

Enantioselective extraction of fenvaleric acid enantiomers by two-phase (W/O) recognition chiral extraction

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Abstract To establish an extraction method for fenvaleric acid (FA) enantiomers using L-iso-butyl-L-tartaric esters and hydroxypropyl- β -cyclodextrin (HP- β -CD) as chiral selector, the distribution of FA enantiomers was examined in methanol aqueous solution containing HP- β -CD and 1,2-dichloroethane organic solution containing L-iso-butyl-L-tartaric esters. The influences of the concentration of L-iso-butyl-L-tartaric esters and HP- β -CD, organic diluent, pH, extraction temperature and the concentration of methanol aqueous solution on the partition coefficient (k) and separation factor (α) of FA were investigated. The experiment results showed that the complex formed by L-iso-butyl-L-tartaric esters with S-enantiomer is stabler than that with R-enantiomer. With the increase of the concentration of L-iso-butyl-L-tartaric ester, k and α increased; With the increase of the concentration of HP- β -CD, k increased firstly, and then decreased, but α increased all the while, k was the highest when the concentration of HP- β -CD was 4 mmol L⁻¹. 1,2-dichloroethane organic diluent was better than the others. With the increase of pH, k and α decreased; with further increasing concentration of methanol aqueous solution, k and α decreased, k and α were the highest when the concentration

of methanol aqueous solution was 10%. The extraction temperature had a great influence on k and α , too.

Keywords Chiral extraction · L-iso-butyl-L-tartaric esters · HP- β -CD · Fenvaleric acid enantiomers

Introduction

At present, the gain of optically pure medicine, pesticide, perfume, essence, food additives, and new materials have been a research focus in corresponding fields [1–4]. Chiral pesticide used in the market are produced and used mostly in the form of racemate, but different enantiomers have big differences active action for target organism, as we are known, so if we produce optically pure and high active pesticide, it will improve pesticide effect, save cost, and reduce the pollution in the environment [5–8]. And it is an important significance for us to gain optically pure compound.

Hydroxypropyl- β -cyclodextrin (HP- β -CD) and L-iso-butyl-L-tartaric esters as the chiral electors are a research focus in the resolution of chiral enantiomers [9, 10]. If we use HP- β -CD and L-iso-butyl-L-tartaric esters as chiral selector simultaneously, comparing with L-iso-butyl-L-tartaric esters as chiral selectors individually, we expect to get the better extraction efficiency.

Fenvaleric acid (FA), 3-methyl-2-(4-chlorophenyl) butyrate, is an important intermediate for synthesis of chrysanthemum ester. The stereostructure of fenvaleric acid can be seen in Fig. 1, which is enantiomers, and R-fenvaleric acid has high active action for target organism [11]. In this paper, the extraction and distribution of FA was studied, using L-iso-butyl-L-tartaric esters and HP- β -CD as chiral selectors, the influences of the concentration of chiral selectors, organic diluent, pH and the concentration of methanol aqueous

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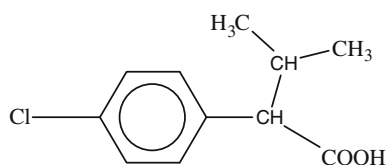


Fig. 1 Stereostructure of FA

solution on the partition coefficient (k) and separation factor (α) of FA were investigated.

Experimental

Apparatus and chemicals

HPLC were taken on Agilent 1200, which have Photodiode Array Detector chiral column (150 × 4.6 mm ID, Daicel, made in Japan). Fenvaleric acid is purchased in Nanjin, All chemicals reagents used are of analytical pure grade.

Chromatographic conditions

Chromatographic conditions was referred to Ref. [12]: mobile phases was acetonitrile, water (volume ratio: 90:10), which contained 3% acetate, and controlled the pH = 6.0 using ammonia. Analysis was accomplished at a constant flow rate of 0.65 mL min⁻¹ with the detection wavelength at 230 nm, and column temperature at 25 °C. Chromatogram of fenvaleric acid enantiomers were showed as Fig. 2.

Partition experiments

A certain concentration of fenvaleric acid enantiomers was prepared in methanol aqueous solution dissolving the extractant of HP- β -CD, and the pH was adjusted with Na₂HPO₄-H₃PO₄ buffer solution. An organic solution was prepared by dissolving the extractant L-iso-butyl-L-tartaric

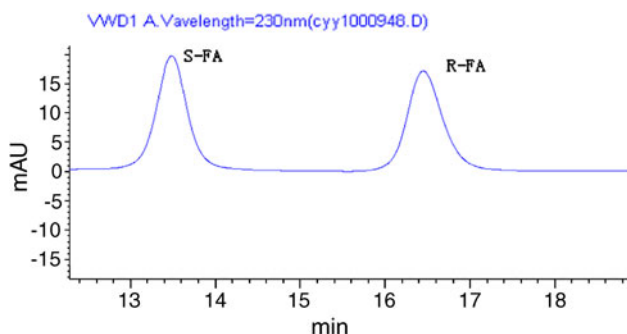


Fig. 2 Chromatogram of fenvaleric acid enantiomers on CHIRALPAK QN-AX column

esters in organic diluents. Equal volume (5 mL) solutions were placed in a centrifugal tube and stirred for 0.5 h at room temperature. After phase separation, the concentration of R- and S-enantiomer in methanol aqueous solution was determined by HPLC, then the concentration in organic diluents calculated by $C_O = C - C_W$, where C is the concentration in the methanol aqueous solution before extraction, and C_W , C_O is the concentration in the methanol aqueous solution and organic diluents after extraction, and the change of the volume was ignored. The partition coefficients (k_R and k_S) can be expressed as $k_R = C_{RO}/C_{RW}$ and $k_S = C_{SO}/C_{SW}$, where C_{RO} , C_{SO} is the concentration of R- and S-enantiomer in organic diluents and C_{RW} , C_{SW} is the concentration of R- and S-enantiomer in the methanol aqueous solution. The separation factor α is the ratio of partition coefficients of k_S to k_R [13].

Results and discussion

Effect of different organic diluents on extraction

The extraction performance of different organic diluents for fenvaleric acid enantiomers on k and α was listed in Table 1, which other conditions kept no change. Organic diluents such as halogenated hydrocarbon, alkane, alcohol, ester were investigated. And the results indicates that extraction and separation performance is the best if using 1,2-dichloroethane as organic diluents alkane and ester have the best extraction performance, but the separation performance is very bad, so it is no good choice.

Effect of concentration of L-iso-butyl-L-tartaric esters on k and α

The influence of concentration of L-iso-butyl-L-tartaric esters on k and α was investigated. It is found from Fig. 3 that the partition coefficients k and separation factor α increase with the increase of concentration of L-iso-butyl-L-

Table 1 Effect of different organic diluent on extraction

Organic diluent	k_R	k_S	α
1,2-Dichloroethane	2.0848	3.0428	1.4595
<i>n</i> -Heptane	1.0448	1.1344	1.0458
Chloroform	3.3675	4.1326	1.2272
<i>n</i> -Hexyl alcohol	4.0325	4.7844	1.1865
Ethyl acetate	15.3044	16.4625	1.0757

Extraction condition: 0.1 g L⁻¹ fenvaleric acid enantiomers was prepared in 20% methanol aqueous solution containing 2 mmol L⁻¹ HP- β -CD at pH = 4, the organic solution was prepared by dissolving 0.3 mol L⁻¹ concentration of L-iso-butyl-L-tartaric esters in different organic diluent

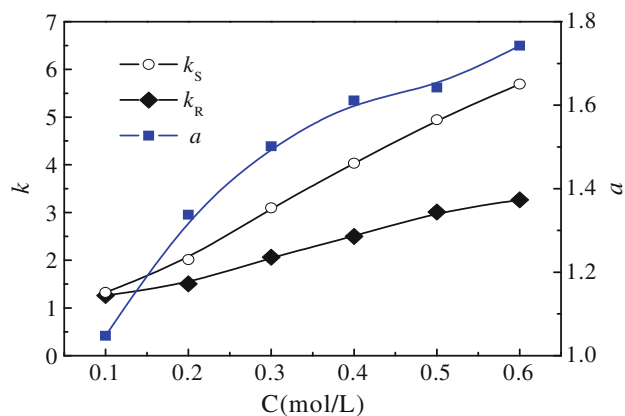


Fig. 3 Effect of concentration of L-iso-butyl-L-tartaric esters on extraction. Extraction condition: 0.1 g L⁻¹ fenvaleric acid enantiomers was prepared in 20% methanol aqueous solution containing 2 mmol L⁻¹ HP- β -CD at pH = 4, the organic solution was prepared by dissolving different concentration of L-iso-butyl-L-tartaric esters in 1,2-dichloroethane

tartaric esters, and k_S is always bigger than k_R in the range of experimental concentration. It can be explained that L-iso-butyl-L-tartaric esters can form diastereomeric complexes with S- and R-fenvaleric acid enantiomers in the process of extraction, but L-iso-butyl-L-tartaric esters forms a more stable complex with S-enantiomer than R-enantiomer.

Effect of concentration of HP- β -CD on k and α

Hydroxypropyl- β -cyclodextrin (HP- β -CD) has special chemical structure, good water solubility, which can form inclusion compounds with fenvaleric acid enantiomers, but are different for R- and S- enantiomers in hydrogen bonding, the inclusion effect, hydrophobic interaction, Van der Waals interactions and so on [14]. The effect of concentration of HP- β -CD on the partition coefficient k and separation factor α was investigated. It is found from Fig. 4 that the partition coefficients k increase with the increase of concentration of HP- β -CD, when concentration of HP- β -CD reach to 4 mmol L⁻¹, k reaches the maximum. With the further increasing of the HP- β -CD, k begins to decrease, this may be related to diastereomeric complexes with fenvaleric acid enantiomers in the process of extraction, but separation factor α increase with the increase of concentration of HP- β -CD. And the separation factor α is 1.2, when only using 0.3 mol L⁻¹ L-iso-butyl-L-tartaric esters as chiral selectors, but the separation factor α is up to 1.8, when using the same concentration L-iso-butyl-L-tartaric esters and HP- β -CD as chiral selectors, so it can be seen that biphasic chiral extraction is better than single chiral extraction, and the mechanism is under way.

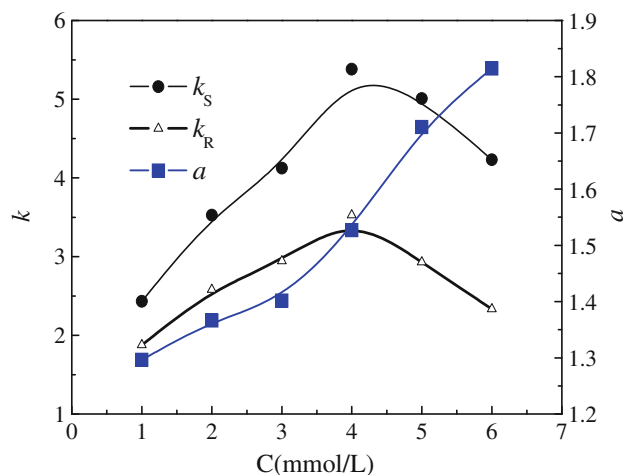


Fig. 4 Effect of HP- β -CD concentration on extraction. Extraction condition: 0.1 g L⁻¹ fenvaleric acid enantiomers was prepared in 20% methanol aqueous solution containing different concentration of HP- β -CD at pH = 4, the organic solution was prepared by dissolving 0.3 mol L⁻¹ L-iso-butyl-L-tartaric esters in 1,2-dichloroethane

Effect of pH of aqueous phase on k and α

Fenvaleric acid have a carboxy group, which can be seen in Fig. 1, so it is necessary to investigate the effect of pH on k and α . It is found from Fig. 5 that k and α decrease with the increase of pH. This may be because the fenvaleric acid in ionic state increase, decrease in molecularity, with the increase of pH. The difference of the partition coefficient of fenvaleric acid in two phase indicated that the selectivity between chiral selectors and enantiomers are different.

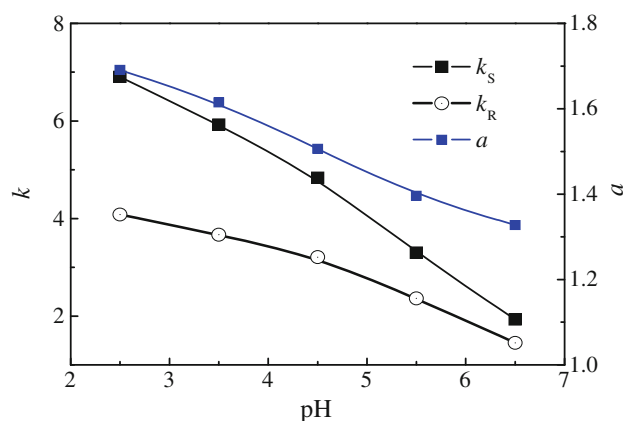


Fig. 5 Effect of pH of aqueous phase on extraction. Extraction condition: 0.1 g L⁻¹ fenvaleric acid enantiomers was prepared in 20% methanol aqueous solution containing 2 mmol L⁻¹ HP- β -CD in the range of pH = 2.50–6.50, the organic solution was prepared by dissolving 0.3 mol L⁻¹ L-iso-butyl-L-tartaric esters in 1,2-dichloroethane

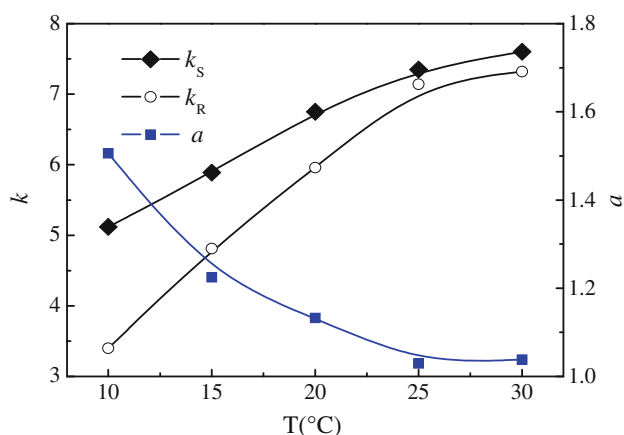


Fig. 6 Effect of temperature on extraction. Extraction condition: 0.1 g L^{-1} fenvaleric acid enantiomers was prepared in 20% methanol aqueous solution containing 2 mmol L^{-1} HP- β -CD in the range of $\text{pH} = 4.0$, the organic solution was prepared by dissolving 0.3 mol L^{-1} L-iso-butyl-L-tartaric esters in 1,2-dichloroethane

Effect of extraction temperature on k and α

The temperature on the separation of fenvaleric acid enantiomers was investigated. It is found from Fig. 6 that the partition coefficient increases with the increase of temperature, but the separation factor decrease, because the solubility of R- and S-enantiomers increase with the increase of temperature, but the interactions such as hydrogen bonding, the inclusion effect, hydrophobic interaction, Van der Waals interactions and so on between chiral selectors and R- and S-enantiomers are different, and decrease with the increase of temperature.

Effect of concentration of methanol on k and α

The solubility of fenvaleric acid enantiomers in aqueous is poor, but it has good solubility in the mixture of methanol aqueous solution. So it is necessary to investigate the effect of concentration of methanol on extraction. It is found from Fig. 7 that in certain concentration of methanol aqueous solution, the concentration of methanol has important effect on the extraction experiments and the partition coefficient and the separation factor decrease with the increase of temperature, but if the concentration of methanol is too low, it will be unfavorable to the dissolution of fenvaleric acid enantiomers. And when the concentration of methanol is too high (above 95%), most of solution is methanol, the hydrogen bonding among the methanols is poor comparing with water molecules, because the polarity of methanol is poorer than water molecule, then the organic solvent can go into the aqueous phase, mixing and dissolving. So the concentration of methanol is in the range of 10–80% in this experiment. It is found from Fig. 7 that the best concentration of methanol is in 10%.

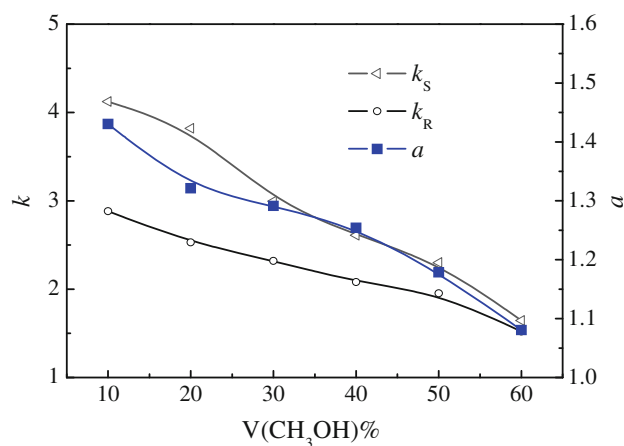


Fig. 7 Effect of concentration of methanol on extraction. Extraction condition: 0.1 g L^{-1} fenvaleric acid enantiomers was prepared in 10–80% methanol aqueous solution containing 2 mmol L^{-1} HP- β -CD in the range of $\text{pH} = 4.0$, the organic solution was prepared by dissolving 0.3 mol L^{-1} L-iso-butyl-L-tartaric esters in 1,2-dichloroethane

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