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Enantioseparation of D/L-mandelic acid with L-phenylalanine in diastereomeric crystallization☆

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ABSTRACT

A mechanistic study of the chiral resolution of mandelic acid by diastereomeric crystallization with L-phenylalanine as the resolving agent was performed. Also, the efficiency of the resolving agent for chiral separation was evaluated. The carboxyl and amine groups of L-phenylalanine were hydrogen-bonded with the hydroxyl and carboxyl groups of mandelic acid for the preferential formation of a complex of L-mandelic acid-L-phenylalanine due to the stereo-configurations of the functional groups, and crystallized out as diastereomeric salt. As a result, L-mandelic acid was enriched up to 85% in the resulting diastereomeric crystals. Moreover, the chiral purity of the diastereomeric crystals depended on the molar ratio of mandelic acid to L-phenylalanine in the solution. With molar ratios ranging from 0.7 to 6.0, the purity of L-mandelic acid in the diastereomeric crystals was improved when increasing the molar ratio, while the molecular ratio of mandelic acid to L-phenylalanine in the diastereomeric crystals remained at 1:1. However, outside this range, there was no chiral separation of mandelic acid, and only racemic crystals of mandelic acid were produced. In addition, XRD and DSC analyses revealed that the structure of the resulting diastereomeric crystals was identical with that of pure L-mandelic acid-L-phenylalanine crystals. Therefore, it was concluded that L-mandelic acid was the template for the diastereomeric crystals, while D-mandelic acid was incorporated in the crystals as an impurity in a solid solution.

1. Introduction

The chirality of enantiomers has attracted great interest worldwide [1], as the majority of bioorganic molecules in living organism are chiral [2–4]. In addition, enantiomers in drugs, pesticides, and waste compounds have distinctly different pharmacological activities and pharmacokinetic and pharmacodynamic effects [5]. Thus, to avoid possible undesirable side effects from chiral drugs, new technology is needed for the separation of enantiomers.

Among the various methods that have been developed to prepare chiral compounds [3,4,6,7], crystallization is one of the most popular practical techniques used in industry. According to Roozeboom [8,9], there are three kinds of racemate in crystallization: conglomerates, racemic compounds, and solid solutions. In the chiral compounds, two enantiomers can interact with a proper reagent to form new complex compounds of diastereomers. Since the two resulting diastereomers have different physicochemical properties, one can be selectively crystallized through traditional techniques. This optical resolution of enantiomers via the formation of corresponding diastereomeric salts is called diastereomeric crystallization [3,10–12]. Thus, the relative simplicity and low cost of diastereomeric crystallization makes it one of the preferred methods for separating racemic compounds into enantiomers for industrial and clinical use [11,12].

Although diastereomeric crystallization was discovered by Pasteur nearly 160 years ago [13], the selection of an appropriate resolving agent remains a serious challenge. While much effort has been made to develop resolving agents, no general chiral resolving agent has been identified that is applicable to all racemates, thus selecting a suitable resolving agent is still a matter of trial and error [11,12]. Besides, to utilize the diastereomeric crystallization for chiral separation, several recent studies have attempted to clarify the important physical properties of diastereomeric salts by using phase diagrams for solid–liquid equilibria [14], and estimating the thermodynamic stability of less- and more-soluble diastereomeric salts [15–21]. For the molecular design of a resolving agent, it is also studied to clarify the relationship between the above-mentioned physical properties of pairs of diastereomeric salts and the characteristics of their molecular and/or crystal structures. [22–30].

However, at the viewpoint of molecular recognition of the diastereomer, a mechanistic study of the diastereomeric resolution by crystallization has scarcely been achieved yet. Accordingly, using

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D/L-mandelic acids as the racemate materials for chiral resolution, the present study attempted to mechanistically investigate the formation of diastereomeric salts and resolution of racemate in the diastereomeric crystallization via varying the molar ratio of racemate materials to the resolving agent. Also, various amino acids and substances with a similar molecular structure to mandelic acid were examined as potential resolving agents for the mandelic acids.

2. Experiment

2.1. Diastereomeric crystallization

The enantiomer reagents, mandelic acid racemate, and resolving agents, such as L-alanine and L-phenylalanine etc, were all supplied by the TCI company (ACS grade, Japan) and used without further purification.

The chiral resolution of the resolving agents was examined based on diastereomeric crystallization with D/L-mandelic acid (racemate). Thus, a resolving agent of equivalent molecules was dissolved in 10 ml of a racemic mandelic acid solution of 1.3 M, then heated up to 80 °C for complete dissolution. Thereafter, the clear solution was cooled down to 25 °C with a cooling rate of 30 °C/h for the induction of the diastereomeric crystallization, and left for two hours. The crystals were then filtrated out through a 0.45 μm micromembrane filter, dried in an oven at room temperature, and the enantiomer purity of the crystals was analyzed by HPLC using a Kromasil 100-5-TBB chiral column (250 mm × 4.6 mm), as described below.

With L-phenylalanine as the optimal resolving agent, D/L-mandelic acids were diastereomeric-crystallized at various racemic concentrations from 0.145–2.171 M. Here, the concentration of the resolving agent was always fixed as 0.362 M due to the limitation of its solubility in water. The crystallization was carried out in a double-jacketed Ruston reactor with a 50 ml working volume. The solution was heated up to 80 °C for complete dissolution of the resolving agent, then cooled down to 25 °C at a cooling rate of 30 °C/h, as mentioned above. The crystal product was then filtered out, dried and analyzed the optical purity, structure, and thermal properties of the crystals.

2.2. Analysis

2.2.1. HPLC

HPLC (Agilent 1100 series, Agilent, U.S.A.) was used to analyze the composition of the diastereomers. As such, the molar composition of mandelic acids and the resolving agent in the diastereomers was analyzed with a Pickle Covalent (S,S) Whelk-01 reverse column (250 mm × 4.6 mm), where the mobile phase used an aqueous solution of 1.0% (v/v) acetic acid at a flow rate of 1 ml/min. Here, a UV detector at a 254 nm wavelength was used to monitor the concentrations of mandelic acid and the resolving agent.

In addition, a Kromasil 100-5-TBB column (250 mm × 4.6 mm) was used to analyze the enantiomer purity in the diastereomers. The mobile phase used to separate the mandelic acid was a mixture of hexane, tert-butyl methyl ether, and formic acid at a ratio of 75, 24.5 and 0.5% (v/v), respectively, with a flow rate of 1 ml/min. The enantiomer concentrations of the mandelic acids were also detected with a UV detector at a 254 nm wavelength.

2.2.2. DSC

The melting point and enthalpy of the diastereomeric crystals were measured using a photo-calorimeter (DSC Q100 system, U.S.A.). Samples of the diastereomeric crystals air-tightly sealed in aluminum pans were thermally scanned from 300 to 573 K at a heating rate of 5 K min^{-1} under a nitrogen atmosphere (nitrogen flow rate of 50 cm^3 min^{-1}).

2.2.3. XRD

To monitor the molecular structure of the diastereomeric crystals, a powder X-ray diffraction analysis was conducted with a diffractometer (M18XHF-SRA, Mac Science, Japan) using CuK_α radiation at 40 kV, 300 mA with a scanning range of 3.5–45° and scanning rate of 5° min^{-1}.

3. Results and discussion

3.1. Evaluation of resolving agents

In chiral resolution based on the formation of diastereomeric salts, the chiral selectivity is directly determined by the molecular configuration of the resolving agent, yet selecting a suitable resolving agent is still a matter of trial and error [10–12]. However, it is generally recognized that the chiral recognition ability of the resolving agent is more effective when the resolving agent has a similar molecular configuration to the target enantiomer [2,20]. Accordingly, the present study attempted to identify an optimal resolving agent from among compounds with a compatible molecular configuration and functional groups to bind with mandelic acid.

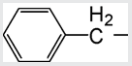
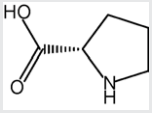
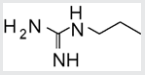
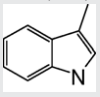
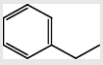
As summarized in Table 1, various resolving agents based on amino acids were used with different functional groups and residues in their molecular configuration. Since the $–NH_2$ in the amino acids bound with the –COOH in the mandelic acid through electrostatic interactions, diastereomeric crystals of mandelic acid and the resolving agent were mostly formed. However, amino acids of L-histidine, L-lysine, and L-tryptophan did not produce diastereomeric crystals, as the resolving agents included incompatible residues for mandelic acid. In addition, it was found that resolving agents based on organic acids, such as L-lactic acid, R-2-phenylpropionic acid, and S-3-phenyl lactic acid, bound with the mandelic acid via an interaction between the –OH in the resolving agents and the –COOH in the mandelic acid. Nonetheless, although this interaction between the functional groups of –OH and –COOH was evident when using S-2-phenylethanol and R-1-phenylethane-1,2-diol as the resolving agents, it was generally difficult to achieve a high chiral selectivity for L-mandelic acid with non-amino-acid resolving agents, due to the low steric effect of the functional groups on chiral recognition ability.

Furthermore, the chiral selectivity of the resolving agents depended on the configuration of their residues. Thus, in the case of L-phenylalanine, its toluene group residue was highly compatible with the mandelic acid configuration, resulting in a high chiral selectivity for L-mandelic acid (e.e. = 52.3%). However, a low chiral selectivity was obtained when using L-tyrosine (e.e. = 6.8%) and L-Phenylglycine (e.e. = 6.0%), although their residues were slightly different from those of L-phenylalanine. It should be noted that the high chiral recognition ability exhibited by L-alanine (e.e. = 49.0) was due to hydration during the diastereomeric crystal formation, even though the residue configuration of L-alanine was quite different from that of mandelic acid.

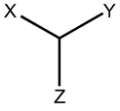
3.2. Diastereomeric crystallization

For the chiral separation of mandelic acid, diastereomeric crystallization was carried out while varying the molar ratio of racemic mandelic acid to L-phenylalanine, as a critical factor in the formation of diastereomers and in determining the chiral selectivity. In the present study, the amount of L-phenylalanine in the solution remained fixed at 0.362 M due to the limited solubility of L-phenylalanine in water, while the amount of racemic mandelic

Table 1
Evaluation of chiral recognizability of organic compounds as resolving agents.

Run	Resolving agent	Functional group (X, Y)	Residue (Z)	Purity of L-mandelic acid (%)	e.e. for L-mandelic acid (%)
1	L-Phenylglycine	NH_2, COOH		53.0	6.0
2	L-Phenylalanine	NH_2, COOH		76.2	52.3
3	L-Tyrosine	NH_2, COOH		53.4	6.8
4	L-Alanine	NH_2, COOH	CH_3–	74.6	49.0
5	L-Serine	NH_2, COOH	OH–CH_2–	53.3	6.6
6	L-Cystein	NH_2, COOH	HS–CH_2–	53.1	6.2
7	R-2-Aminobutyric acid	NH_2, COOH	CH_3–CH_2–	57.0	14.0
8	L-Aspartic acid	NH_2, COOH	HOOC–CH_2–	53.2	6.4
9	L-Glutamic acid	NH_2, COOH	HOOC–$(CH_2)_2$–	51.7	3.4
10	L-Threonine	NH_2, COOH	CH_3–CH(OH)–	51.9	3.8
11	L-Methionine	NH_2, COOH	CH_3S–$(CH_2)_2$–	53.3	6.6
12	L-Proline	NH_2, COOH		53.4	6.8
13	L-Arginine	NH_2, COOH		53.1	6.2
14	L-Histidine	NH_2, COOH		–	No crystal
15	L–Lysine	NH_2, COOH	NH_2–$(CH_2)_4$–	–	No crystal
16	L-Tryptophan	NH_2, COOH		–	No crystal
17	L-Lactic acid	OH, COOH	CH_3–	53.3	6.6
18	R-2-Phenyl propionic acid	OH, COOH		53.5	7.0
19	S-3-Phenyl lactic acid	OH, COOH		53.6	7.2
20	R-Phenylethylamine	NH_2, CH_3		55.6	11.2
21	R-1-Phenylethane-1,2-diol	OH, CH_2OH		53.4	6.8

Remark: The above organic compounds of resolving agents are configured on basis of standard format as



acid was changed from 0.145 to 2.171 M. Therefore, a molar ratio of less than 1.0 indicated an excess of L-phenylalanine to mandelic acid in the diastereomeric crystallization, whereas a molar ratio greater than 1.0 indicated an excess of mandelic acid to L-phenylalanine.

Within a molar ratio range of 0.7–6.0, as shown in Fig. 1, crystals with a 1:1 molecular ratio of mandelic acid to L-phenylalanine, implying a diastereomer, were produced and the enantiomer purity of the crystals was enhanced from 75 to 85% when increasing the molar ratio. However, with a molar ratio above 7.0, the enantiomer purity of the resulting crystals suddenly dropped to 55% and the molecular ratio of mandelic acid to L-phenylalanine increased to 1.7:1, indicating the simultaneous crystallization of both crystals of diastereomer and mandelic acid. In addition, it was interesting to note that increasing the molar ratio up to 8.0 produced simultaneously both crystals with a 3.5:1 molecular ratio of mandelic acid to L-phenylalanine and a further reduction in the enantiomer purity of the product crystals to about 40%, indicating a shift in the chiral selectivity of the crystals from L-mandelic acid to D-mandelic acid. The sudden drop of enatiomer purity of the product crystals were possibly due to the D-rich mandelic acid crystals which were simultaneously crystallized with diastereomeric crystals at high molar ratio. That is, from the molecular ratio of 1.7:1, the enantiomer purity of mandelic acid crystals could be estimated as about 81% of D-isomer on basis of about 80% purity (L-mandelic acid) of diastereomer crystals. Also, the molecular ratio of 3.5:1 in the resulting crystals led to the estimation of the enatiomer purity in the mandeic acid crystals as 83% of D-isomer. Those estimated purities were highly consistent and allowed us to guess that the

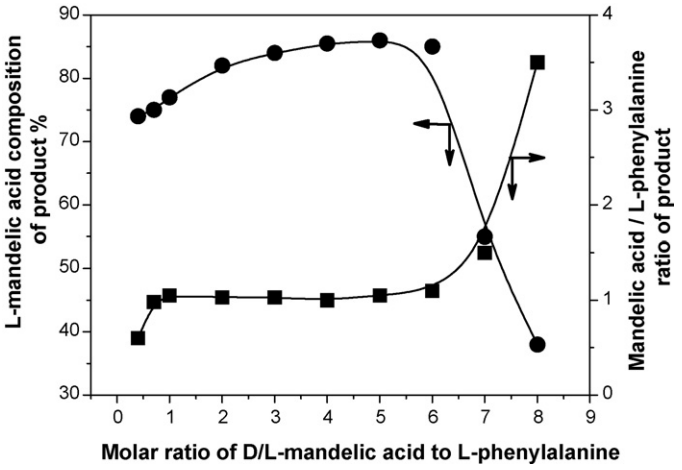


Fig. 1. Effect of molar ratio of D/L-mandelic acid to L-phenylalanine on optical purity of chiral resolution.

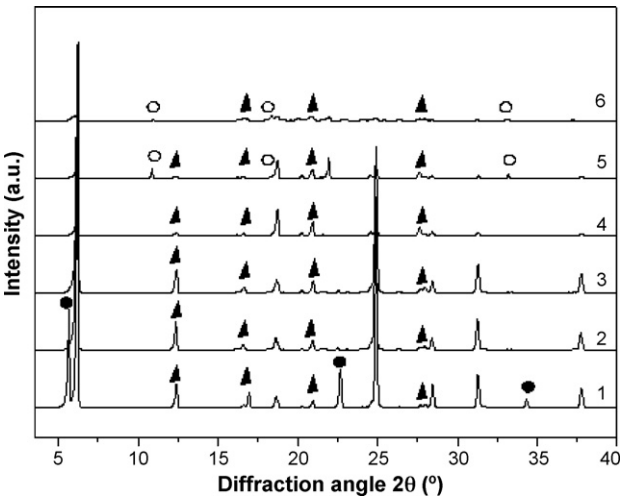


Fig. 3. XRD patterns of diastereomer crystals produced in diastereomeric crystallization along with variation of molar ratio of mandelic acid to L-phenylalanine (R). 1. R = 0.4; 2. R = 0.7; 3. R = 1.0; 4. R = 6.0, 5. R = 7.0 and 6. R = 8.0.

enatiomer putity drop of the product crystals at high molar ratios of 7.0 and 8.0 was due to the simultaneous crystallization of D-rich mandelic acid. Our hypothesis will be further discussed with experimental evidence in Fig. 5. Meanwhile, at a low molar ratio of 0.4, the enantiomer purity of the resulting crystals remained high at almost 75%, despite a dramatic deviation of the crystals in the molecular ratio of mandelic acid to L-phenylalanine from the diastereomeric ratio of 1:1.

The crystal structures resulting from the diastereomeric crystallization were examined using powder XRD, as shown in Figs. 2 and 3. For mandelic acid and L-phenylalanine, the crystal structure of each compound exhibited a unique pattern of characteristic peaks (Fig. 2), where the L-phenylalanine peaks appeared at $2\theta = 5.64^\circ$, 22.64°, and 34.3°, while the D- and L-mandelic acid peaks were identical at $2\theta = 11.9^\circ$, 30.1°, and 36.8°. However, in the case of enantiomeric diastereomer crystals of L-mandelic acid-L-phenylalanine (L-L diastereomer) and D-mandelic acid-L-phenylalanine (D-L diastereomer), the structures were quite different.

The crystal structures of the L-L and D-L diastereomer mixture were shown in Fig. 3, where the structural change in the resulting crystals was only minimal in relation to the molar ratio of mandelic acid to L-phenylalanine in the diastereomeric crystallization. As such, the crystals produced from molar ratios ranging from 0.7 to 6.0 exhibited the same XRD patterns, which were identical to the XRD pattern of the L-L diastereomer crystal. However, outside this range (molar ratios of 0.4, 7, and 8), the XRD patterns differed from those of the enantiomeric diastereomers.

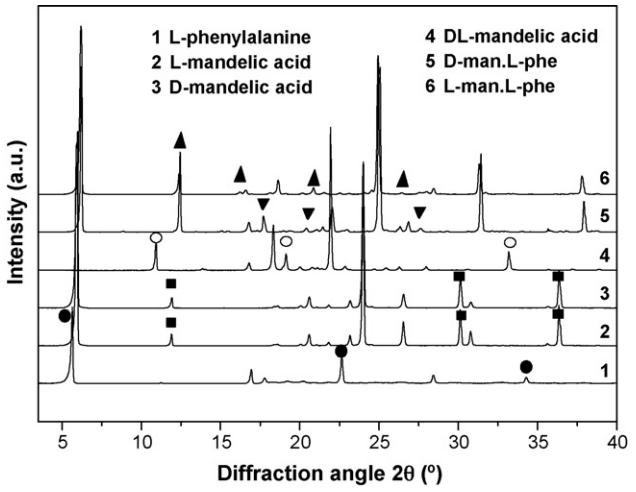


Fig. 2. XRD patterns of standard crystals used as reference structure in experiments. 1. L-phenylalanine; 2. L-mandelic acid; 3. D-mandelic acid; 4. D/L-mandelic acid, 5. D-mandelic acid-L-phenylalanine diastereomer; and 6. L-mandelic acid-L-phenylalanine diastereomer.

Therefore, the XRD results inferred several interesting things. First, the diastereomeric crystals produced with molar ratios ranging from 0.7 to 6.0 were exclusively templated by L-mandelic acid, due to the stronger hydrogen bonding of L-mandelic acid with L-phenylalanine compared to D-mandelic acid [31]. Hence, the crystal structure of the diastereomer mixture was identical to that of the L-L diastereomer, with D-mandelic acid incorporated as an impurity in a solid solution. Second, at a low molar ratio of 0.4, when comparing the XRD patterns for the enantiomeric diastereomers (L-L and D-L diastereomers) and L-phenylalanine, the crystals resulting from the crystallization were a mixture of diastereomer crystals and L-phenylalanine crystals. Due to the excessive L-phenylalanine to mandelic acid, the L-phenylalanine was crystallized out at the same time as the diastereomer crystallization. This was also confirmed by photo images that revealed two distinctive crystal shapes: rod-shaped diastereomer crystals (area marked A in Fig. 4(e)) and hairy-shaped L-phenylalanine crystals (area marked B in Fig. 4(e)), as shown in Fig. 4. Moreover, this explains the high chiral selectivity (about 75%) of the resulting crystals for L-mandelic acid, even though the apparent molecular ratio of mandelic acid to L-phenylalanine in the resulting crystals was 0.5:1. Consistently, in addition, typical crystal shapes (Fig. 4(f) and (g)) obtained from the molar ratios ranging from 0.7 to 6.0 were well marched with the rod-shape crystals of L-L diastereomers (Fig. 4(c)). However, with a high excess of mandelic acid to L-phenylalanine (molar ratio of 7.0), the XRD patterns of the resulting crystals revealed a mixture of diastereomer crystals and mandelic acid crystals. Thus, due to the simultaneous crystallization of diastereomer crystals and mandelic acid, the apparent molecular ratio of mandelic acid to L-phenylalanine in the resulting crystals was as high as 1.7 and the chiral selectivity (55%) of the resulting crystals for L-mandelic acid was close to that for a racemate. In this case, the powdery crystals were produced, as shown in Fig. 4(h)).

The crystals resulting from the diastereomeric crystallization were also examined with a differential scanning calorimeter (DSC), as shown in Fig. 5. According to the thermal profile of the DSC, the melting point of L-L diastereomer crystal (185 °C) was much higher

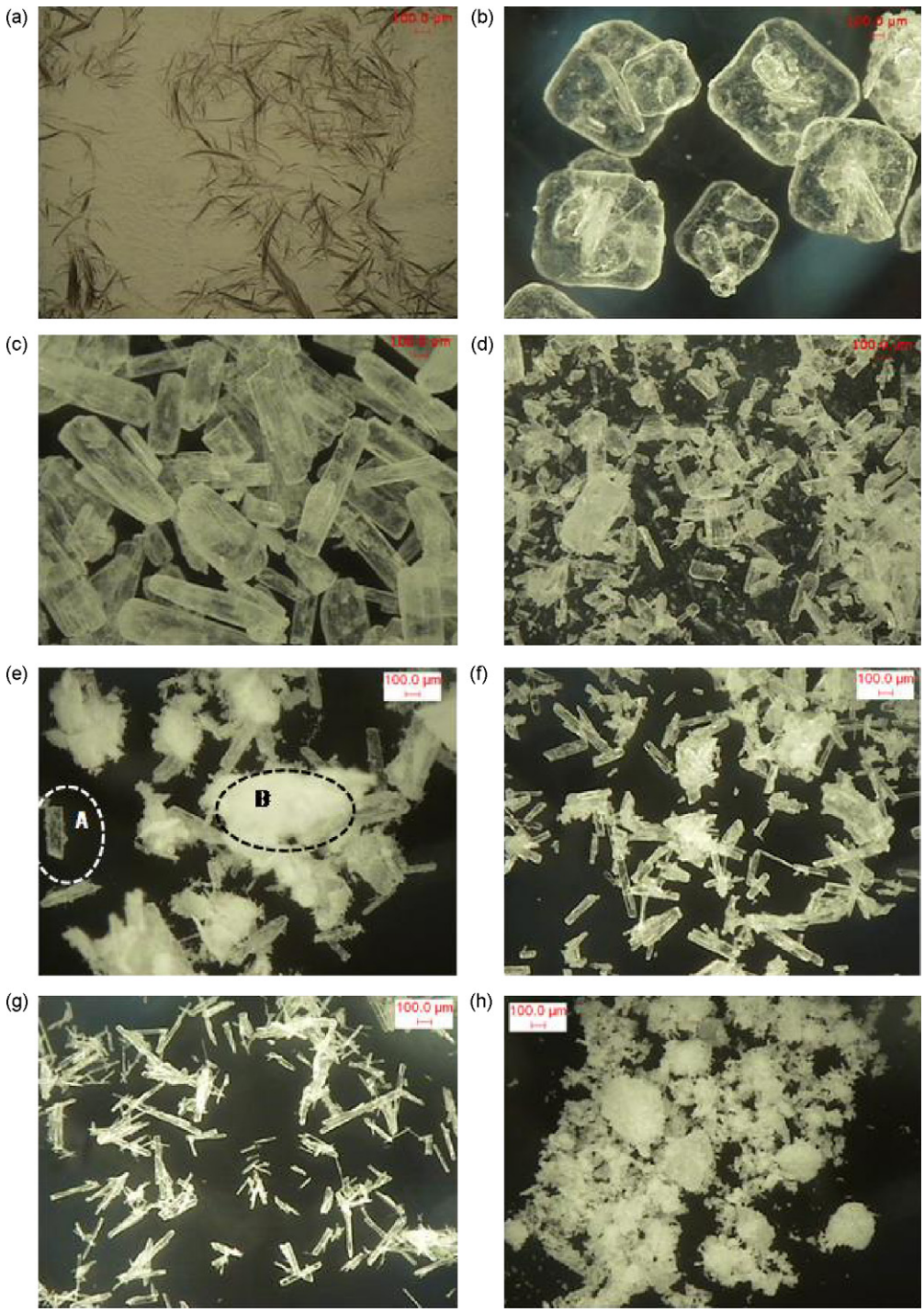


Fig. 4. Typical morphology of crystals produced by diastereomeric crystallization when varying molar ratio of mandelic acid to L-phenylalanine (R): (a) crystal of L-phenylalanine, (b) crystal of D/L-mandelic acid, (c) crystal of L-mandelic acid-L-phenylalanine diastereomer, (d) crystal of D-mandelic acid-L-phenylalanine, (e) diastereomeric crystal obtained at R = 0.4, (f) diastereomeric crystal obtained at R = 3.0, (g) diastereomeric crystal obtained at R = 6.0, and (h) diastereomeric crystal obtained at R = 7.0.

than that of D-L diastereomer crystal (160 °C), due to the stronger hydrogen bonding in L-L structure than in D-L structure [31]. For the diastereomers crystallized with various molar ratios from 0.7 to 6.0, it was interesting to note that their thermal profiles were highly similar to that for the L-L diastereomer, yet their melting points increased with the molar ratio, due to the enhanced enantiomer purity (L-mandelic acid) of the diastereomer. However, at a high molar ratio of 7.0, the thermal scan of the resulting crystals exhibited two characteristic peaks at around 118 and 169 °C. The similar DSC profile of crystals produced at the molar ratio of 8.0 was obtained. In this case, the first peak at 118 °C was due to mandelic acid in the resulting crystals, while the second peak at 169 °C was due to the diastereomers in the crystals. According to the phase diagram of mandelic acid [32], the melting point of mandelic acid was also varied with the composition and exhibited 118 °C of the mandelic acid composed of 80% of D-isomer and 20% of L-isomer which was closely matched with above two crystal purities of mandelic acid estimated from the molecular rations (1.7:1 and 3.5:1 in Fig. 1). Thus, it might be concluded that the sudden purity drop of the resulting crystals at high molar ratio was due to

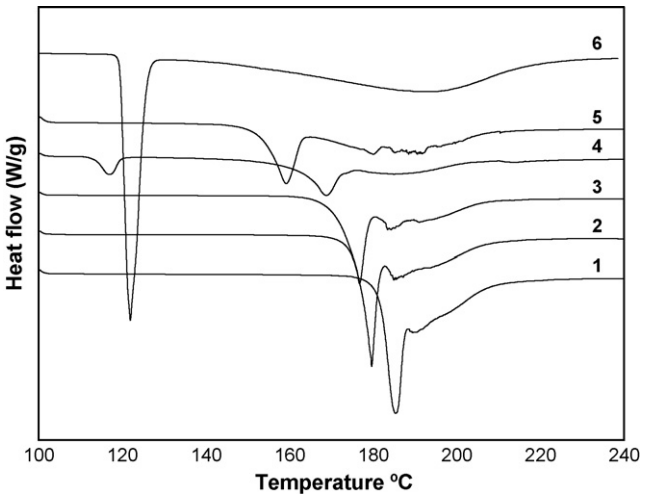


Fig. 5. Thermal analysis of crystals produced by diastereomeric crystallization when varying molar ratio of mandelic acid to L-phenylalanine (R): 1. crystal of L-mandelic acid-L-phenylalanine diastereomer, 2. diastereomeric crystal obtained at R = 6.0, 3. diastereomeric crystal obtained at R = 1.0, 4. diastereomeric crystal obtained at R = 7.0, 5. crystal of D-mandelic acid-L-phenylalanine diastereomer, and 6. crystal of D/L-mandelic acid.

the D-rich mandelic acid crystals simultaneously crystallized with diastereomer.

4. Conclusion

When investigating a suitable resolving agent for the chiral resolution of mandelic acid via diastereomeric crystallization, functional groups of amine and carboxyl in the resolving agent were found to interact preferentially with L-mandelic acid to form a diastereomer due to their stereo-configuration. In addition, the chiral selectivity of the resolving agent towards L-mandelic acid was significantly influenced by the residues of the resolving agent. Thus, after screening resolving agents with a variety of functional groups and residues, L-phenylalanine was identified as the most effective resolving agent.

When using L-phenylalanine as the resolving agent for the chiral separation of mandelic acid by diastereomeric crystallization, the enantiomeric purity of the diastereomer was significantly determined by the molar ratio of mandelic acid to the resolving agent. With molar ratios from 0.7 to 6.0, diastereomer crystals were produced and their chiral selectivity of L-mandelic acid improved up to almost 85% when increasing the molar ratio. XRD and DSC analyses also revealed that the crystal structure of the diastereomers was predominantly templated by L-mandelic acid and identical to that of L-L diastereomer. However, with a low molar ratio of 0.4, a mixture of diastereomer crystals and L-phenylalanine crystals was obtained due to the excess of the resolving agent, whereas crystallization with a high molar ratio of 7.0 resulted in a crystal mixture of diastereomer crystals and mandelic acid crystals due to the excess of mandelic acid.

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