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Enantioseparation of Phenylsuccinic Acid Enantiomers by Solvent Sublation with Collaborative Selectors

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Abstract A new solvent sublation (SS) system for chiral separation is introduced by using phenylsuccinic acid (H_2A) as the model enantiomers. The experiments were carried out in a traditional SS apparatus but with collaborative chiral selectors: dibenzoyl-*L*-tartaric acid (*L*-DBTA) in the organic phase and hydroxypropyl-β-cyclodextrin (HP-β-CD) in the aqueous phase. The chiral recognition abilities of the two selectors are opposite for the H_2A enantiomers. Several important parameters were investigated. The results demonstrate that enantioselective sublation and partitioning behavior are mainly dependent on the pH of the solution, the concentrations of chiral selectors and H_2A. Furthermore, the flow rate of air and flotation time also have some effects on the enantioseparation. Under the optimized conditions, the enantioselectivity expressed by the separation factor (β) and enantiomer excess (*e.e.*%) are 2.47 and 29.50%, and the yields of R-H_2A and S-H_2A are 0.23 and 0.13 $g{\cdot}L^{-1}$, respectively. Compared with the SS system with the single selector HP-β-CD in the aqueous phase (or *L*-DBTA in the organic phase), the increased values of β and *e.e.*% in the new SS system with collaborative selectors are 1.31 (or 1.38) and 5.90% (or 13.82%), respectively.

Keywords Solvent sublation · Enantiomers · Phenylsuccinic acid · Preferential recognition · Enantioseparation

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1 Introduction

Chirality has become a very important topic in the pharmaceutical industry, agrochemicals, and food industry since a thorough assessment of potential chiral drug candidates is required by the Food and Drug Administration (FDA) [1–3]. To date, many researchers have attempted to obtain enantiopure compounds. The current separation techniques such as crystallization, chromatography, kinetic resolution, chiral extraction, or membrane separation are not always applicable for racemic compounds [4–7]. Selective extraction by a solvent extraction system is a powerful technique for the separation and purification of biomolecules and pharmaceutical products [8–10]. The available works most often deal with the enantioselective extraction in O/W two-phase systems [8, 11], which are not suitable for continuous processes and the enantioselectivity is always low. Therefore, it is necessary to find and develop new technologies for chiral separation.

SS, which was originally introduced by Sebba, has been developed in recent years [12–17]. SS increases in importance because this system presents many advantages, including, high biocompatibility, a mild operation environment, easy amplification, and low amounts of organic solvent [18, 19]. Furthermore, solvent sublation (SS) processes are always simple to generalize to multi-stage operations, which will enable the possible full separation of target compounds in a continuous fashion. To date, a large number of studies related to SS have been conducted on the separation and purification of metal ions and biological materials [20–23]. However, the applications of SS systems for chiral separation are very limited, and no report for enantioseparation by the SS method with collaborative selectors has been mentioned.

It is considered that the induction of chirality and the resolution of racemic compounds necessitates the presence of a chiral environment. For this purpose, chiral auxiliaries or selectors are needed [1]. The commonly used chiral selectors include β-CD, crown ethers, and tartaric acid derivatives [7, 24]. Due to their low cost and excellent enantioseparation, the applications of tartaric acid derivatives and cyclodextrin derivatives for resolution in SS system are preferred. Cyclodextrin derivatives, which are types of cyclic oligosaccharides, are optically active materials. They interact with guest molecules selectively, and form inclusion complexes on the basis of the size, shape and polarity of the guest molecules and various interactions. They can greatly improve the solubility of hydrophobic enantiomers in the aqueous phase. In most cases, to further improve the solubility of hydrophobic enantiomers and the enantioseparation efficiency, more hydrophilic β-CD derivatives such as methyl-β-cyclodextrin and hydroxypropyl-β-cyclodextrin (HP-β-CD) are used [11, 25]. In our study, HP-β-CD was chosen as the hydrophilic selector because of its higher enantioselectivity. Besides, tartaric acid derivatives are normal hydrophobic chiral selectors for many enantiomers; according to a recent report [26], dibenzoyl-*L*-

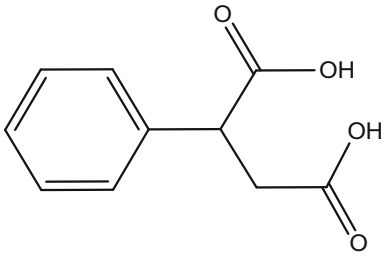

Fig. 1 The chemical structure of phenylsuccinic acid

tartaric acid (*L*-DBTA) was employed as the chiral selector in the organic solvent. H_2A (Fig. 1) is an important intermediate of *N*-methyl-α-phensuximide representing an important class of antitumor agents, and thus it was used as the model enantiomers.

In this study, with the aid of collaborative selectors, a new SS system was introduced and tried for enantioseparation using phenylsuccinic acid (H_2A) as the model enantiomers. Various process parameters, including the concentration of H_2A and chiral selectors, pH, air flow rate, and sublation time were investigated and optimized. Compared to the SS systems with single selectors, the new SS system with collaborative selectors should provide a more efficient approach to chiral separation.

2 Experimental Section

2.1 Materials

H_2A (racemate, purity 99%) was purchased from Dibo Chemical Co. Ltd. (Shanghai China). The aqueous chiral selector HP-*β*-CD was purchased from Yuanye Biotech Co. (Shanghai China) and the organic chiral selector *L*-DBTA with a purity of 99% was from Sanen Chemical Technology Co. Ltd. (Shanghai China). *n*-Octanol (analytically pure) was purchased from Hengxing Chemical Material Co. (Tianjin, China). The solvent for chromatography was of HPLC grade. All other chemicals were of analytical reagent grade. Double distilled and deionized water was used throughout the experiments.

2.2 Preparation of the SS System

All experiments were performed at room temperature. For each sublation experiment, The SS system included two phases. A 100 mL H_2A aqueous solution with a given concentration of HP-*β*-CD was used as the lower phase, while 10 mL *n*-octanol with a given concentration of *L*-DBTA formed the upper phase. The pH of the H_2A aqueous solution was adjusted with a K_2HPO_4–KH_2PO_4 buffer solution and measured using a pH meter.

The experiments for enantioseparation by the new SS system were carried out in a traditional SS apparatus that was designed in our laboratory (Fig. 2, assembled by Hunan University Instrument Plant, China). The whole apparatus consists of two basic parts: a glass column (45 cm × 25 mm i.d.) with a porous sintered glass disc at the bottom, that is used to store the prepared phases and used as the container for enantioseparation. The other part is an air pump with a rotameter to control the gas flow velocity, which is connected to the column through a silicone rubber tube and used to send air to the column. When the air passes through the porous sintered glass disc, a lot of bubbles are generated and then rise up to the upper organic phase. Meanwhile, H_2A enantiomers and the complexes formed by H_2A and HP-*β*-CD also rise up with the bubbles to the upper phase. The complexes don't dissolve in the organic phase and will come back to the lower aqueous phase after the bubbles burst at the interface of the two phases. HP-*β*-CD preferentially recognizes *R*-H_2A rather than *S*-H_2A, while *L*-DBTA has the opposite recognition tendency. Finally, more *R*-H_2A occurs in the lower aqueous phase compared to *S*-H_2A, and thus the enantioseparation purpose is achieved. It should be noted that the equipment used in SS is very simple, and all the operator needs to do is to collect the lower aqueous layer for the sequential analysis or further treatment.

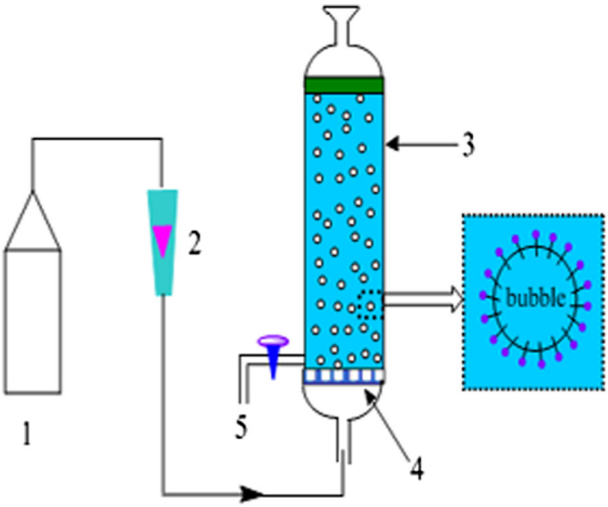

Fig. 2 Schematic showing the apparatus used in this work. 1—Air pump, 2—rotameter, 3—sample pool, 4—porous sintered glass disc (G4 porosity), 5—sampling vent

2.3 HPLC Analysis

After each sublation process, the concentration of H_2A enantiomers in the aqueous phase was analyzed by HPLC (Shimadzu, Japan) using a Kromail C_{18}-WP column (250 mm × 4.6 mm i.d.) (Hanbon Sci. Technol. Co. Ltd., China) and a UV spectrophotometer detector (Shimadzu, Japan). The quantification of H_2A enantiomers in the organic phase was calculated by the subtractive method. Each experiment was conducted in triplicate and the standard deviation should be less than ± 3%. The mobile phase for analyzing H_2A enantiomers was as follows: acetonitrile aqueous solution (20%, v/v) containing 8 mmol·L^{-1} HP-β-CD and 0.05% trifluoroacetic acid (v/v) at a flow of 1.0 mL·min^{-1}. The UV spectrometer was operated at 254 nm, while the column temperature was set at 25 °C. The injection volume was 20 μL [27]. The chromatograms are

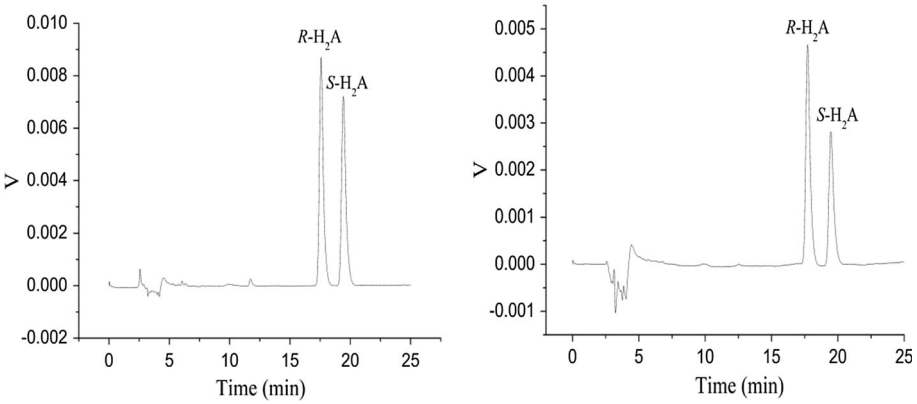

Fig. 3 HPLC chromatograms of H_2A: before and after solvent sublation

shown in Fig. 3. The retention time of *R*-H_2A was approximately 17.32 min while it was about 19.16 min for *S*-H_2A.

2.4 Theory of SS Enantioseparation

Partitioning and enantioselectivity, which are expressed in terms of the distribution coefficient (D), separation factor (β) and enantiomer excess ($e.e.\%$), are important parameters to estimate the performance of SS enatioseparation. They can be calculated by the following formulae:

$$D_{R(S)} = \frac{\text{initial } [R] \text{ or initial } [S]}{[R] \text{ or } [S]} - 1 \tag{1}$$

$$\beta = \frac{\text{distribution ratio of } S - \text{enantiomer}}{\text{distribution ratio of } R - \text{enantiomer}} \tag{2}$$

$$e.e.\% = \frac{[R](\text{or}[S]) - [S](\text{or}[R])}{[R] + [S]} \tag{3}$$

for which [ ] denotes a concentration ($mg \cdot mL^{-1}$) of the enantiomer in the aqueous phase.

3 Results and Discussion

3.1 Influence of pH in the Aqueous Phase

Since pH impacts the existing form of H_2A, stringent control of the pH is recommended in all experiments. The effect of pH on distribution coefficients and enantioselectivities was investigated with the H_2A concentration 1.0 $g \cdot L^{-1}$, HP-β-CD of 0.015 $mol \cdot L^{-1}$, *L*-DBTA of 0.7 $mol \cdot L^{-1}$, the air flow rate of 30 $mL \cdot min^{-1}$, and sublation time of 2 h. It can be inferred from Fig. 4 that increasing the pH from 2.5 to 5.0 caused the decreases of D_R and D_S. The reason may be that increasing pH value makes the reaction equilibria move to the right side [24].

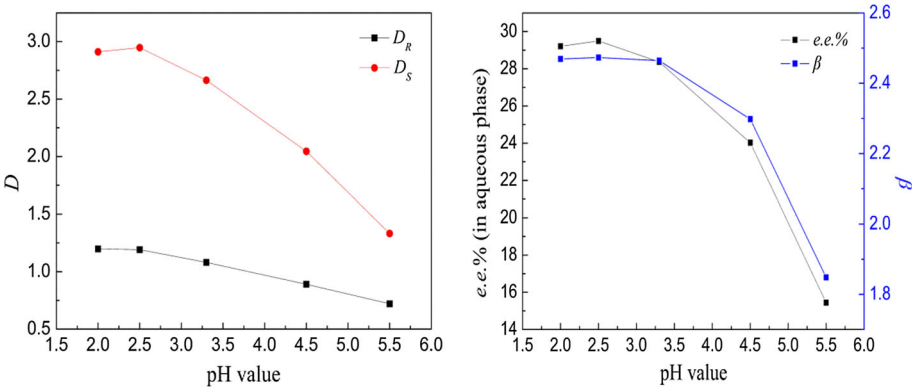

Fig. 4 Influence of the pH on the distribution behavior. Initial concentrations of H_2A enantiomers, *L*-DBTA, and HP-β-CD: 1.0 $g \cdot L^{-1}$, 0.70 $mol \cdot L^{-1}$, and 0.015 $mol \cdot L^{-1}$, sublation time 2 h and flow rate 30 $mL \cdot min^{-1}$

$$H_2A \rightleftharpoons H^+ + HA^- \quad (4)$$

$$HA^- \rightleftharpoons H^+ + A^{2-} \quad (5)$$

The amount of dissociated forms of H_2A increased while that of molecular H_2A decreased with the rise of pH. HP-β-CD and *L*-DBTA mainly have chiral recognition ability and affinity for molecular H_2A, but not for dissociated H_2A. Ionic species of H_2A only exist in the aqueous phase. The concentrations of complexes formed by selectors and H_2A enantiomers decreased with the increase of pH. When pH < 2.5, D and β showed almost no changes. Therefore, the pH value of 2.5 was adopted in further experiments.

3.2 Influence of Initial Concentration of H_2A Enantiomers

The influence of the H_2A enantiomer concentrations on enantioseparation efficiency was investigated as shown in Fig. 5 with the other experimental conditions being the same as those for studying the effect of pH. It can be seen that all of the distribution coefficients increased with the increases in the initial concentration of H_2A enantiomers. This can only be caused by non-selective partitioning. However, the values of enantioselectivities increased before the H_2A concentration reached 1.0 g·L^{-1} and then decreased with a further increase of the H_2A concentration. This was due to the fact that, at low concentrations, most selectors action was through enantioselective complexation and, at higher concentrations, more non-selective partitioning was occurring. Therefore, 1.0 g·L^{-1} was the optimized H_2A concentration for this system.

3.3 Influence of Concentration of HP-β-CD

The influence of HP-β-CD concentration was investigated by varying the HP-β-CD concentration from 0.0025 to 0.02 mol·L^{-1} with other parameters being held constant. The results are depicted in Fig. 6. As can be seen, D decreased remarkably as the concentration of HP-β-CD increased to 0.015 mol·L^{-1}. Meanwhile, the opposite tendency was observed for β and *e.e.%*, indicating improved chiral separation ability. The reason may be that, with

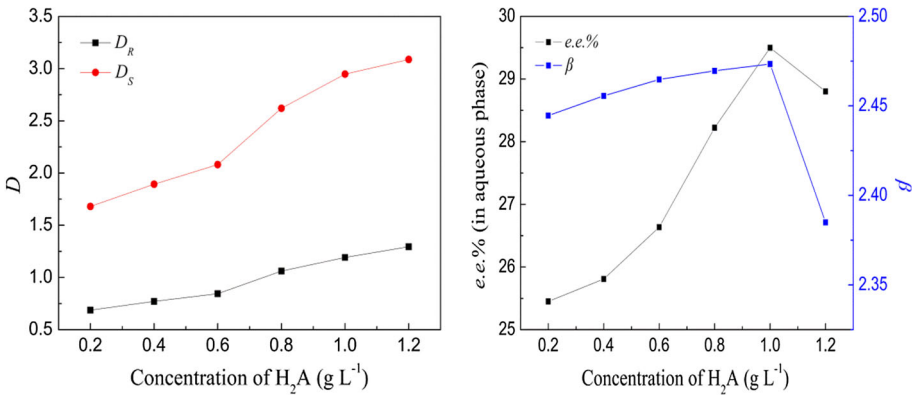

Fig. 5 Influence of the initial concentration of H_2A enantiomers on the distribution behavior. Initial concentrations of *L*-DBTA and HP-β-CD: 0.70 and 0.015 mol·L^{-1}, pH = 2.5, sublation time 2 h and flow rate 30 min·L^{-1}

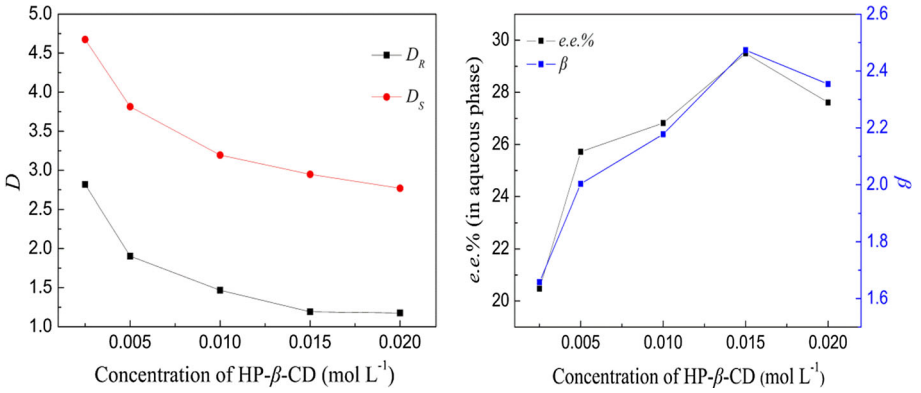

Fig. 6 Influence of HP-β-CD concentration on the distribution behavior. The concentrations of H_2A enantiomers and *L*-DBTA: 1.0 g·L^{-1} and 0.70 mol·L^{-1}, pH = 2.5, sublation time 2 h and flow rate 30 mL·min^{-1}

increasing HP-β-CD concentration more complexes formed in aqueous phase that did not dissolve in the organic phase. So, under the same operation conditions, fewer H_2A molecules were transported to the organic phase and this resulted in the decrease of *D*. Due to the preferential recognition for *R*-H_2A by HP-β-CD, D_R decreased more than D_S corresponding to the increase of β and *e.e.%*. When the selector concentration was increased from 0.015 to 0.025 mol·L^{-1}, *D* continued to decrease with the reason being the same as above. However, the decrease of β and *e.e.%* should be attributed to the increasing amounts of complexes formed by HP-β-CD and *S*-H_2A compared to those formed by HP-β-CD and *R*-H_2A in the SS process when excess HP-β-CD is present. Therefore, the difference of concentrations between the two enantiomers at aqueous or organic phase diminished.

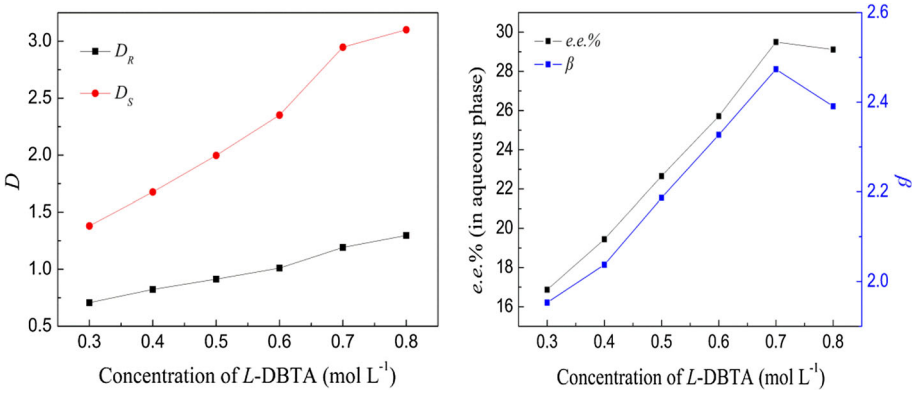

Fig. 7 Influence of the concentration of *L*-DBTA on the distribution behavior. The concentrations of H_2A enantiomers and HP-β-CD: 1.0 g·L^{-1} and 0.015 mol·L^{-1}, pH = 2.5, sublation time 2 h and flow rate 30 mL·min^{-1}

3.4 Influence of Concentration of L-DBTA

The influence of *L*-DBTA concentration on enantioseparation behavior is summarized in Fig. 7 with the other experimental conditions being the same as those for studying the effect of pH. With the increase of *L*-DBTA concentration, the distribution coefficients were greatly increased. Meanwhile, the enantioselectivities all increased until the concentration of *L*-DBTA was 0.70 mol·L^{-1}. The reason is that, with the increase of *L*-DBTA concentration, more complexes H_2A and *L*-DBTA formed in the organic phase. So, at the same operation conditions, more H_2A molecules were transported to the organic phase and resulted in the increase of *D*. Due to the preferential recognition for *S*-H_2A by *L*-DBTA, D_S increased more than D_R leading to the increase of β and *e.e.*%. When the concentration of *L*-DBTA was increased further, *D* continued to increase for the same reason as above, whereas the enantioselectivities followed the opposite trend. This was because greater amounts of complexes are formed by *L*-DBTA and *R*-H_2A than are formed by *L*-DBTA and *S*-H_2A in the SS process when excess *L*-DBTA is present. As a result, the difference of concentrations between the two enantiomers in the aqueous or organic phases was diminished.

3.5 Influence of the Air Flow Rate

Figure 8 shows the effect of varying the air flow rate on SS for the separation of H_2A enantiomers. The air flow rate was examined in the range of 10–50 mL·min^{-1}, which could significantly influence the velocity of mass transfer of H_2A between the aqueous and organic phases. Generally, the rate of gas–liquid interfacial area generation can be increased by increasing the air flow rate. However, a too high flow rate should be avoided because a turbulent mixing may occur at the interface between the organic and aqueous phases. Such mixing can promote the redissolution of the floated product in the aqueous phase. In actual operation, the two-phase interface area increased until the air flow rate was up to 30 mL·min^{-1} but then the two phase interface decreased with the increase of air flow rate. From these experimental results, the air flow rate was finally fixed at 30 mL·min^{-1}.

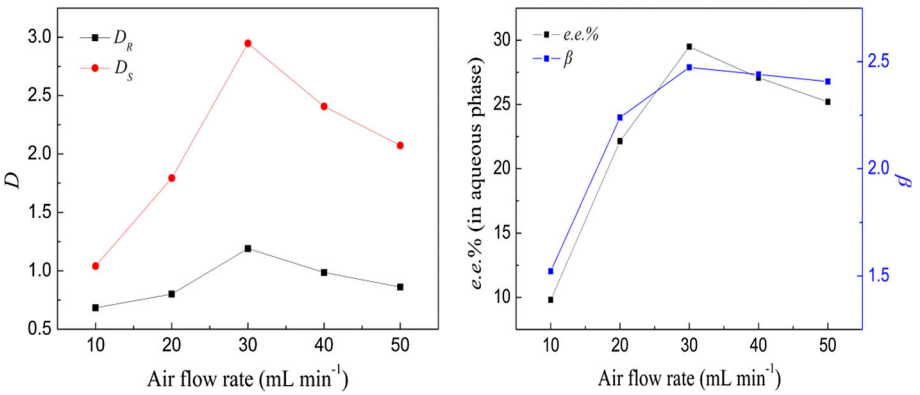

Fig. 8 Influence of the air flow rate on the distribution behavior. The concentrations of H_2A enantiomers, *L*-DBTA and HP-β-CD: 1.0 g·L^{-1}, 0.70 mol·L^{-1} and 0.015 mol·L^{-1}, pH = 2.5 and sublation time 2 h

3.6 Influence of the Sublation Time

The effect of the sublation time on the enantioseparation is listed in Fig. 9. The results suggest that the distribution coefficients and enantioselectivities increase rapidly for sublation times less than 2 h but then tended to smooth out at longer times. This was because the interphase force and the contact area of the interphase increase when the sublation time is extended, in which cases the distribution coefficients and enantioselectivities show an increase and finally reach equilibrium. Therefore, the sublation time was fixed at 2 h.

3.7 Comparison of Single Selectors and Collaborative Selectors in the SS System

Under the optimal conditions, H_2A was separated by the new SS system, while, at the same time, the SS system with HP-β-CD or *L*-DBTA as a single selector were also analyzed for comparison. As we designed in our experiments, when 0.015 mol·L^{-1} HP-β-CD was used as single selector in SS system, there was no *L*-DBTA in the system. The situation of *L*-DBTA as a single selector was analogous to that for HP-β-CD. Compared the results shown in Table 1, it was found that the SS system with collaborative selectors has a much stronger chiral separation ability than that with a single selector. Obviously, this should be attributed to the combination of the enantioseparation abilities of both HP-β-CD and *L*-DBTA.

3.8 Reasonable Enantioseparation Mechanisms

Enantioseparation mechanisms are of critical importance for understanding and optimizing a chiral separation process. As a result, the possible mechanisms for H_2A enantioseparation by the SS method with collaborative chiral selectors were explored systematically in our work. H_2A is a type of binary acid with two ionization equilibria being present:

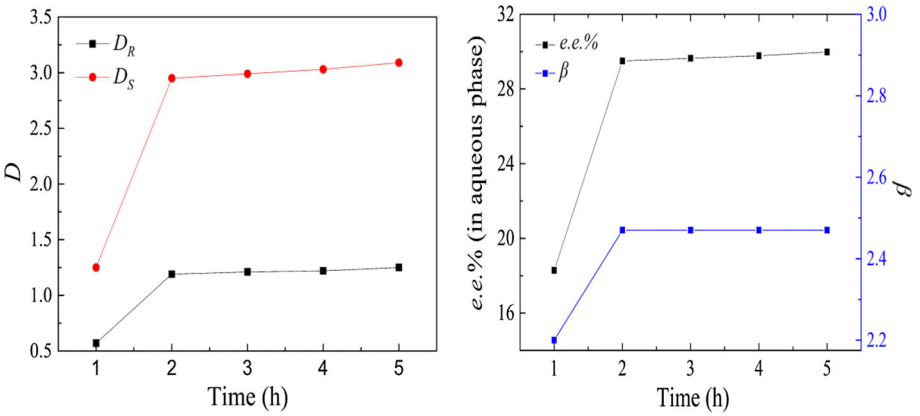

Fig. 9 Influence of sublation time on the enantioseparation. The concentrations of H_2A enantiomers, *L*-DBTA and HP-β-CD: 1.0 g·L^{-1}, 0.70 mol·L^{-1} and 0.015 mol·L^{-1}, pH = 2.5 and flow rate 30 mL·min^{-1}

Table 1 Comparison between single selectors and collaborative selectors in SS systems

Items	Collaborative selectors		HP-β-CD		*L*-DBTA	
	AVG	S	AVG	S	AVG	S
D_R	1.19	0.0306	0.59	0.0265	6.12	0.1060
D_S	2.95	0.0300	0.77	0.0400	8.45	0.1114
β	2.47	0.0781	1.31	0.0833	1.38	0.0208
e.e.%	29.50	1.0214	5.90	1.0137	13.82	0.8293

$$H_2A \overset{K_{a1}}{\rightleftharpoons} H^+ + HA^- \tag{6}$$

$$HA^- \overset{K_{a2}}{\rightleftharpoons} H^+ + A^{2-} \tag{7}$$

The most plausible enantioseparation mechanisms that mainly influence the distribution coefficient and selectivity of H_2A enantiomers in the sublation process can be explained by the following equations:

$$(H_2A)_a + \text{HP-}\beta\text{-CD} \overset{K_1}{\rightleftharpoons} H_2A - \text{HP-}\beta\text{-CD} \tag{8}$$

$$HA^- + \text{HP-}\beta\text{-CD} \overset{K_2}{\rightleftharpoons} (HA - \text{HP-}\beta\text{-CD})^- \tag{9}$$

$$A^{2-} + \text{HP-}\beta\text{-CD} \overset{K_3}{\rightleftharpoons} (A - \text{HP-}\beta\text{-CD})^{2-} \tag{10}$$

$$(H_2A)_o + L\text{-DBTA} \overset{K_4}{\rightleftharpoons} H_2A - L\text{-DBTA} \tag{11}$$

$$HA^- + L\text{-DBTA} \overset{K_5}{\rightleftharpoons} (HA - L\text{-DBTA})^- \tag{12}$$

$$A^{2-} + L\text{-DBTA} \overset{K_6}{\rightleftharpoons} (A - L\text{-DBTA})^{2-} \tag{13}$$

$$(H_2A)_o \rightleftharpoons (H_2A)_a \tag{14}$$

where $(H_2A)_a$, $(H_2A)_o$ represent H_2A in the aqueous phase and organic phases, respectively. The new SS enantioseparation process includes three steps. In the first step, some H_2A enantiomers are complexed by HP-β-CD, as expressed in Eqs. 8–10. To be emphasized, HP-β-CD is inclined to recognize *R*-H_2A preferentially in this process and the stability of H_2A − HP-β-CD was better than for other inclusion complexes [25]. In the second step, the inclusion complexes and free H_2A rose up with bubbles and was concentrated at the interface between the aqueous and organic phases. The third step took place when the bubbles reached the interface, releasing of the molecules. The solubility of complexes formed by H_2A and HP-β-CD is poor in the organic phase, where H_2A has better solubility than in the aqueous phase. So, the free H_2A enantiomers were transported to the organic phase and interacted with *L*-DBTA, as expressed in Eqs. 11–13. Note that, *L*-DBTA recognized *S*-H_2A preferentially in this process and the stability of H_2A − *L*-DBTA was better than for other complexes. From the considerations of the first and third steps, the amount of *S*-H_2A in the transport process was greater than for *R*-H_2A. Consequently, more *S*-H_2A was concentrated in the organic phase after the sublation process and enantioseparation was thus achieved.

4 Conclusion

In this work, a solvent sublation (SS) system using dibenzoyl-*L*-tartaric acid (*L*-DBTA) and hydroxypropyl-β-cyclodextrin (HP-β-CD) as collaborative selectors was introduced for separating phenylsuccinic acid (H_2A) enantiomers. Hydrophobic *L*-DBTA and hydrophilic HP-β-CD preferentially recognize *S*-H_2A and *R*-H_2A, respectively. Different factors that influence the final enantioselectivity were investigated. Under the optimized conditions: H_2A concentration 1.0 $g{\cdot}L^{-1}$, HP-β-CD 0.015 $mol{\cdot}L^{-1}$, *L*-DBTA 0.70 $mol{\cdot}L^{-1}$, pH = 2.5 in the aqueous phase, air flow rate of 30 $mL{\cdot}min^{-1}$ and sublation time of 2 h, the separation factor (β) and enantiomer excess (*e.e.*%) values reached 2.47 and 29.50%, respectively, and yields of R-H_2A and S-H_2A were 0.23 and 0.13 $g{\cdot}L^{-1}$, also respectively. What's more, by combining the advantages of SS and recognization abilities of chiral selectors, this new enantioseparation method can be also employed for the separation of other hydrophobic enantiomers through optimizing of the compositions of the SS system, the kinds of chiral selectors and other related sublation parameters. In conclusion, the explorations in our study will further enrich the enantioseparation methods and pave a way for the application of SS in the chiral separation field.

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