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ORIGINAL ARTICLE

Equilibrium studies on reactive extraction of naproxen enantiomers using hydrophilic β-cyclodetrin derivatives extractants

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Abstract A simple and low-cost method using liquid–liquid extraction coupled with complexation reactive technique has been developed for enantioselective separation of naproxen enantiomers. Three kinds of modified β-cyclodextrins including methyl-β-cyclodextrin (Me-β-CD), hydroxyethyl-β-cyclodextrin (HE-β-CD) and hydroxypropyl-β-cyclodextrin (HP-β-CD), were selected as hydrophilic chiral selectors for extraction naproxen from organic phase to aqueous phase. A systematic study of the factors affecting chiral separation performance were investigated. The experiment results obtained show that, HP-β-CD, HE-β-CD and Me-β-CD has stronger recognition abilities for *S*-naproxen than those for *R*-naproxen. Among the β-CD derivatives studied, HP-β-CD has the strongest ability for chiral recognition and separation. Excellent enantioselectivity (*a*) of 1.59 is obtained under the optimal conditions of pH of 2.5 and temperature of 5 °C.

Keywords Chiral separation · Reactive extraction · β-Cyclodextrin derivatives · Naproxen enantiomers

List of symbols

A^-	Anion of naproxen
HA	Neutral molecule of naproxen
HE-β-CD	Hydroxyethyl-β-cyclodextrin
HP-β-CD	Hydroxypropyl-β-cyclodextrin
K_a	Dissociation constant
Me-β-CD	Methyl-β-cyclodextrin
NAP	Naproxen enantiomers
k	Distribution coefficient, dimensionless
a	Enantioselectivity, dimensionless
β-CD	β-Cyclodextrin

Subscripts

O,R	*R*-Enantiomer in organic phase
O,S	*S*-Enantiomer in organic phase
R	*R*-Enantiomer
S	*S*-Enantiomer
W,R	*R*-Enantiomer in aqueous phase
W,S	*S*-Enantiomer in aqueous phase

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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 [2–7]. To obtain optically pure products, it is, in most of the cases, necessary to separate racemic mixtures. The most common technique used for obtaining enantiopure compounds on a commercial scale is diastereomeric crystallization [8]. However, this technique is generally considered as inflexible and thus its development for each new racemic mixture is quite time consuming. This process is also relatively slow, difficult to control and requires complicated handling of solids/slurries [9]. In order to avoid these problems caused by diastereomeric crystallization, asymmetric synthesis and kinetic resolution are usually considered as promising alternatives [10]. While these processes require the development of an appropriate path for each product, leading to considerable costs and long development periods.

Analytical resolution methods, although available for practically all the racemates, are usually not adequate for large-scale production [8]. Membrane-based approaches will most certainly become very important for continuous operation, but at the moment still suffer from being generally less enantioselective [11–13]. The principle of ligand-exchange has been shown to be a powerful tool for the chiral separation of various compounds [14]. Currently, the chiral ligand-exchange concept has been successfully transferred to liquid–liquid extraction technology and obtained high enantioselectivities holding advantages over chiral ligand-exchange chromatography for large-scale applications [15]. The application of ligand-exchange in liquid–liquid reactive extraction technology was reported [16]. Enantioselectivities for some aromatic acid enantiomers have been improved greatly by biphasic recognition chiral extraction [2, 6, 17]. Liquid–liquid reactive extraction requires an enantioselective selectors dissolved in the extract phase which reacts with the solute in the feed. This process is expected to be cheaper and easier to scale up to commercial scale. Liquid–liquid reactive extraction may be attractive in this respect.

As well known the chiral selectors play the most important role in the separation efficiency for liquid–liquid reactive extraction. There are several normal chiral selectors used for this purpose, such as tartaric acid derivatives [18, 19], crown ethers [20], cholesteryl L-glutamate [21], and so on [22]. Unfortunately, the low enantioselectivities of these selectors limit theirs wider application. So looking for new chiral selectors with high enantioselectivity will speed up the application of liquid–liquid reactive extraction, and realize large-scale production with low energy cost. Over the last few years, with the development of supramolecular chemistry, much attention has been drawn to CD derivatives. Despite the original chiral recognition ability shown by native cyclodextrins, many cyclodextrin derivatives are prepared for chiral selectors, which give more interesting enantioseparation ability. The application of cyclodextrin to the separation of enantiomers is a natural extension of their inclusion properties [23]. Their chiral discrimination ability results from the free difference in the complexes. The interaction of each enantiomer occurs through inclusion inside the CD annuli, along with dipole–dipole, hydrophobic, Van der Waals, electrostatic, and hydrogen bonding interaction, etc. [24], which cooperatively contribute to the molecular recognition and separation process. At present, there is no report on separation of enantiomers by reactive extraction with cyclodextrin derivatives. We are trying to improve the separation factors for enantiomers by utilizing the separation abilities of hydrophilic cyclodextrin derivatives in aqueous phase, and realize the separation of hydrophobic drug enantiomers from organic phase to aqueous phase.

Naproxen (NAP), 6-methoxy-amethyl-2-naphthaleneacetic acid is a kind of an important group of medicines called non-steroidal anti-inflammatory drug with analgesic and anti-pyretic properties, which is widely used in the treatment of rheumatic and other inflammatory and for the relief of mild to moderate pain [25]. The chemical structure of NAP is shown in Fig. 1. It has one stereogenic center which gives rise to two optical isomers in which pharmacological activity resides in the (*S*)-enantiomer, while the (*R*)-enantiomer causes some unwanted side effects [6]. Therefore, separation of racemic NAP is necessary for assuring good quality in pharmaceutical production of naproxen and in other naproxen-related scientific research work as well.

Chiral separation of naproxen enantiomers by capillary electrophoresis has been demonstrated with various cyclodextrins [26–32]. There are many reports on separation of naproxen enantiomers by liquid chromatography using chiral stationary phases [33–40]. Naproxen enantiomers were separated by high performance liquid chromatography with β-cyclodextrin derivatives as mobile phase additives [41, 42]. Yang et al. [43] reported separation of naproxen enantiomers by supercritical/subcritical fluid chromatography. S-(+)-Naproxen enantiomer was resolved from the racemates by crystallization using N-octyl-D-(−)-glucamine as the chiral host [44]. Naproxen enantiomers were resolved from the racemate methyl ester by enzymatic kinetic method [45]. Sakaki applied a lipase-immobilized membrane reactor for the optical resolution of racemic naproxen [46]. Such chiral separation technologies accelerate researches about naproxen enantiomers, but there still exist some defects with respect to a large-scale production.

This paper presents a liquid–liquid reactive extraction technology with chiral selectors of hydrophilic β-cyclodextrin (β-CD) derivatives dissolved in aqueous phase which can form diastereomeric complexes with NAP enantiomers dissolved in organic phase to achieve the purpose of chiral separation. The main objective of this study was to exploit the potentiality for the enhancement of enantioselectivity in chiral separation by liquid–liquid reactive extraction and a determination of optimal conditions of enantioseparation by this method. The factors affecting the extraction efficiency were investigated, namely types of solvent and β-CD derivatives, chiral selector concentration, temperature as well as pH value of

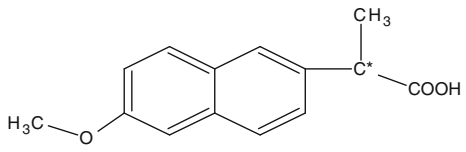

Fig. 1 Chemical structure of naproxen

aqueous phase. This work has been carried out for the preparative separation of aromatic acid enantiomers.

Experimental

Materials

The aqueous phase was prepared by dissolving β-cyclodextrin derivative (HP-β-CD, HE-β-CD or Me-β-CD) as the chiral selector in 0.1 mol/L NaH_2PO_4/H_3PO_4 buffer solution. Three kinds of hydrophilic chiral selectors selected, namely, HP-β-CD, HE-β-CD and Me-β-CD, were purchased from Shandong Xinda Fine Chemical Co., Ltd. The organic phase was a solution of naproxen enantiomers (NAP) in proper organic solvent and NAP enantiomers were brought from Xianju Chemical & Co. Inc. (Zhejiang, China). Solvent for chromatography was of HPLC grade. Analytical reagent grade chemicals were used. All other chemicals were bought from different suppliers.

Analytical method

The quantification of NAP enantiomers in the aqueous phase was performed by HLPC. An Agilent 1100 series liquid chromatograph (Agilent Technologies Corporation, USA) equipped with a UV detector was employed. A lichrospher C_{18} column (250 mm × 4.6 mm i.d., 5 μm) (Hanbon Science & Technology Co. Ltd., China) was utilized. The analytical method was described in detail in the literature [47]. The mobile phase was a mixture of 0.5% triethylamine buffer solution (pH = 3.5):ethanol (85:15, v/v) containing 25 mmol/L HP-β-CD at a flow rate of 1.0 mL/min. The column temperature was maintained at fixed temperature and the detection was monitored at a wavelength of 254 nm. The injection volume was 20 μL. The pH of the aqueous phases was measured with a pH electrode and a pH meter (Orion, model 720A, USA).

Extraction methods

All liquid–liquid reactive extraction experiments were carried out in a 10 mL plastic-stoppered tube placed in a thermostat bath to enable temperature control. In each experiment, both 2.0 mL of the aqueous and organic phases were mixed together and shaken sufficiently (5 h) before being kept in a water bath at a fixed temperature to reach equilibrium. After phase separation, a sample of 50 μL was taken from the aqueous phase, the concentrations of NAP enantiomers in the aqueous phase were measured by HPLC. The total amount of each enantiomer in the organic and aqueous phases after extracting was consistent with their initial amount included in organic phase. Each experiment was duplicated under identical conditions and the standard deviation is in the range of 2%. Since the change in volume is very small, it can be seen as negligible. The concentrations of NAP enantiomers in organic phase were calculated from the mass balance by subtractive method.

A schematic representation of the liquid–liquid reactive extraction system studied is given in Fig. 2. From Fig. 2, there exist two dissociation reactions and two inclusion reactions for NAP enantiomers in aqueous phase.

The distribution coefficients of *S*-NAP and *R*-NAP enantiomer can be calculated by the following formulas, respectively

$$k_S = C_{W,S}/C_{O,S} \tag{1}$$

$$k_R = C_{W,R}/C_{O,R} \tag{2}$$

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

Enantioselectivity (separation factor) is defined as

$$a = k_S/k_R \tag{3}$$

$$-\Delta(\Delta G) = \mathrm{RT}\ln\alpha \tag{4}$$

According to the possible mechanism for chiral reactive extraction of NAP enantiomers, kind of organic solvent, type and concentration of β-CD derivatives, pH value of aqueous phase, temperature and concentration of enantiomers may affect the extraction efficiency.

Results and discussion

Influence of organic solvents

The inclusion reactions between naproxen enantiomers and HP-β-CD are known to have 1:1 stoichiometry [48] (Fig. 3). The chiral extraction is carried out by the

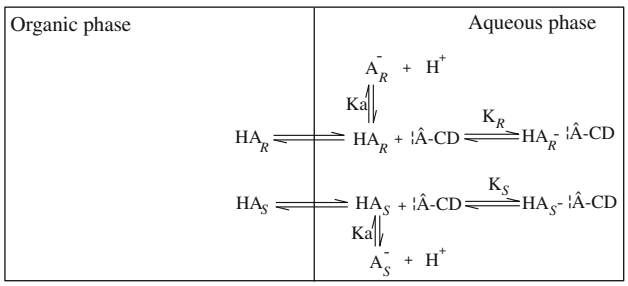

Fig. 2 Diagram of distribution of enantiomers in a chiral reactive extraction system

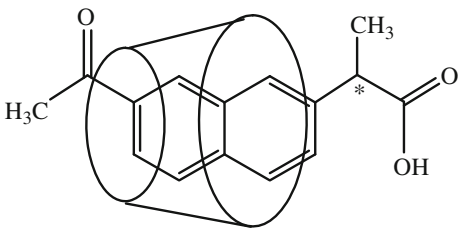

Fig. 3 Proposed inclusion complex between naproxen and -β-CD

formation of two inclusion complexes between naproxen enantiomers and HP-β-CD. The difference in free energy between the two complexes (–$\Delta(\Delta G)$) is the driving forces for separation of enantiomers.

The influence of organic solvents on distribution behavior was investigated in various liquid–liquid reactive extraction systems containing 0.1 mol/L HP-β-CD in aqueous phase and NAP enantiomers in different organic solvents (Table 1). With *n*-heptane as solvent, big distribution coefficients were obtained, although low enantioselectivity was found. While *n*-octanol was used as solvent, HP-β-CD showed the enantioselectivities on NAP enantiomers but with very small distribution coefficients. Enantioselectivities and distribution coefficients for NAP enantiomers were relatively higher with 1,2-dichloroethane and methylene chloride as solvents. Highest enantioselectivity was achieved with 1,2-dichloroethane as solvent. It is not found from our experiment that hydroxypropyl-β-cyclodextrin complexes with the partitioning solvent of 1,2-dichloroethane. This is the reason that the sizes of the guests of 1,2-dichloroethane does not fit into the cavity of β-CD derivatives, and the interaction between 1,2-dichloroethane and HP-β-CD is very weak. Cyclodextrins show negligible solubilities in organic liquids and can be modified to achieve high solubility in water. The hydrophilic cyclodextrins used in this paper do not partition into organic solvents, and their complexes do not partition into organic solvents. The cyclodextrins and their complexes only partition in aqueous phase in the different systems. Based on this screening, 1,2-dichloroethane was selected as an alternative solvent for extraction of NAP enantiomers.

Table 1 Influence of organic solvent

Organic solvent	k_S	k_R	a	$-\Delta(\Delta G)$ (kJ)
1,2-Dichloroethane	0.37	0.23	1.59	1.07
n-Octanol	0.07	0.04	1.56	1.03
n-Heptane	0.33	0.33	1.01	0.02
Methylene chloride	0.29	0.20	1.45	0.86

Aqueous phase: [HP-β-CD] = 0.1 mol/L, pH = 2.5; organic phase: [NAP] = 1.0 mmol/L, temperature 5 °C

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 intermolecular forces. 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 sizes of the guests of NAP enantiomers fit into the cavity of β-CD derivatives, so β-CD derivatives can form complexes with NAP enantiomers. But to what extent a complex is formed is dependent on the polarity of β-CD derivatives. Therefore, three types of β-CD derivatives may show different enantioselectivities on NAP enantiomers.

Enantioselectivities and distribution coefficients for NAP enantiomers were investigated in several liquid–liquid reactive extraction systems containing different β-CD derivatives (Me-β-CD or HE-β-CD or HP-β-CD) in aqueous phase (Table 2). From Table 2, it was clearly seen that the enantioselectivities of the three β-CD derivatives were always above 1, which indicated they had stronger recognition ability for *S*-NAP than that for *R*-NAP. Among the three β-CD derivatives, HP-β-CD had the highest enantioselectivity. It was also found that the three β-CD derivatives of Me-β-CD, HE-β-CD and HP-β-CD have stronger inclusion abilities for S-naproxen than for R-naproxen, among which, HP-β-CD has the strongest inclusion ability (Me-β-CD < HE-β-CD < HP-β-CD).

Influence of pH value

Each NAP enantiomers (*HA*) has one carboxylic group and aromatic group. Two dissociation equilibria exist in aqueous solutions. Therefore, there exists influence of pH on distribution behavior of NAP enantiomers in a liquid–liquid reactive extraction system. The relationship between the relative concentrations of all HA species and the pH values of the solution at a given temperature was determined by Matlab (Fig. 4). δ_1 and δ_0 represented the percentage distributions of two NAP species of neutral molecule (HA) and anion (A^-), respectively. From Fig. 4,

Table 2 Chiral recognition ability of different β-CD derivatives

Extractant	k_S	k_R	α	$-\Delta(\Delta G)$ (kJ)
HE-β-CD	0.27	0.20	1.36	0.71
Me-β-CD	0.21	0.18	1.16	0.34
HP-β-CD	0.37	0.23	1.59	1.07

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; organic phase: [NAP] = 1.0 mmol/L, temperature 5 °C

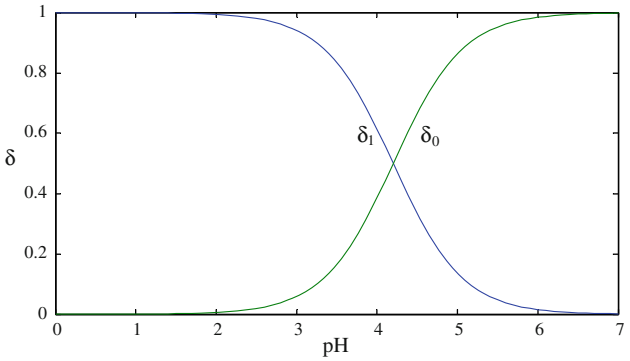

Fig. 4 Percentage distribution of naproxen species as a function of pH

it was found that neutral molecule (HA) was the main species of NAP at pH $\leq$ 3.0, NAP enantiomers exist in the two forms of neutral molecule and anion round the isoelectric points (pH = 4.2), and the main form of NAP is anion (A^-) at pH > 6. It can be predicted that high enantioselectivities for HA enantiomers will be obtained at low pH ($\leq$2.5), because only the neutral molecule of NAP (HA) can be discriminated by HP-β-CD.

To better understand the effect of pH on the distribution behavior, distribution coefficients and enantioselectivity were investigated in the reactive extraction systems containing 0.1 mol/L HP-β-CD in 0.1 mol/L NaH_2PO_4/H_3PO_4 buffer solution at different pH values (Fig. 5). It was shown from Fig. 5 that the influence of pH on distribution behavior was notable. This new organization of the results, as a function of pH, allowed us to observe more clearly that all the distribution coefficients of NAP enantiomers increased when increasing the pH of the aqueous phase, while the enantioselectivities for NAP enantiomers followed opposite tendency.

The possible reasons for these may be that the neutral molecule of NAP enantiomers can interact with HP-β-CD in the aqueous phase to produce diastereomeric complexes, but the ionic forms of NAP enantiomers can not. Ionic NAP (A^-) increased with the rise of the pH, while molecular NAP (HA) decreased with the rise of the pH value. With the increase of the pH value, more molecular NAP (HA) in organic phase were transferred to aqueous phase and changed into ionic NAP (A^-), which lead to the results that the non-selective physical partitioning of NAP and HP-β-CD complexation decrease. As a result, distribution coefficients increased with the rise of the pH, but enantioselectivities obviously decreased with pH increasing. Therefore, it should be kept at comparatively low pH ($\leq$3.0) to perform the extraction process.

Influence of HP-β-CD concentration

β-CD derivatives and NAP enantiomers can form two diastereomeric complexes with different stabilities due to molecular interactions, which not only enhance the solubility of the enantiomers in buffer solution, but also improves the enantioselectivities for NAP enantiomers. Therefore, the concentration of HP-β-CD has a great influence on distribution coefficients and enantioselectivities.

Figure 6 showed the influence of HP-β-CD concentration on distribution behavior of NAP enantiomers in the reactive extraction systems by varying the concentration from 0 to 150 mmol/L at a fixed pH value of 2.5 and temperature of 5 °C. It was found from Fig. 6 that distribution coefficients and enantioselectivities all increased with the rise of the concentration of HP-β-CD, which can be explained by a larger amount of complexes formed in aqueous phase.

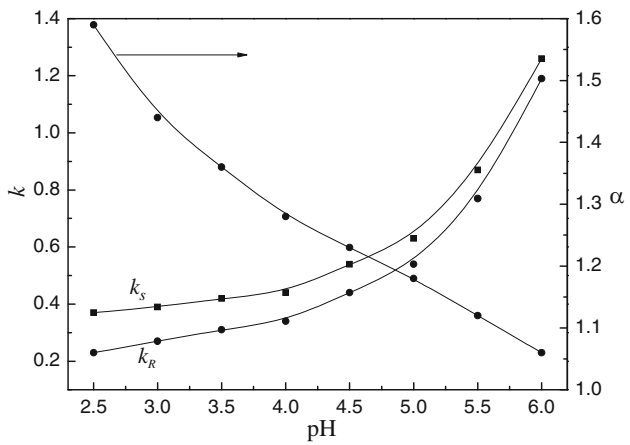

Fig. 5 Influence of pH on k and α. [HP-β-CD] = 0.1 mol/L, [NAP] = 1.0 mmol/L, temperature 5 °C

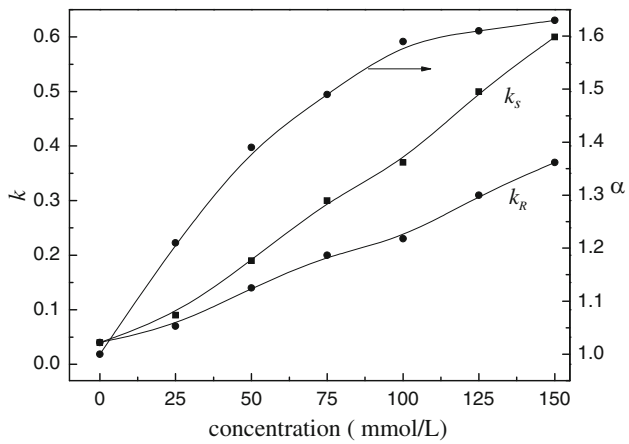

Fig. 6 Influence of concentration of HP-β-CD on k and α.[NAP] = 1.0 mmol/L, pH = 2.5, and temperature 5 °C

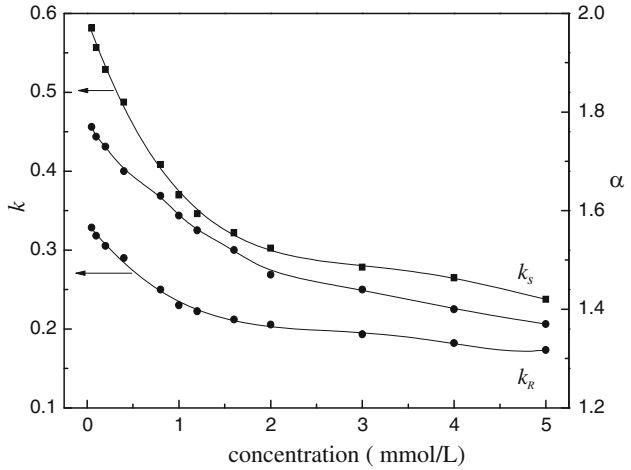

Fig. 7 Effect of initial concentration of NAP on k and α.[HP-β-CD] = 0.1 mol/L, pH = 2.5, and temperature 5 °C

Influence of NAP enantiomers concentration

The influence of NAP enantiomers concentration on extraction efficiency was studied in Fig. 7. It was shown from Fig. 7 that all distribution coefficients and enantioselectivities decreased with the increasing of the initial concentration of NAP enantiomers, which indicated a better enantioseparation efficiency at low initial concentrations.

This could be due to the fact that the non-selective physical partitioning of NAP in organic phase was enhanced upon on the increase of the initial concentration of NAP enantiomers, but the percent of NAP enantiomers which formed complexes with HP-β-CD decreased with rise of the initial concentration of NAP enantiomers. It was concluded that at low concentrations most extraction was through enantioselective complexation and at higher concentrations more non-selective partitioning occurred in organic phase.

Keurentjes et al. [18] reported enantioselective separation of several racemic mixtures at initial concentrations of 1.0 mg/g with tartaric acid derivatives as the selectors, the enantioselectivities obtained were all less than 1.2. In this reactive extraction with HP-β-CD as chiral selector at high initial concentrations of NAP enantiomers (1.2 mg/g), the enantioselectivity was still relatively high for chiral extraction.

Influence of temperature

As for the influence of operating temperature on the distribution behavior, six temperatures (5, 10, 15, 20, 25 and 30 °C) were investigated with racemic NAP as the solute in the organic phase (Fig. 8). It was observed from Fig. 8 that higher temperature led to a decrease in distribution

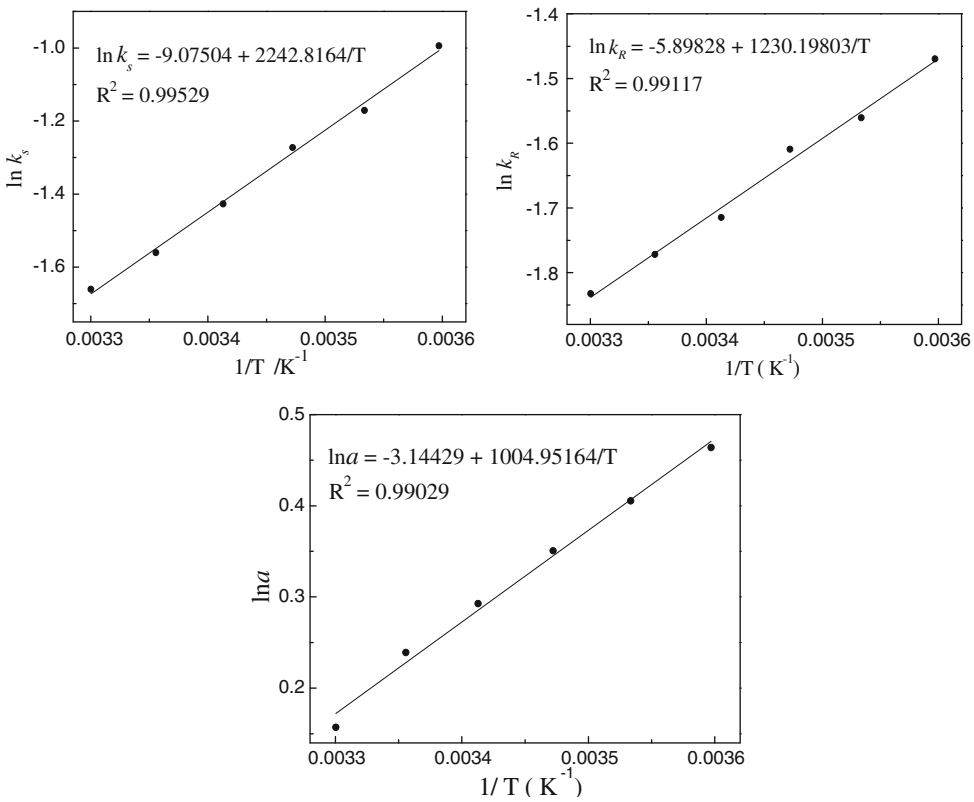

Fig. 8 Influence of temperature on the enantioseparation of NAP. [HP-β-CD] = 0.1 mol/L, [NAP] = 1.0 mmol/L, pH = 2.5

coefficients and enantioselectivities. At higher temperatures, the molecular motion is more intense, causing the inclusion complexes to dissociate. The fact that the decreasing distribution coefficients was obtained indicated that the non-selective physical partitioning of NAP in organic phase increased with temperature and HP-β-CD complexation decreased with temperature. A decrease in enantioselectivities was explained that the selector-enantiomers interaction weakened with temperature and the discrimination ability of the selectors for NAP enantiomers weakened as well.

The variations of ln k and ln α versus 1/T was shown in Fig. 8. The results was described as fitting very well with the Van't Hoff model, indicating that the complexes did not change in conformation and that enantioselective interactions remained unchanged in the temperature range studied.

Conclusions

In this paper, liquid–liquid reactive extraction has been proposed and evaluated as an alternative industrial separation technique for chiral separation of NAP enantiomers. It was found that hydrophilic hydroxypropyl-β-cyclodextrin has sufficient potential to be used for selective extracting NAP enantiomers from 1,2-dichloroethane to aqueous phase. The efficiency of extraction depends on process parameters given above, and the optimum extraction conditions are achieved to improve the enantioselectivities. A better enantioseparation efficiency can be obtained at low initial concentration. Higher temperature leads to a decrease in distribution coefficients and enantioselectivities. A good enantioseparation efficiency with a maximum enantioselectivity of 1.59 is obtained at pH of 2.5 and temperature of 5 °C. Full separation of NAP enantiomers can be carried out by multistage extraction. The recovery of target product will be carried out by back-extraction of aqueous phase with n-octanol, and the aqueous phase can be reused. It can be envisioned that liquid–liquid reactive extraction will allow enantioselective separations of various aromatic acid enantiomers at a large-scale.

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