm{ee} = \frac{\dfrac{C_R}{1 + \dfrac{1}{k_R}} - \dfrac{C_S}{1 + \dfrac{1}{k_S}}}{\dfrac{C_S}{1 + \dfrac{1}{k_S}} + \dfrac{C_R}{1 + \dfrac{1}{k_R}}} \tag{14}$$

$$\phi_S = \frac{C_{S,w}}{C_S} = \frac{k_S}{k_S + 1} \tag{15}$$

$$\phi_R = \frac{C_{R,w}}{C_R} = \frac{k_R}{k_R + 1} \tag{16}$$

$$\mathrm{pf}_R = \phi_R\mathrm{ee} \tag{17}$$

## RESULTS AND DISCUSSION

**Physical Distribution Coefficient $P_0$ and $P_i$.** Physical distribution coefficients for molecular PRA ($P_0$) and ionic PRA ($P_i$) were determined through a series of physical extraction experiments. The apparent partition coefficients, $P_{app}$, were determined at different pH values. As described in Figure 1, both the molecular and the ionic PRA distribute between the organic and

**Table 1. Influence of Organic Solvent Type**[a]

| organic solvent | $k_R$ | $k_S$ | $\alpha$ |
|---|---|---|---|
| dichloromethane | 0.50 | 0.47 | 1.06 |
| 1,2-dichloroethane | 1.16 | 0.87 | 1.33 |
| cyclohexane | 4.81 | 4.27 | 1.13 |
| *n*-heptane | 11.63 | 8.91 | 1.30 |
| *n*-octanol | 0.19 | 0.18 | 1.06 |
| *n*-heptanol | 0.09 | 0.08 | 1.13 |

[a] Aqueous phase: $C_{Me\text{-}\beta\text{-}CD}$ = 0.1 mol·kg$^{-1}$, pH = 2.5. Organic phase: PRA in different organic solvents with the same molarity of 0.001 mol·L$^{-1}$ (i.e., $7.54\cdot10^{-4}$ mol·kg$^{-1}$ in dichloromethane, $7.96\cdot10^{-4}$ mol·kg$^{-1}$ in 1,2-dichloroethane, $1.28\cdot10^{-3}$ mol·kg$^{-1}$ in cyclohexane, $1.46\cdot10^{-3}$ mol·kg$^{-1}$ in *n*-heptane, $1.21\cdot10^{-3}$ mol·kg$^{-1}$ in *n*-octanol, and $1.22\cdot10^{-3}$ mol·kg$^{-1}$ in *n*-heptanol); temperature: 10 °C.

the aqueous phases. Then, $P_{app}$ is given by

$$P_{app} = \frac{[PRA]_w + [PRA^-]_w}{[PRA]_o + [PRA^-]_o} \quad (18)$$

where $[PRA]_w$ and $[PRA^-]_w$ represent the concentrations of the molecular PRA enantioners and ionic PRA enantioners in the aqueous phase, respectively; $[PRA]_o$ and $[PRA^-]_o$ represent the concentrations of the molecular PRA enantiomers and ionic PRA enantiomers in the organic phase, respectively.

Therefore, $P_{app}$ can be derived as

$$P_{app}\left(\frac{1}{P_0} + \frac{1}{P_i}\cdot\frac{K_a}{[H^+]}\right) = 1 + \frac{K_a}{[H^+]} \quad (19)$$

eq 19 can be transformed into

$$\frac{1}{P_{app}}\left(\frac{[H^+]}{K_a} + 1\right) = \frac{1}{P_0}\cdot\frac{[H^+]}{K_a} + \frac{1}{P_i} \quad (20)$$

The plot of $(1/P_{app})([H^+]/K_a + 1)$ versus $[H^+]/K_a$ yielded a straight line. The $P_0$ and $P_i$ calculated from the slope and intercept are 0.031 and 25.304, respectively.

**Complexation Constants $K_R$ and $K_S$.** Phase distribution diagrams for *R*- and *S*-PRA in the aqueous phase describe the concentrations of *R*- and *S*-PRA increase with increasing the concentration of Me-$\beta$-CD at 10 °C. The diagrams for *R*- and *S*-PRA both show a linear trend. Consequently, the diagrams can be classified as $A_L$ type, which indicates the formation of a 1:1 inclusion complex between *R*- (or *S*-) PRA and Me-$\beta$-CD. The slope for *R*-PRA is larger than that for *S*-PRA, indicating Me-$\beta$-CD preferentially recognizing *R*-PRA. According to the method described in the literature,[35] $K_R$ and $K_S$ calculated from the slope and the intercept of the straight lines of the phase distribution diagrams are 367 and 269, respectively. The intrinsic selectivity $\alpha_{int}$ is estimated by the following equation as 1.36, which is the theoretical maximum of enantioselectivity:

$$\alpha_{int} = \frac{K_R}{K_S} \quad (21)$$

**Influence of Organic Solvent.** To identify a suitable solvent for chiral reactive extraction, preliminary screening experiments were carried out in various extraction systems with 0.1 mol·kg$^{-1}$ Me-$\beta$-CD in aqueous phases and PRA enantiomers in different organic solvents at 10 °C. It is observed from Table 1 that distribution ratios and enantioselectivities are clearly influenced by the organic solvents. With alkanes as organic solvents, high distribution ratios are obtained with moderate enantioselectivities. When 1,2-dichloroethane is used, the highest enantioselectivity of 1.33 is achieved with suitable distribution ratios. Therefore, 1,2-dichloroethane is selected as the optimal organic solvent.

**Table 2. Influence of Hydrophilic Extractant Type**[a]

| extractant | $k_R$ | $k_S$ | $\alpha$ |
|---|---|---|---|
| Me-$\beta$-CD | 1.16 | 0.87 | 1.33 |
| HE-$\beta$-CD | 1.08 | 1.01 | 1.07 |
| 2-HE-$\beta$-CD | 0.95 | 0.83 | 1.14 |
| HP-$\beta$-CD | 0.75 | 0.67 | 1.12 |
| SBE-$\beta$-CD | 2.07 | 1.88 | 1.10 |

[a] Aqueous phase: $C_{Me\text{-}\beta\text{-}CD}$ = 0.1 mol·kg$^{-1}$, $C_{HE\text{-}\beta\text{-}CD}$ = 0.1 mol·kg$^{-1}$, $C_{2\text{-}HE\text{-}\beta\text{-}CD}$ = 0.1 mol·kg$^{-1}$, $C_{HP\text{-}\beta\text{-}CD}$ = 0.1 mol·kg$^{-1}$, $C_{SBE\text{-}\beta\text{-}CD}$ = 0.1 mol·kg$^{-1}$, pH = 2.5. Organic phase: $C_{PRA} = 7.96\cdot10^{-4}$ mol·kg$^{-1}$ in 1,2-dichloroethane; temperature: 10 °C.

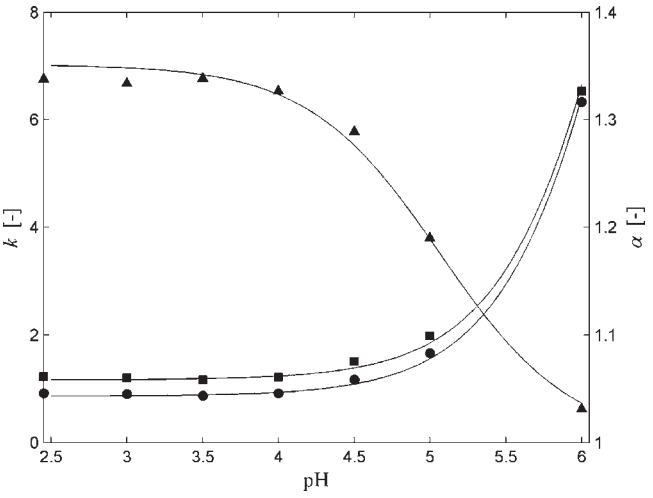


**Figure 2.** Influence of pH on $k$ and $\alpha$. Solid lines: model predictions. Symbols, experimental data: ■ represents $k_R$; ● represents $k_S$; ▲ represents $\alpha$. $C_{PRA} = 7.96\cdot10^{-4}$ mol·kg$^{-1}$ in 1,2-dichloroethane, $C_{Me\text{-}\beta\text{-}CD}$ = 0.1 mol·kg$^{-1}$, temperature 10 °C.

**Influence of $\beta$-CD Derivatives.** Extraction experiments with different $\beta$-CD derivatives (Me-$\beta$-CD, HE-$\beta$-CD, 2-HE-$\beta$-CD, HP-$\beta$-CD, and SBE-$\beta$-CD) in aqueous phases and PRA enantiomers in the 1,2-dichloroethane organic phase were carried out subsequently to identify a suitable $\beta$-CD derivative for chiral reactive extraction. Distribution ratios and enantioselectivities for PRA enantiomers are shown in Table 2, from which the clear influence of the type of $\beta$-CD derivatives on the extraction efficiency is observed. The highest distribution ratios are achieved with SBE-$\beta$-CD as a chiral selector, but the enantioselectivity is very low. When Me-$\beta$-CD is used as a chiral selector, the highest enantioselectivity is obtained, and the distribution ratios are relatively high. Considering that enantioselectivity is the most important parameter for chiral extraction, Me-$\beta$-CD was chosen as the suitable chiral selector in aqueous phase for the extraction of PRA enantiomers.

**Influence of pH.** PRA exists in different states of neutral molecule and ion in aqueous solution (Figure 1). Me-$\beta$-CD can form two inclusion complexes with molecular PRA enantiomers

but not with ionic PRA enantiomers. Therefore, the distribution behavior of PRA enantiomers in a liquid−liquid reactive extraction system can be influenced by the pH value of aqueous phase. To better understand the effect of pH on the distribution behavior, PRA enantiomers were partitioned in 1,2-dichloroethane/water two-phase systems over a range of pH values (in Figure 2). Furthermore, distribution ratios and enantioselectivity for PRA enantiomers in the 1,2-dichloroethane/water reactive extraction systems can be predicted as a function of pH by the two-phase multiple chemical equilibrium model when combined with measured physical distribution coefficients, dissociation constants, and equilibrium formation constants. The comparison of the experimental values with the model predictions of distribution ratio and enantioselectivity is shown in Figure 2 to verify the accuracy of the model predictions.

As shown in Figure 2, $k_R$ and $k_S$ keep nearly unchanged at pH ≤ 4.5 and then increase rapidly with rising pH. But an opposite tendency is observed for enantioselectivity (in Figure 2). This can be due to the fact that at low pH value (pH ≤ 4.5) most extraction is through enantioselective complexation while at a higher pH value (pH > 4.5) nonselective partition of anion increases considerably. At pH ≤ 4.5, PRA molecules hardly dissociate, and the amount of molecule (HA) in aqueous phase is much bigger than that of anion ($A^-$). With the further increase of pH (pH > 4.5), more and more molecular PRA enantiomers are dissociated into ionic PRA enantiomers in aqueous phase, which leads to a partition of more molecular PRA enantiomers from organic phase to aqueous phase. Therefore, it should be kept at low pH (≤ 3.5) to carry out the extraction process.

There is an unexpected phenomenon which is noted at pH ≤ 3.5. The operational selectivity is always lower than the model prediction in this range, and a slight increase of enantioselectivity can be observed which is in opposition to what the model predicting. The unexpected deviation can be explained. There is a nitrogen atom in the chemical structure of PRA which will be protonated at low pH. PRA is partly partitioned and nonselectively distributed into the aqueous phase at pH ≤ 3.5, which will decrease the enantioselectivity. With the increase of pH value, the amount of protonated PRA decreases, and enantioselectivity increases. The decrease of $k_R$ and $k_S$ with a rising pH value at pH ≤ 3.5 also supports the explanation above.

Although the unexpected phenomena occurs, the model still can be used to predict the experimental results because the protonation ability of PRA is weak and the slight deviation can be foreseen. It can be concluded from Figure 2 that the model predictions are in good agreement with the experiment, as shown by a mean relative error of 3.96 % for $k_R$, 4.01 % for $k_S$, and 0.59 % for $\alpha$.

**Influence of Me-$\beta$-CD Concentration.** The influence of Me-$\beta$-CD concentration on distribution behavior of PRA enantiomers was investigated by varying the Me-$\beta$-CD concentration in aqueous phase from 0 mol·kg$^{-1}$ to 0.2 mol·kg$^{-1}$. The influence of Me-$\beta$-CD concentration can also be predicted by the two-phase multiple chemical equilibrium model, which is presented as solid lines in Figure 3. By comparing the experimental data and modeled data, it can be concluded that the model predicts the experimental results accurately, as shown by a mean relative error of 3.87 % for $k_R$, 3.93 % for $k_S$, and 0.30 % for $\alpha$.

It can be found from Figure 3 that $k_R$ and $k_S$ are linearly proportional to the concentration of Me-$\beta$-CD and the operational enantioselectivity also increases rapidly with the increase of Me-$\beta$-CD concentration before the concentration is 0.05 mol·kg$^{-1}$ but

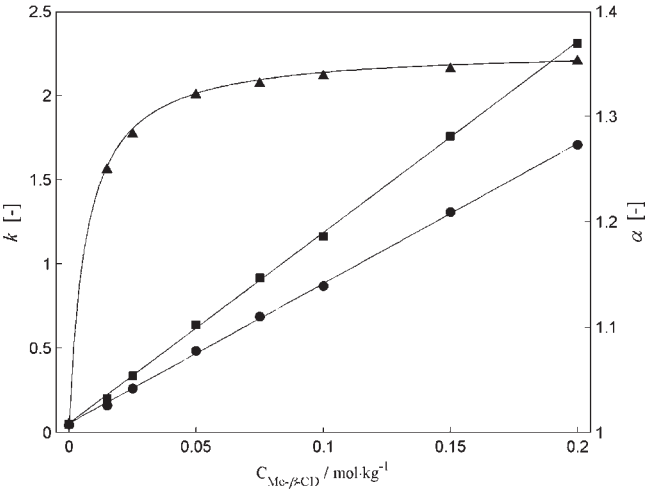


**Figure 3.** Influence of Me-$\beta$-CD concentration on $k$ and $\alpha$. Solid lines: model predictions. Symbols, experimental data: ■ represents $k_R$; ● represents $k_S$; ▲ represents $\alpha$. $C_{PRA}$ = 7.96·10$^{-4}$ mol·kg$^{-1}$ in 1,2-dichloroethane, pH = 3.5, temperature 10 °C.

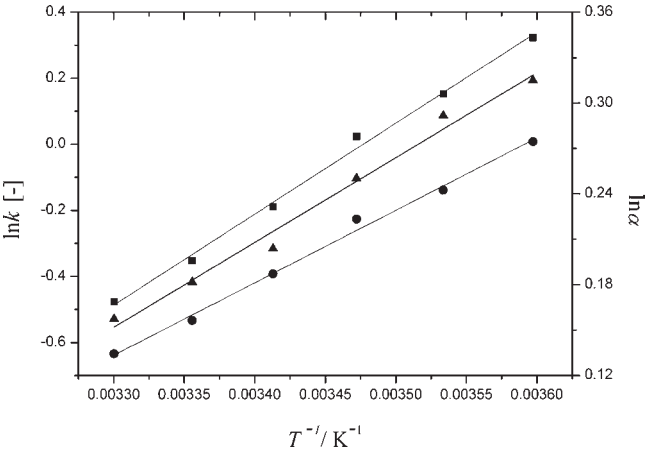


**Figure 4.** Plots of ln $k_R$ (■), ln $k_S$ (●), and ln $a$ (▲) versus 1/$T$. Symbols: experimental data. Lines: line fits, $R^2$ = 0.9946 for ln $k_R$, $R^2$ = 0.9929 for ln $k_S$, and $R^2$ = 0.9840 for ln $a$. $C_{PRA}$ = 7.96·10$^{-4}$ mol·kg$^{-1}$ in 1,2-dichloroethane, pH = 3.5, $C_{Me\text{-}\beta\text{-}CD}$ = 0.1 mol·kg$^{-1}$.

then increases slightly. The reason may be that, with the increase of Me-$\beta$-CD concentration, more diastereomeric complexes are formed in aqueous phase and the distribution ratio consequently increases. Meanwhile Me-$\beta$-CD can recognize PRA enantiomers, and a relatively higher concentration will enhance the recognition ability, which leads to the increase of enantioselectivity.

**Influence of Temperature.** Figure 4 shows the influence of temperature on the distribution ratios and enantioselectivity. It can be seen from Figure 4 that the distribution ratios and enantioselectivity all decrease with the increase of temperature. Rising temperature will decrease distribution ratios and enantioselectivity, which can be explained by the fact that the selector−enantiomer interaction weakens with rising temperature and the discrimination ability of Me-$\beta$-CD for PRA enantiomers weakens as well. In addition, 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.[36]

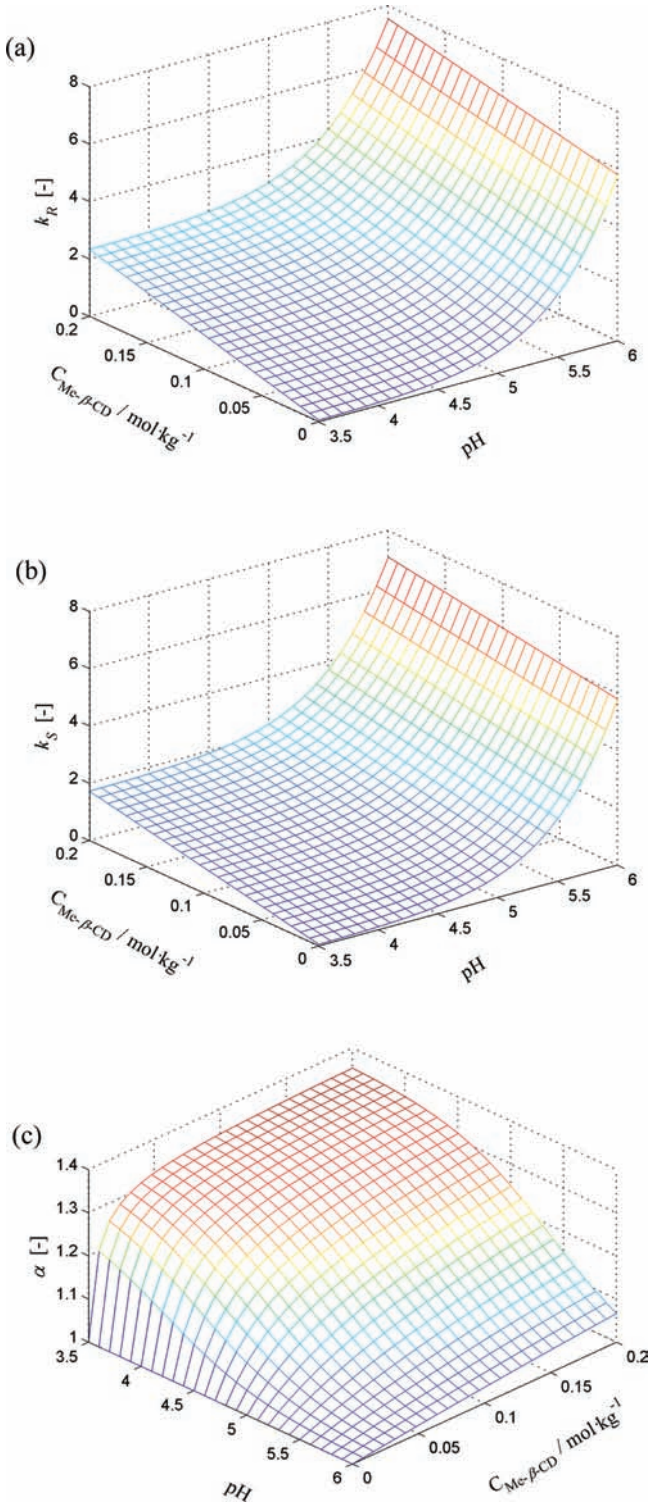


**Figure 5.** Calculated $k_R$ (a), $k_S$ (b), and $a$ (c) for PRA enantiomers as a function of pH and Me-$\beta$-CD concentration. $C_{PRA} = 7.96 \cdot 10^{-4}$ mol·kg$^{-1}$ in 1,2-dichloroethane, temperature 10 °C.

Therefore, it is better to perform the extraction process at relatively low temperatures.

**Model Predictions in the Extraction System.** The good agreement between the modeled and the experimental data indicates the reactive extraction model established in this paper is applicable to predict enantiomer partitioning over a range of experimental conditions. Therefore, we utilized the model to explore the influence of various operating conditions on extraction efficiency in a single stage.

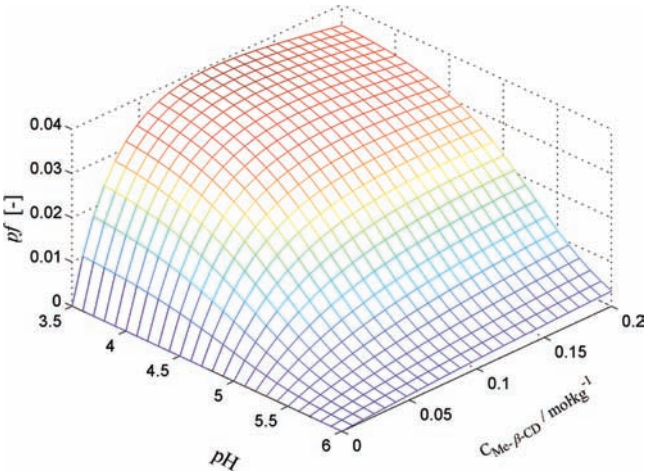


**Figure 6.** Calculated $pf_R$ as a function of pH and Me-$\beta$-CD concentration. $C_{PRA} = 7.96 \cdot 10^{-4}$ mol·kg$^{-1}$ in 1,2-dichloroethane, temperature 10 °C.

Figure 5a, b, and c show the distribution ratios and enantioselctivity for PRA enantiomers as a function of pH and Me-$\beta$-CD concentration, respectively. It can be observed from Figure 5a and b that $k_R$ and $k_S$ follow a similar tendency with the change of pH and Me-$\beta$-CD concentration. The increase of pH and increase of Me-$\beta$-CD concentration can lead to the increase of distribution ratio for the two enantiomers. As shown in Figure 5c, high enantioselctivity will be obtained at conditions where pH is low and Me-$\beta$-CD concentration is high.

Enantiomeric excess (ee) for PRA enantiomers in aqueous phase as a function of pH and Me-$\beta$-CD concentration was calculated. The ee is strongly influenced by pH and Me-$\beta$-CD concentration. The decrease of pH can always lead to an increase of ee, but the change of ee with Me-$\beta$-CD concentration is complicated. The ee for PRA enantiomers increases with the increase of Me-$\beta$-CD concentration and then reaches a maximum. While a further increase of Me-$\beta$-CD concentration after the maximum will lead to a decrease of ee for PRA enantiomers. Therefore, the increase of Me-$\beta$-CD concentration can lead to an increase of enantioselctivity but not always lead to an increase of ee value.

It is difficult to use Figure 5c to identify optimal solution conditions for enantiomer resolution because of the opposing trends of the ee and enantioselectivity. Here, we introduce the performance factor, pf, to facilitate optimization of reactive extraction systems. The pf is defined as the product of the ee in the aqueous phase and the fraction of enantiomer extracted into the aqueous phase. A high pf indicates conditions where the given enantiomer can be purified to high purity with maximum yield.

Figure 6 shows the calculated $pf_R$ (pf for $R$-enantiomer) as a function of pH and Me-$\beta$-CD concentration. It is observed from Figure 6 that the $pf_R$ is strongly influenced by pH and Me-$\beta$-CD concentration. The decrease of pH will help to increase $pf_R$. When Me-$\beta$-CD concentration is low, the increase of Me-$\beta$-CD concentration will help to increase $pf_R$ but when Me-$\beta$-CD concentration is higher than 0.1 mol·kg$^{-1}$, the further increase of Me-$\beta$-CD concentration will lead to a decrease of $pf_R$. Thus the optimal conditions for reactive extraction of PRA enantiomers will be accomplished for pH of 3.5 and Me-$\beta$-CD concentration of 0.1 mol·kg$^{-1}$ at 10 °C.


dx.doi.org/10.1021/je200638z |J. Chem. Eng. Data 2011, 56, 3902–3909

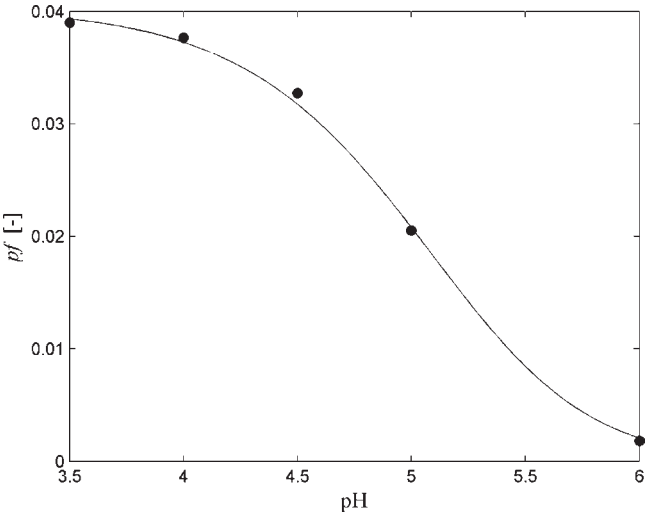


**Figure 7.** $pf_R$ as a function of pH. Solid lines: model predictions. Symbols: experimental data. $C_{PRA}$ = 7.96·10$^{-4}$ mol·kg$^{-1}$ in 1,2-dichloroethane, $C_{Me\text{-}\beta\text{-}CD}$ = 0.1 mol·kg$^{-1}$, temperature 10 °C.

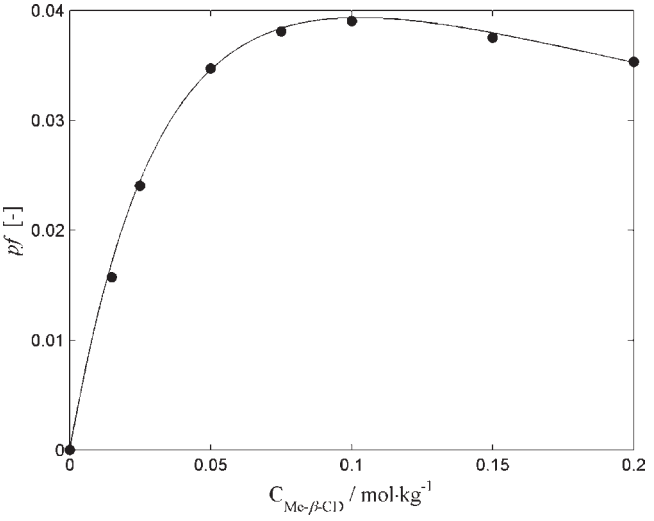


**Figure 8.** $pf_R$ as a function of Me-$\beta$-CD concentration. Solid lines: model predictions. Symbols: experimental data. $C_{PRA}$ = 7.96·10$^{-4}$ mol·kg$^{-1}$ in 1,2-dichloroethane, pH = 3.5, temperature 10 °C.

Experimental $pf_R$ were measured to support the model predictions at solution conditions explored in Figure 6. The experimental values and predictions are plotted in Figures 7 and 8 as a function of pH and Me-$\beta$-CD concentration, respectively. It is shown from Figures 7 and 8 that the model predicts experimental results accurately, as shown by a mean relative error of 3.92 % for Figure 7 and 1.93 % for Figure 8. It is observed from Figure 7 that the $pf_R$ decrease with the increase of pH. It is also observed from Figure 8 that the $pf_R$ reach a maximum at Me-$\beta$-CD concentration of about 0.1 mol·kg$^{-1}$. Therefore, these results validate the multiple-chemical equilibrium model and its application for extraction system optimization.

## CONCLUSIONS

Hydrophobic PRA enantiomers were enantioselectively extracted by hydrophilic selector $\beta$-CD derivatives. Experimental results show that the efficiency of extraction is strongly influenced by the process variables such as types of organic solvents and $\beta$-CD derivatives, concentration of the selector, pH, and temperature. 1,2-Dichloroethane is selected as the most suitable solvent and Me-$\beta$-CD as the best hydrophilic selector for chiral separation of PRA enantiomers.

The enantioselective extraction of *R,S*-PRA with Me-$\beta$-CD was modeled by a homogeneous aqueous phase reaction model which involved physical distribution of molecular and ionic PRA, dissociation of PRA, and complexation between Me-$\beta$-CD and PRA enantiomers. The experimental data were described by the model, and excellent agreement between the model predictions and experimental data was observed with the mean relative error never higher than 5 %. The performance of the extraction process was evaluated using the distribution ratio, enantioselectivity, ee, and pf to obtain the optimum extraction conditions. The best conditions involving the use of 0.1 mol·kg$^{-1}$ Me-$\beta$-CD and a pH value of 3.5 at 10 °C was obtained by the model and experiment. The optimal operational enantioselectivty of 1.33 is close to the theoretical maximum of 1.36, and the pf is up to 0.039. The presented data indicate that the model is a powerful tool for calculating enantiomer distribution ratios and extraction efficiencies in two-phase chiral extraction systems. If the necessary parameters are provided, the model can extend its use for other enantiomers. Full separation of racemic PRA can be achieved by multistage extraction.

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### Funding Sources

This work was supported by the National Natural Science Foundation of China (No. 20976041), the Program for New Century Excellent Talents in University, Hunan Provincial Natural Science Foundation of China (No. 10JJ1004), and the Aid Program for Science and Technology Innovative Research Team in Higher Educational Instituions of Hunan Province.

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