Diastereomeric Resolution of *p*-Chloromandelic Acid with (*R*)-Phenylethylamine

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ABSTRACT The optical resolution of *p*-chloromandelic acid using (*R*)- α -phenylethylamine as resolving agent was presented. The effect of solvents, molar ratio of racemate to the resolving agent, filtration temperature as well as the amount of solvent on resolution was investigated by orthogonal experimentation. The binary melting point phase diagram and crystal structure analysis of diastereomeric salts rationalized the success of the resolution. *Chirality 22:16–23, 2010.* © 2009 Wiley-Liss, Inc.

KEY WORDS: p-chloromandelic acid; phenylethylamine; resolution; diastereomeric salt; crystal structure; binary melting point phase diagram

INTRODUCTION

Enantiopure (R)-p-chloromandelic acid (hereafter (R)-p-CIMA) is a significant chiral intermediate, and has been used to synthesize pharmaceuticals.¹ It is also an efficient resolving agent for chiral amines resolutions.^{2,3} Usually, it is the racemic *p*-chloromandelic acid (hereafter *p*-ClMA) to be obtained by regular chemical synthesis process. Enantiopure (R)-p-ClMA has to be obtained through enantioseparation. Xu and coworkers⁴ prepared (R)-p-CIMA with optical purity 99% e.e. by enantioselective degradation of racemates with a new isolate Pseudomonas putida; Yamaguchi et al.⁵ carried out the optical resolution of racemic organic acids using optically active 4-amino-2-methylbutan-1-ol as resolving agent in isopropanol solvent; Honda et al.⁶ prepared (R)-p-ClMA by optical resolution of mandelic acid derivatives with amino acid hydrazide as resolving agent in 2-propanol.

However, there are some drawbacks such as low yield and high cost of the resolving agent in the aforementioned methods. Herein, optical resolution process of *p*-ClMA with resolving agent (*R*)- α -phenylethylamine (hereafter (*R*)-PEA), which is commercially available and inexpensive, was investigated. The molecular structure of racemate and resolving agent are shown in Figure 1. Experimental results indicated that PEA was an efficient resolving agent for *p*-ClMA and the resulting pair of diastereomeric salts had significant differences in solubilities which led to an efficient resolution.

To get insight to the chiral discrimination mechanism of this resolution system, we further investigated the characteristic differences between the thermodynamic properties and crystal structures of the pair of diastereomeric salts. This approach is widely used to clarify the chiral recognition in diastereomeric salt resolution.^{7–16}

Our investigation indicated that the less soluble salt, (*R*)-PEA·(*R*)-*p*-ClMA with higher melting point and heat of © 2009 Wiley-Liss, Inc.

fusion was much more stable than the more soluble salt, (R)-PEA·(S)-p-ClMA. Examining the crystal structures reveals that the less soluble salt and more soluble salt have similar infinite hydrogen-bonding network perpendicular to *c*-axis in which ammonium cations and carboxylate anions form columnar hydrogen-bonding around a twofold screw axis. The columnar hydrogen-bondings are interlinked by other hydrogen bonds formed between carboxylate oxygens and hydroxyl hydrogens. However, the crystal packing between hydrogen-bonding layers in two salts are significantly different. The less soluble salt has very planar boundary surface among the hydrophobic layers, which is believed to enhance the salt stability by van der Waals interations and thus realize close packing mode. The more soluble salt does not possess this kind of even boundary surface. Therefore, we suggest that van der Waals interaction contribute much to the stability difference of the two salts. The results of the investigation are consistent with the chiral discrimination mechanism in resolutions of mandelic acid, p-methoxymandelic acid, pmethylmandelic acid, and 2-naphthylglycolic acid by PEA. In the latter case, the characteristics of hydrogen-bonding patterns and van der Waals interactions in a pair of diastereomeric salts play the most important role in successful resolution of primary amine and mandelic acid derivatives.14-16

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Fig. 1. Structures of (R)-p-chloromandelic acid and (R)- α -phenyl-ethylamine.

EXPERIMENTAL

p-CIMA with 99% purity was purchased from Alfa Aesar, A Johnson Matthey Company (Ward Hill, MA). PEA with optical purity of 99% ee was purchased from Sigma-Aldrich Canada (Oakville, ON) and used without further purification. Specific rotations of salts were measured by Autopol IV Digital Polarimeter Rudolph America (Hackettstown, NJ) at 589 nm, equipped with a quartz cell of 100 mm path length. Optical purity of (R)-p-CIMA was determined by Chiral HPLC using (R, R) Whelk-O2 column (250 mm \times 4.6 mm) from Regis Tech. (Morton Grove, IL). ¹H NMR spectra were recorded at 500 MHz on AVANCE DRX500 (BRUKER, US) in DMSO solution with tetramethylsilane as an internal standard. IR spectra were recorded on NICO-LET 5SXC spectrometer (NICOLET, US) by KBr pellets. The elemental analysis was performed on Elementar Vario EL (Elementar Analysensysteme, Hanau, Germany).

Optical Resolution of p-CIMA

A standard resolution process example listed as entry 3 in Table 1 is as follows:

To a solution of racemic *p*-ClMA(5.6 g, 0.03 mol) in 48mL 95% aqueous ethanol, (*R*)-PEA (3.8 mL, 0.03 mol) was added. The mixture was heated to 72°C by water bath to dissolve the solid crystals. The solution was kept at 72°C for 15 min and then slowly cooled to 15°C. After standing at 15°C for 15 min, the precipitated crystalline salt was collected by filtration and washed with cold 95% ethanol (2 × 8 mL) to afford diastereomeric salt (4.5 g), mp: 190.8– Resolution processes in other solvents are similar to the above described process.

Preparation of (R)-p-Chloromandelic Acid by Resolution

To a solution of racemic *p*-ClMA (28 g, 0.15 mol) in 180mL 95% ethanol, (*R*)-PEA (19 mL, 0.15 mol) was added. The mixture was heated to reflux for 15 min to dissolve the solid crystals and then slowly cooled to 20°C. The precipitated crystalline salt was collected by filtration to give crude diastereomeric salt (22.6 g), mp: 187.6–193.4°C, specific rotation $[\alpha]_{D}^{22} = -34.5^{\circ}$ (c = 1, C₂H₅OH).

The crude diastereomeric salt (22 g) was recrystallized from 95% ethanol (150 mL) to afford a white needle crystal salt (15.9 g). mp: 191.8–195.4°C, specific rotation $[\alpha]_D^{22} = -45.2^\circ$ ($c = 1, C_2H_5OH$).

Above salt was recrystallized in 95% ethanol (130 mL) again to give (*R*)-PEA·(*R*)-*p*-ClMA (12.6 g), mp: 193.8–195.4°C, specific rotation $[\alpha]_{\rm D}^{22} = -48.5^{\circ}$ (c = 1, C_2H_5OH). The salt was verified by NMR, IR, as well as elemental analysis, and the analytical data are presented as follows:

¹H NMR(500 MHz, DMSO) δ: 1.408(d, 3H, CH₃), 4.291(m, 1H, CHNH₂), 4.531(s, 1H, CHOH), 7.272–7.439 (m, 9H, Ph + PhCl); IR (KBr) ν(cm⁻¹): 3301, 3036, 2535, 1610, 1576, 1531, 1383, 1193, 1072, 776, 705, 553, 478, 446; Element analysis: Calcd for C₁₆H₁₈NO₃Cl (FW307.77) C: 62.40, H: 5.85, N: 4.55; Found C: 62.71, H: 6.26, N: 4.48.

The above (*R*)-PEA·(*R*)-*p*-CIMA salt (12 g, 0.039 mol) was dissolved in H₂O (80 mL), and the resulting solution was acidified with hydrochloric acid (2 N, 0.045 mol) to pH = 1. The liberated acid was extracted by ethyl acetate three times (30 mL, 20 mL, and 20 mL, respectively). The combined extract was dried over Na₂SO₄. Upon removal of solvent under reduced pressure, (*R*)-*p*-CIMA was obtained as white solid (7.0 g, 50% yield based on (*R*)-*p*-

TABLE 1. The effect of solvent on resolution

Entry	Solvent	Diasteromeric salt (R)-PEA·(R)- p -ClMA					
		Yield %	Melting point/°C	Specific rotation/ $^{\circ}$	Diastereomeric purity d.p./%	Resolution efficiency %	
1	Water ^a	114	184.9	24.6	50.7	57.8	
2	Methanol ^a	64.9	192.1	38.2	79.1	51.3	
3	95% Ethanol ^a	97.4	190.8	34.3	71.1	69.3	
4	Ethanol ^a	96.3	190.3	33.7	69.8	67.2	
5	Propanol ^a	98.5	191.2	33.1	68.7	67.7	
6	2-Propanol ^b	112.6	188.0	28.3	58.7	66.1	
7	Ethyl acetate ^b	159.0	174.9	8.72	17.8	28.3	
8	Butyl actate ^b	136.0	179.6	18.2	37.8	51.4	
9	Toluene ^b	152.6	170.8	7.4	14.8	23.4	
10	Chloroform ^b	174.3	164.0	-0.7	1.5	2.6	

 ^{a}p -ClMA = 0.03 mol, (*R*)-PEA = 0.03 mol, solvent = 48 ml.

 ^{b}p -ClMA = 0.03 mol, (*R*)-PEA = 0.03 mol, solvent = 68 ml.

Filtration temperature: 15°C; yield is calculated based on a half amount of *p*-ClMA; diastereomeric purity is the ratio of specific rotation of obtained salt from resolution to the specific rotation of enantiopure diastereomeric salt; the specific rotation of pure (*R*)-PEA·(*R*)-*p*-ClMA is 48.5° (c = 1, 95% ethanol); Resolution efficiency *S* is the product of yield and optical purity.

 TABLE 2. Orthogonal experiment design

Entry	p-ClMA: (R)-PEA	Filtration temperature/°C	95% ethanol/mL
1	1	25	48
2	1	20	36
3	1	15	42
4	0.85	25	36
5	0.85	20	42
6	0.85	15	48
7	0.7	25	42
8	0.7	20	48
9	0.7	15	36

ClMA in starting racemate), mp: 118.5–121.2°C; specific rotation $[\alpha]_D^{22} = -133.3^\circ$ (c = 0.3, C_2H_5OH). The enantiomeric purity of (R)-p-ClMA was determined to be 99% *ee* by HPLC analysis on chiral column (Regis (R, R)-Whelk-O2). The mobile phase was H₂O/CH₃OH (70/30) with 0.1% acetic acid and flow rate was 0.8 mL/min under detection wavelength of 225 nm.

Binary Phase Diagram of Diastereomeric Salts

The preparation of pure salts (*R*)-PEA·(*R*)-*p*-ClMA and (*R*)-PEA·(*S*)-*p*-ClMA has been introduced in our previous work focused on single X-ray crystallographic analysis.^{17,18}

A weighed amount of pure (R)-PEA·(R)-p-ClMA and (R)- $PEA \cdot (S)$ -p-ClMA were mixed and crushed in a mortar to obtain a uniform mixture with different diastereomeric composition. The resolution of the electronic balance was 0.00001 g. The binary melting point phase diagram was developed using Mettler Toledo DSC 822e differential scanning calorimeter (Greifensee, Switzerland) by measuring the temperature at the beginning and the end of fusion of diastereomeric salt mixture. The samples (3-12 mg) were prepared in a covered aluminum crucible having pierced lids to allow the escape of volatiles. The sensors and samples were under nitrogen purge of flow rate of 50 ml/min during the experiments. The temperature calibration was carried out using melting point of highly pure indium in a medium temperature range. Heating rates of 3, 5, 10°C/min were used. The heating rate did not affect the results. The heating rate of 5°C/min was used.

RESULTS AND DISCUSSION Solvent Screening and Resolution Condition Determination

Attempted experiment proved that (R)-PEA was able to resolve the *p*-ClMA. Because solvent plays an important role in resolution process, screening suitable solvents is of importance. In this work, the resolution of *p*-CIMA by (*R*)-PEA was performed respectively in water, ethyl acetate, alcohols, and other solvents as shown in Table 1. Diastereomeric separations took place in all the cases. However, the resolution efficiency varied significantly in different solvents. The resolution results were evaluated by resolution efficiency S, which was calculated as the product of yield and diastereomeric purity of diastereomeric salts obtained. Experimental results indicated that the diastereomeric purity of salts was high in several alcohol solvents but quite low in chloroform and toluene. Taking the resolution efficiency as well as the cost and toxicity of the solvents into consideration, 95% aqueous ethanol was chosen as the most suitable solvent.

Once the optimum choice of solvent was made, the other factors affecting the resolution process including molar ratio of *p*-ClMA to (*R*)-PEA, the amount of 95% ethanol solvent, and filtration temperature were investigated. To reduce the experimental work, the three-factor and three-level factorial experimental design, 2^3 , shown in Table 2 was used. The experimental results are summarized in Table 3. In the optical resolution via diastereomeric salts formation, with the increase of diastereomeric salts yield, the diastereomeric purity of diasteromeric salts usually decreases. The comparison between entry 2 and 5 in Table 3 shows that when the yield decreased from 101.9% to 80.2%, the diastereomeric purity increased slightly only from 70.5% to 71.8%. In addition, reduction in the amount of solvent and decrease in the temperature increased the yield of salt. The lower the ratio of p-ClMA to (R)-PEA resulted in lower yield and higher diastereomeric purity. Therefore, according to the results of factorial experiments, the optimal resolution conditions were determined as follows: the ratio of p-ClMA to PEA was 1.0, the filtration temperature of 20°C and the amount of solvent was 120 ml 95% ethanol/0.1mol p-ClMA. Furthermore, the resolution was performed under this optimal condition. The diastereomeric salt was recrystallized twice in 95% ethanol

TABLE 3. Resolution results in various conditions

Entry	Diasteromeric salt (R)-PEA·(R)- p -CIMA							
	Quantity/g	Yield/%	Melting point/°C	Specific rotation/ $^{\circ}$	Diastereomeric purity <i>d.p.</i> /%	Resolution efficiency %		
1	4.3	93.2	191.1	34.0	70.5	65.7		
2	4.7	101.9	190.6	34.0	70.5	71.8		
3	4.3	93.2	190.8	33.2	68.9	64.2		
4	3.9	84.6	188.5	33.5	69.5	69.1		
5	3.7	80.2	191.6	34.6	71.8	67.8		
6	3.9	84.6	191.6	34.6	71.8	71.4		
7	2.8	60.7	192.1	37.1	77.0	46.7		
8	3.5	73.8	191.3	36.4	75.5	55.7		
9	3.3	71.5	189.6	35.1	72.8	52.1		

p-ClMA = 0.03 mol in all cases.

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TABLE 4. Thermodynamic properties of diastereomeric salts

Diastereomeric salt	Melting point/°C	Heat of fusion/Jg $^{-1}$	Solubility ^a /g
(R)-PEA (R)-p-CIMA (less)	$194.60 \\ 141.76$	223.73	2.0
(R)-PEA (S)-p-CIMA (more)		105.41	18.2

^aWeight (g) of the solute dissolved in 100 g of 95% ethanol at 22°C.

and high purity (*R*)-PEA·(*R*)-*p*-CIMA was obtained. The (*R*)-*p*-CIMA was liberated from the diastereomeric salt to give white powder solid with optical purity of 99% *ee* and yield of 50%. Detailed description is presented in experimental section 2.2.

Thermodynamic Properties of Diastereoemric Salts

The above efficient resolution is presumed to be due to the large difference in physicochemical properties of the pair of diastereomeric salts, (R)-PEA·(R)-p-CIMA and (R)- $PEA \cdot (S) - p$ -CIMA. It is mostly common that efficient separation can be expected when the difference of melting point of diastereomeric salt is larger than 20°C, and the trend of solubilities difference between distereomeric salts parallels that of difference in melting point and heat of fusion.^{19,20} Table 4 lists some of the physical properties of (R)-PEA·(R)-p-ClMA and (R)-PEA·(S)-p-ClMA. As shown in Table 4, the conditions for efficient resolution are fulfilled in this system. The melting point of less soluble salt exceeds that of the corresponding more soluble salt by 54°C. The solubility ratio of more soluble salt to less soluble salt is 9.1, which is very large. It is strongly suggested that the less soluble salt is thermodynamically more stable than the corresponding more soluble salt. Consequently, such large stability difference leads to an efficient resolution.

Furthermore, we established the binary melting point phase diagram of diastereomeric salts. In general, diaster-



Fig. 2. Binary melting point phase diagram of diastereomeric salts. The solid curves represent calculated values based on Schröder-van Laar equation; Circle and diamond represent the temperatures of the beginning and the end of fusion. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

eomeric-salt mixtures are classified into three types: a eutectic conglomerate, a 1:1 addition compound, and a solid solution.²¹ The type of diastereomeric salt mixture can be identified on the basis of the binary melting point phase diagram. The formation of eutectic conglomerate is the primary condition for resolution. Figure 2 shows binary melting point phase diagrams for a mixture of (R)- $PEA \cdot (R) - p$ -CIMA and $(R) - PEA \cdot (S) - p$ -CIMA constructed by detailed DSC analysis of mixture with different composition of $X_{\rm R}$, which is the molar fraction of less soluble salt (R)-PEA·(R)-p-ClMA. The system was a eutectic mixture, and the eutectic composition $X_{\rm e}$ was 0.1 from experimental results, which was in good agreement with the $X_{\rm e}$ of 0.09 calculated theoretically from thermodynamic Schröder-van Laar equation.²¹ The fact that the system is a eutectic mix-ture indicates that the resolution efficiency primarily depends on the difference in stability between the less and more soluble salts.

For a better interpretation of stability difference between disatereomeric salts, we then focused on the crystal structures of the less and more soluble salts to find which property of the diastereomeric salt crystal is correlated to the difference in stability.

Crystal Structures of Diastereomeric Salts

Fortunately, both well-formed single crystals of less and more soluble salts were obtained for X-ray crystallographic analysis although the single crystal of (R)-PEA·(S)-p-CIMA was not easy to prepare due to its high solubility. Crystals of (R)-PEA·(R)-p-CIMA are colorless rod crystallized in orthorhombic P2₁2₁2₁ space group and unit cell contains four (R)-p-ClMA anion and (R)-PEA cation. Crystals of (R)- $PEA \cdot (S)$ -p-ClMA are colorless plate crystallized in monoclinic $P2_1$ space group and unit cell contains two (S)-p-CIMA anion and (R)-PEA cation. Detailed crystal data have been reported in authors' previous work.17,18 It is generally believed that pattern of hydrogen-bonding and crystal packing mode account the chiral discrimination.^{8,12,13,15,16} Therefore, special attention was paid to the characteristics of hydrogen-bonding network in the crystal structures.

In the crystal of less soluble salt, the typical packing structure were acid–base salt structure containing (R)-p-ClMA anions and the (R)-PEA cations, supported by electrostatic interaction, hydrogen-bonding, and van der Waals interactions. All the hydrogen bonds are listed in Table 5.

TABLE 5. Hydrogen-bonding geometry of (R)-PEA·(R)-p-CIMA [Å and °]

D-Н…А	d(D-H)	d(H…A)	d(D…A)	<(DHA)
D9-H9A…O11 ^a N13-H13A…O12 N13-H13B…O11 ^b N13-H13C…O12 ^c	0.82 0.89 0.89 0.89	2.09 2.00 1.99 2.04	2.848 (2) 2.863 (2) 2.869 (3) 2.878 (3)	154 157 167 156

Symmetry transformations used to generate equivalent atoms:

 $x^{a}x - 1/2, -y, +5/2, -z.$

 ${}^{\mathrm{b}}x - 1/2, -y + 3/2, -z.$

 $c_x + 1/2, -y + 3/2, -z.$

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Fig. 3. Atomic-numbering molecule schemes. The dashed lines represent the hydrogen bond. (a) less solule salt (*R*)-PEA·*R*-(*p*)-CIMA; (b) more soluble salt (*R*)-PEA·(*S*)-*p*-CIMA. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

The atomic-numbering schemes are graphically illustrated in Figure 3a. The ammonium hydrogen formed three hydrogen bonds, namely N13-H13A-O12, N13-H13B-O11(ii), and N13-H13C-O12(iii) with carboxylate oxygens of adjacent (R)-p-ClMA. Thus, a columnar hydrogen-bonding network was formed around a twofold screw axis by ammonium hydrogens and carboxylate oxygens. Schematic illustration of 2_1 column structure is shown in Figure 4. Additionally, there was another hydrogen bond O9-H9A-O11(i) between hydroxy hydrogen of (R)-p-ClMA and carboxylate oxygen of another (R)-p-ClMA which interlinked the neighboring 2_1 columns. These hydrogen bonds formed 2-dimentional network perpendicular to c-axis, extending infinitely. This characteristic 2-dimentional hydrogen-bonding network was commonly observed in other salts of primary amine and mandelic acid derivatives investigated by Kinbara et al.^{15,16} who proposed that for a successful resolution, it was necessary to form this kind of hydrogen-bonding layer, consisting of stable 21 columns and having planar boundary surfaces in the less soluble salts crystals. The crystals with this kind of hydrogenbonding structure are considered to be stabilized from the viewpoint of both their hydrogen-bonding and van der Waals interactions. Crystal structure of (R)-PEA·(R)-p-CIMA has these two features shown in Figure 5. 2_1 column hydrogen bonds along a-axis were formed between carboxylate oxygens and ammonium hydrogens. Neigh-Chirality DOI 10.1002/chir



Fig. 4. Schematic illustration of 2_1 column hydrogen-bonding pattern. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]



Fig. 5. Crystal structure of less soluble salt. (a) viewed from *c*-axis; (b) viewed from *a*-axis; (c) viewed from *b*-axis. The dashed lines represent hydrogen bonds. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

boring 2_1 columns were interlinked by hydrogen bond between the hydroxy hydrogen of one (*R*)-*p*-ClMA molecule and the carboxylate oxygen of another (*R*)-*p*-ClMA molecule. Viewed from *a*-axis and *b*-axis directions, this hydrogen-bonding layer had planar boundary surfaces as shown in Figures 5b and 5c, respectively, which could be efficiently stabilized by van der Waals interactions between layers. As a consequence, close packing was realized in this crystal, which was believed to be important to the stability of the solid salt. In the crystal of more soluble salt, there were more complicated hydrogen bonds as listed in Table 6. The atomic-numbering schemes are graphically illustrated in Figure 3b. The ammonium hydrogen formed three hydrogen bonds, namely N13-H13A-O12(ii), N13-H13B-O11, and N13-H13C-O12(iii) with carboxylate oxygens of adjacent (*S*)-*p*-CIMA. Additionally, there are hydrogen of (*S*)-*p*-CIMA and carboxylate oxygen of another (*S*)-*p*-CIMA as well as O9-H9A-O9(i) between hydroxy hydrogen of (*S*)-*p*-CIMA and hydroxy oxygen of another (*S*)-*p*-CIMA. All these



Fig. 6. Crystal structure of more soluble salt. (a) Viewed from *c*-axis; (b) viewed from *a*-axis; (c) viewed from *b*-axis. The dashed lines represent hydrogen bonds. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

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D-H…A	d(D-H)	d(H…A)	d(DA)	<(DHA)
09-H9A…O9 ^a	0.84	2.26	2.939 (2)	139
O9-H9A…O11 ^a	0.84	2.09	2.826 (2)	146
N13-H13A…O12 ^b	0.91	1.89	2.798 (2)	172
N13-H13B…O11	0.91	1.83	2.731 (2)	169
N13-H13C…O12 ^c	0.91	1.88	2.779 (2)	171

 TABLE 6. Hydrogen-bonding geometry of (R)-PEA (S)-p-CIMA [Å and °]

Symmetry transformations used to generate equivalent atoms: $a^{-}x + 1$, y + 1/2, -z + 1.

$$^{\rm D}x, y - 1, z.$$

 $^{c}-x+2, -y-1/2, -z+1.$

hydrogen bonds also formed an infinite 2-dimentional network perpendicular to *c*-axis as shown in Figure 6. The pattern of this hydrogen-bonding network was different from the one in the corresponding less soluble salt. Although similar 2_1 column structures were also observed as shown in Figure 6a, but interlinks between 21 columns were different. Except the hydrogen-bonding between hydroxy hydrogen and carboxylate oxygen, there were zig-zag hydrogen-bonding lines formed between hydroxy hydrogens and hydroxy oxygens. It is noteworthy that the hydrogen acceptor was hydroxy oxygens in this hydrogen bond, which were less favorable than carboxylate oxygens. This fact was not in accordance with the rule of hydrogen bonding proposed by Etter²² that the best hydrogen donor will form a hydrogen bond with the best hydrogen acceptor. The intermolecular distance between O...O in this hydrogen bond (2.939 Å) was longer than O-O distance (2.825 Å) between hydroxy hydrogen and carboxylate oxygen and N…O distance (average 2.769 Å) between ammonium hydrogen and carboxylate oxygen. These observations are strong indication that this kind of hydrogen-bond is weaker than other hydrogen bonds. On the other hand, the boundary surfaces of the layer shown in Figures 6b and 6c seemed not as planar as those in the less soluble salt. The substituent on the phenyl ring projected out of the layer and made the boundary surface not even. So, close packing of the layers is not as efficient as that in the less soluble salt from the viewpoint of van der Waals interactions between the layers.

These comparisons of the crystal structures of diastereomeric salts indicate the less-soluble salt are much more stable than the corresponding more soluble salt, resulting in its preferential precipitation upon resolution. The characteristics hydrogen-bonding network in this system coincides with hydrogen-bonding pattern existed in other successful resolutions of mandelic acid derivatives with phenylethylamine. This study adds further supports to the chiral discrimination mechanism proposed by Kinbara et al.^{13,15} that formation of hydrogen-bonding network containing both 2_1 column and planar boundary surfaces services the stability of diastereomeric salt and is necessary for the efficient resolution.

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CONCLUSIONS

p-Chloromandelic acid was resolved by (R)- α -phenylethylamine via diastereomeric salt formation. The suitable resolution conditions were determined. This successful resolution was realized by significant stabilities difference between the less and more soluble salts. The 2₁ column hydrogen-bonding network and van der Waals interactions between planar boundary surface in the less soluble (R)-PEA·(R)-*p*-CIMA crystal, commonly found in less soluble salts of PEA and other mandelic acid derivatives reported in literature,^{15,16} is believed to dramatically stabilize the less soluble salt. Thermodynamic and crystal structure studies in this article provide a good interpretation to chiral discrimination mechanism in *p*-CIMA and (R)-PEA resolution system.

LITERATURE CITED

- Adams AD, Jones AB, Berger JP. Preparation of 2-aryloxy-2-arylalkanoic acids for diabetes and lipid disorders. WO2002064094, 2002.
- Klaus D, Wolfgang S. Optically active amines and their production. WO200138292, 2001.
- Deng JG, Wu TF, Cui X, Chen YC, Jiang YZ. Process for preparing optical-purity Fluoxetine. CN1294120A, 2001.
- Huang HR, Xu JH, Xu Y. Preparation of (S)-mandelic acids by enantioselective degradation of racemates with a new isolates Pseudomonas Putida ECU1009. Tetrahedron Asymmetry 2005;16:2113–2117.
- Yamaguchi Y, Hamanaka K, Shibuya N. Optical resolution of racemic organic acids using optically active 4-amino-2-methylbutan-1-ol. JP2002030032, 2002.
- Honda Y, Nakamura M, Yugawa T. Optical resolution of mandelic acid derivative. JP1221345, 1989.
- Liao L, Peng XH, Zhang JH, Yu KB, Cui X, Zhu J, Deng JG. Facile resolution of racemic terbutaline and a study of molecular recognition through chiral supramolecules based on enantiodifferentiating selfassembly. Org Biomol Chem 2003;1:1080–1085.
- Marchini N, Bombieri G, Artali R, Bolchi C, Pallavicini M, Valoti E. Influence of (S)-1-phenylethylamine *para* substitution on the resolution of (+/-)-1,4-benzodioxane-2-carboxylic acid: a crystallographic, theoretical and morphologic approach. Tetrahedron Asymmetry 2005;16:2099–2106.
- Yoshioka R, Hiramatsu H, Okamura K, Tsujioka I, Yamada S. Crystal structure-solubility relationships in optical resolution by diastereomeric salt formation of DL-phenylglycine with (1S)-(+)-camphor-10-sulfonic acid. J Chem Soc Perkin Trans 2 2000;10:2121–2128.
- Langkilde A, Oddershede J, Larsen S. Diastereomeric salts of lactic acid and 1-phenyl-ethylamine, their structures & relative stabilities. Acta Crystallogr Sect B 2002;58:1044–1050.
- 11. Saigo K, Kobayashi Y. The role of CH/π interaction in the stabilization of less-soluble diastereomeric salt crystals. Chem Rec 2007;7:47–56.
- Kobayashi Y, Hiroaki H, JIN M, Saigo K. Factors determining the pattern of a hydrogen-bonding network in the diastereomeric salts of 1-arylethylamines with enantiopure P-chiral acids. Chirality 2008;20: 577–584.
- Kinbara K, Kobayashi Y, Saigo K. Systematic study of chiral discrimination upon crystallisation. Part 2. Chiral discrimination of 2-arylalkanoic acids by (1R, 2S)-2-amino-1, 2-diphenylethanol. J Chem Soc Perkin Trans 2 1998;8:1767–1775.
- Kinbara K, Harada Y, Saigo K. A high-performance, tailor-made resolving agent: remarkable enhancement of resolution ability by introducing a naphthyl group into the fundamental skeleton. J Chem Soc Perkin Trans 2 2000;7:1339–1347.
- 15. Kinbara K, Sakai K, Hashimoto Y, Nohira H, Saigo K. Chiral discrimination upon crystallization of the diastereomeric salts of 1-arylethylamines with mandelic or p-methoxymandelic acid: interpretation of

the resolution efficiencies on the basis of the crystal structures. J Chem Soc Perkin Trans 2 1996;12:2615–2622.

- Kinbara K, Harada Y, Saigo K. 2-Naphthylglycolic acid: a tailored resolving agent for p-substituted 1-arylethylamines. Tetrahedron Asymmetry 1998;9:2219–2222.
- He Q, Jennings M, Rohani S, Zhu J, Gomaa H. (R)-Phenylethylammonium (S)-4-chloromandelate. Acta Crystallogr Sect E 2008;64: 0559.
- He Q, Jennings M, Rohani S, Zhu J, Gomaa H. (R)-Phenylethylammonium (R)-4-chloromandelate. Acta Crystallogr Sect E 2007;63: 04199.
- Bolchi C, Pallavicini M, Fumagalli L. Highly efficient resolutions of 1, 4-benzodioxane-2-carboxylic acid with para substituted 1-phenylethylamines. Tetrahedron Asymmetry 2005;16:1639–1643.
- Leusen FJJ, Noordik JH, Karfunkel HR. Tetrahedron. Racemate resolution via crystallization of diastereomeric salts: thermodynamic considerations and molecular mechanics calculations. Tetrahedron 1993; 49:5377–5396.
- Jacques J, Collet A, Wilen SH. Enantiomers, racemates and resolutions. New York: Wiley; 1981.
- Etter MC. Encoding and decoding hydrogen-bond patterns of organic compounds. Acc Chem Res 1990;23:120–126.