Resolution of Sertraline with *(R)*-Mandelic Acid: Chiral Discrimination Mechanism Study

QUAN HE, SOHRAB ROHANI,* JESSE ZHU, AND HASSAN GOMAA

Department of Chemical and Biochemical Engineering, The University of Western Ontario, London, Ontario, Canada

ABSTRACT The chiral discrimination mechanism in the resolution of sertraline with mandelic acid was investigated by examining the weak intermolecular interactions (such as hydrogen bond, CH/π, and van der Waals interactions) and molecular packing difference in crystal structures of the resulting diastereomeric salts. A new one-dimensional chain-like hydrogen-bonding network and unique supramolecular packing mode are disclosed. The investigation demonstrated that stable hydrogen-bonding pattern, herringbone-like arrangement of aromatic rings, and planar boundary surface in the hydrophobic region are the three most important structural characteristics expected in less soluble diastereomeric salts. The existence and magnitude of hydrogen bond, CH/π interaction, and van der Waals interaction related to three characteristic structures, determine the stability of diastereomeric salt. The hydrogen bond is not necessarily the dominant factor while the synergy and optimization of all weak intermolecular interactions attribute to the chiral recognition. *Chirality 24:119–128, 2012.*

KEY WORDS: sertraline; mandelic acid; crystallization resolution; diastereomeric salt; chiral discrimination; chiral recognition; hydrogen bond; CH/π interaction; crystal packing

INTRODUCTION

There is a growing demand for enantiopure drugs in the pharmaceutical industry as a pair of enantiomers of racemate can present different biological effect.[1] Crystallization resolution via diastereomeric salt formation continues to be one of the most efficient and practical techniques to produce enantiopure drugs on an industrial scale. Statistical data demonstrates that more than half of the chiral drugs in the current pharmaceutical market are produced by this method.[2]

The method of diastereomeric resolution involves an enantiopure resolving agent that reacts with the racemate to form a pair of diastereomeric salts. The solubility difference between the pair of resulting salts allows an efficient enantioseparation by crystallization of the less soluble salt. After removal/recovery of the resolving agent, the desired enantiomer can be isolated. Development of an efficient diastereomeric resolution relies heavily on the selection of a suitable resolving agent. However, the general understanding of chiral recognition ability of a resolving agent is very limited. The selection of resolving agent for a given racemate is still based on an experimental trial and error procedure.

For the past several decades, numerous efforts have been made to understand the chiral discrimination mechanism and thus to develop a quick and rational way to screen optimal resolving agent for a target racemate. Some researchers[3–5] proposed a methodology to choose resolving agents based on thermal analysis of the diastereomeric salts. If the pair of diastereomeric salts formed with a certain resolving agent exhibited large difference in melting point and heat of fusion, the resolving agent would be a good candidate. However, the method needs a number of experiments to collect basic physicochemical data, before applying them to the target resolution. In addition, the method requires pure enantiomers which limit its application. Leusen[6,7] and Price[8,9] quantitatively correlated the resolution efficiency to the lattice energy difference between resulting diastereomeric salts. The optimal resolving agent was screened and designed based on computationally predicting the crystal structure of diastereomeric salt pairs and calculating the lattice energy difference between a pair of diastereomeric salts. However, the prediction of crystal structure of salts is very challenging in that the smallest asymmetric unit in a salt crystal contains two crystallographically independent ions resulting in significant increase in the number of possible packing arrangements. Furthermore, it is not easy to accurately calculate the lattice energies as the predicted energy difference is particularly sensitive to the balance between the intramolecular and intermolecular forces since the ions are very flexible in three-dimensional orientation. Therefore, the method is applicable in very limited systems.

A promising method to study chiral discrimination mechanism and further provide the criteria for resolving agent selection is to experimentally obtain crystal structure of diastereomeric salts followed by qualitative analysis of the difference in weak intermolecular interactions of their crystal structures. The method is widely employed by many researchers and a number of successful resolutions were developed using resolving agent selected on the basis of the method.[10–15]

In this method, the efficiency of resolution depends on the solubility difference between the pair of diastereomeric salts formed between racemate and the resolving agent. This solubility difference is related to the stability difference of salts and stability of salts originates from their crystal structures.

Additional Supporting Information may be found in the online version of this article.

Contract grant sponsor: NSERC.

*Correspondence to: Sohrab Rohani; Department of Chemical and Biochemical Engineering, The University of Western Ontario, London, Ontario, N6G 4R3, Canada. E-mail: srohani@uwo.ca

Received for publication 27 September 2010; Accepted 10 August 2011
DOI: 10.1002/chir.21033
Published online 16 December 2011 in Wiley Online Library (wileyonlinelibrary.com).

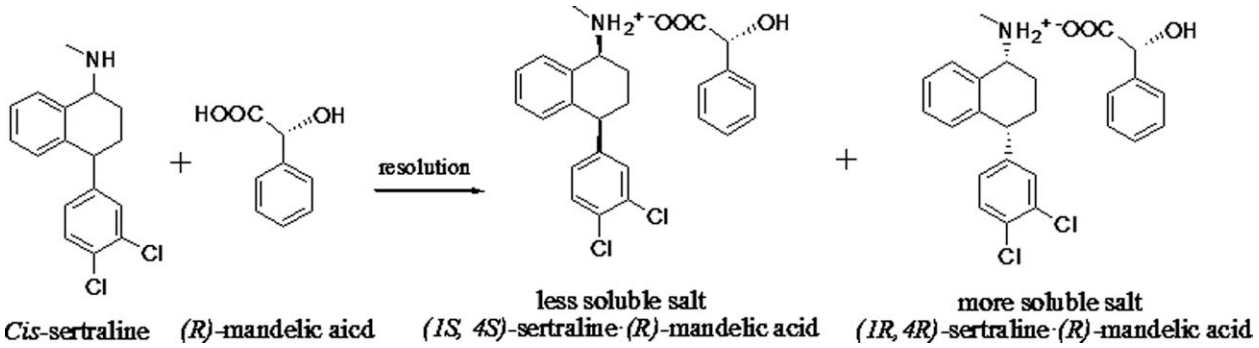

Fig. 1. Resolution of sertraline with (*R*)-mandelic acid.

The arrangement and packing of molecules in a crystal lattice, depends on numerous weak intermolecular forces such as hydrogen bonds, CH/π interactions, and van der Waals interactions. Therefore, the stability difference between the less and more soluble diastereomeric salts depends on the existence and/or magnitude of these intermolecular interactions in the crystals. By examining these weak intermolecular interactions as well as supramolecular assembly mode in diastereomeric salts, dominant interactions and characteristic packing features that favor the stability of distereomeric salts will be identified.

The hydrogen-bonding network has been considered to be the most important factor contributing to the chiral discrimination since the hydrogen bond is stronger than other intermolecular interactions to determine the stability of crystal structure. The hydrogen-bonding patterns in less and more soluble diastereomeric salts are usually different. Hydrogen-bonding networks of less soluble salts in the high efficiency resolutions have certain characteristics in common. Some characteristic hydrogen-bonding patterns such as 2_1 column,[10,16,17] closed globular cluster,[18,19] and two-dimensional (2D) sheet[20,21] have been identified to be able to stabilize the less soluble salt leading to the success of resolution. The existence of hydroxy group in resolving agent is believed to cause formation of additional hydrogen bonds to link the 2_1 hydrogen-bonding columns, thus leading to a reinforced hydrogen-bonding network.[10,11]

The molecular lengths of racemate and resolving agent have been identified to be another significant factor to the chiral recognition. It is generally believed that the same or close molecular lengths of racemate and resolving agent is favorable to form planar boundary surface of hydrophobic layers. The planar boundary surface is beneficial to realize the tight packing of molecules in terms of enhancing the van der Waals interactions.[10,12,22,23]

Recently, CH/π interaction that was conventionally believed to be very weak[24,25] has raised much attention.[11,26–29] Improved resolution efficiency was achieved by intentionally introducing the CH/π interaction sites such as naphthyl groups that enhanced the interaction.[11,26,27] In our previous work,[30] it was demonstrated that CH/π interaction could become the dominant interaction in chiral recognition of 4-chloromandleic acid/3-chloromandelic acid by (*R*)-phenylethylamine since the hydrogen-bonding patterns were almost identical in less and more soluble salts.

Although, up to now, there is no general agreement on dominant factors accounting for the stability of diastereomeric salts, it is widely accepted that the hydrogen-bonding network, stacking pattern of aromatic groups, planar hydrophobic boundary surface, and similar molecular length factors are important structural features. The chiral discrimination is largely dependent on the existence and magnitude of intermolecular interactions related to these structural characteristics.

Sertraline is an antidepressant of the selective serotonin reuptake inhibitor class which was introduced to the market by Pfizer in 1991. In 2007, it was the most prescribed antidepressant on the U.S. retail market, with 29,652,000 prescriptions.[31] Its chemical name is (*1S, 4S*)-4-(3, 4-dichlorophenyl)-1, 2, 3, 4-tetrahydro-N-methyl-1-naphthaleneamine. There are a number of approaches reported for the synthesis of enantiomer sertraline. Most of them involve introducing the chirality to sertraline by the resolution of racemate *cis*-sertraline with (*R*)-mandelic acid as the resolving agent in methanol and ethanol.[32,33] The resolution efficiency can reach 82%, which is extremely high compared with other industrial scale resolution processes. Therefore, it is a good example to investigate the chiral discrimination mechanism.

In this work, to reveal the excellent chiral discrimination ability of (*R*)-mandelic acid in the case of sertraline, we synthesized the corresponding pair of diastereomeric salts, namely, less soluble salt (*1S,4S*)-sertraline·(*R*)-mandelic acid (hereafter (*1S,4S*)-sertraline·(*R*)-MA) and more soluble salt (*1S,4S*)-sertraline·(*S*)-mandelic acid (hereafter (*1S,4S*)-sertraline·(*S*)-MA). (*1S,4S*)-Sertraline·(*S*)-mandelic acid is the enantiomer of the more soluble salt (*1R,4R*)-sertraline·(*R*)-mandelic acid, which has the same properties as it. The thermal properties such as melting point, enthalpy of fusion, and solubility of these salts were measured. The crystal structure of diastereomeric salts was determined by an X-ray crystallographic analysis and structural characteristics and weak intermolecular interaction of less soluble salt were systematically examined. The chiral discrimination was well interpreted in terms of the contribution of various intermolecular interactions on the stability of the less soluble salt. The resolution of sertraline with (*R*)-MA is illustrated in Figure 1.

TABLE 1. Thermal properties of diastereomeric salts

Diastereomeric salt	Melting point (C)	Heat of fusion (kJ mol^{-1})	Solubility[a] (g/100 mL)
Less soluble salt	191.7	65.6	0.42
More soluble salt	87.3	48.3	3.61

[a]All data in table 1 are a average value of triple measurements; solubility was measured in ethanol at room temperature 23 C.

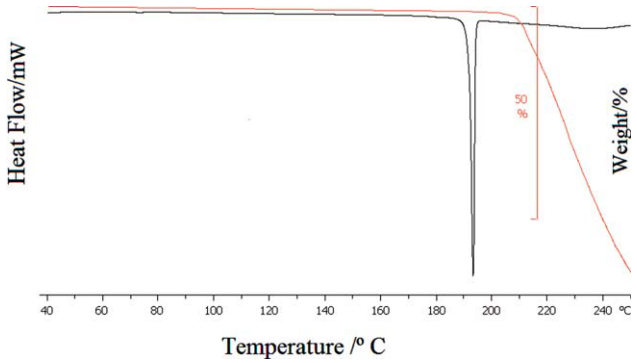

Fig. 2. The DSC and TGA curves of less soluble salt. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

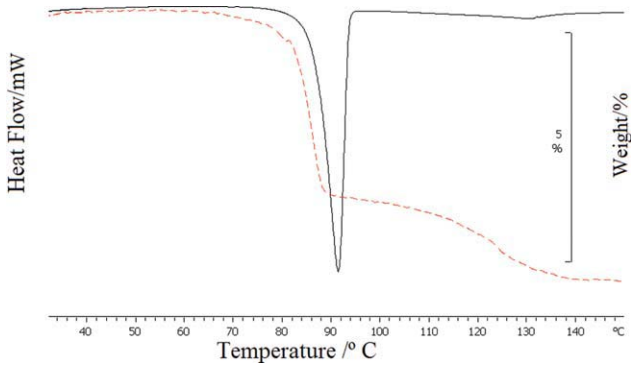

Fig. 3. The DSC and TGA curves of more soluble salt. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

EXPERIMENTAL

Materials

Sertraline enantiomer and sertraline racemate hydrochloride salts were donated by Apotex PharmaChem (Canada). (*R*)-Mandelic acid with 99% purity and (*S*)-mandelic acid with 99% purity was purchased from Alfa Aesar, A Johnson Matthey Company (Ward Hill, MA). All solvents were HPLC grade and were used without further purification.

Analytical Methods

The melting point and heat of fusion of diastereomeric salts were determined by Mettler Toledo DSC 822^e differential scanning calorimeter (Greifensee, Switzerland) with heating rate 5°C/min. ^{1}H NMR chemical shifts were recorded on a Varian INOVA 600 spectrometer at 25°C and DMSO-d_6 as solvent. The X-ray powder diffraction spectra were collected on a Rigaku-Miniflex powder diffractometer (Carlsbad, CA) using Cu-Kα (λ for Kα = 1.54059Å) radiation obtained at 30 kV and 15 mA. The scans were run from 5.0° to 40.0° 2θ, increasing at a step size of 0.02° 2θ with a counting time of 5 s for each step. 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.

Single crystals of (*1S, 4S*)-sertraline-(*R*)-mandelate were grown from a concentrated ethanol solution by slow evaporation at room temperature. The single crystal was mounted on a glass fiber and data were collected at the temperature of 22°C on a Nonius kappa-CCD area detector diffrac-

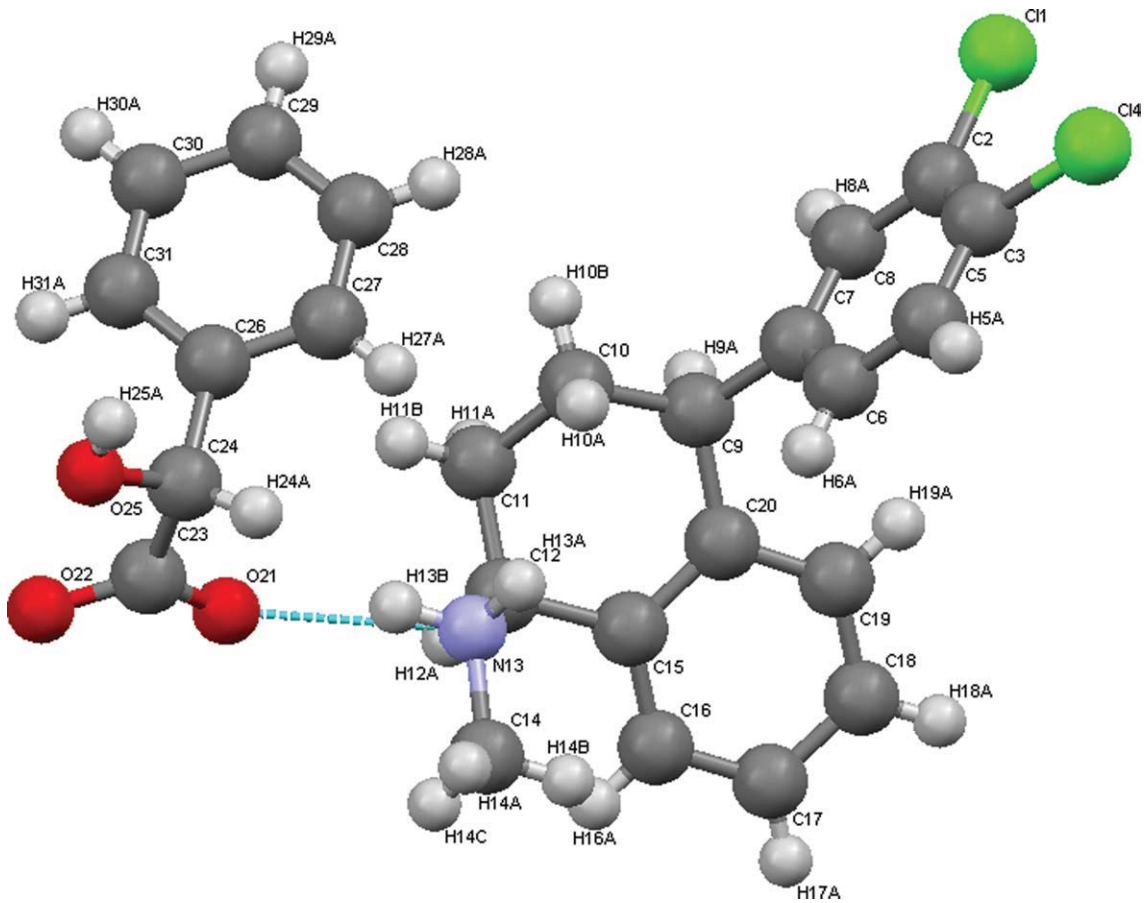

Fig. 4. Atomic-numbering scheme of less soluble salt. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE 2. Crystal structure data of less soluble salt

	(*1S,4S)*-sertraline·(*R)*-MA
Empirical formula	$C_{25}H_{25}Cl_2NO_3$
Formula weight (g/mol)	458.36
Temperature (K)	293
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P 1 2_1 1
a (Å)	7.8029(2)
b (Å)	9.0423(4)
c (Å)	16.3615(8)
α ()	90
β ()	95.594(3)
γ (°)	90
V (Å^3)	1148.91(2)
D_{calc} (g/cm^3)	1.325
Z	2
Crystal size (mm)	0.04 × 0.05 × 0.26
Reflections collected	8819
Goodness-of-fit on F^2	1.019
Final *R* indices [$I > 2\sigma(I)$]	*R*1 = 0.045
	w*R*2 = 0.1087
R indices (all data)	*R*1 = 0.0679
	w*R*2 = 0.1223

tometer with COLLECT using monochromatic Mo-Kα radiation (λ = 0.71073Å). The structures were solved with direct method using the SHELXS-97 program and refined on F^2's by full-matrix least-squares with SHELXS-97 program.

Preparation of Less Soluble Salts

The less soluble salts were synthesized by enantiopure (*1S, 4S)*-sertraline and (*R)*-MA. Enantiopure (*1S, 4S)*-sertraline was isolated from

TABLE 3. Hydrogen bond geometry (d in Å and angle in °)

D-H. . .A	*d*(D-H)	*d*(H. . .A)	*d*(D. . .A)	<(DHA)
N13-H13A. . .O22[a]	0.90	1.92	2.781(4)	158.2
N13-H13B. . .O21	0.90	1.89	2.756(4)	160.6

[a] −x, y+1/2, −z.

(*1S, 4S)*-sertraline hydrochloride by the method described in the literature.[36] To a solution (*1S, 4S)*-sertraline (10 g, 0.033 mol) in 100 ml ethanol, (*R)*-MA (5.0 g, 0.033 mol) were added gradually to afford white crystals. The slurry was heated to reflux and then cooled to room temperature slowly. The suspension was put in fridge overnight. The crystals were collected by filtration and washed with 4°C ethanol twice (2 × 20 mL) to give optical pure (*1S, 4S)*-sertraline·(*R)*-MA (14.2 g, yield 94%). Melting point was 192.67–191.57°C (onset of DSC). ^{1}H NMR (d_6-dimethyl sulfoxide (DMSO)/tetramethylsilane (TMS)), δ (ppm): 1.87–2.11 (*m*, 4H), 2.53 (*s*, 3H), 4.12 (*m*, 2H), 4.68 (*s*, 1H), 6.74 (*d*, 1H),7.17–7.27 (*m*, 6H), 7.38 (*d*, 2H),7.52 (*m*, 2H), 7.55 (*d*, 1H).

Preparation of More Soluble Salts

More soluble salts were synthesized by enantiopure (*1S, 4S)*-sertraline and (*S)*-MA. To a solution (*1S, 4S)*-sertraline (10 g, 0.033 mol) in a mixture of solvents (70% hexane and 30% ethanol, v/v), (*S)*-MA (5.0 g, 0.033 mol) were added gradually to afford a clear solution. The solution was heated to reflux and then cooled to room temperature. The solution was put under a fume hood to evaporate solvent to afford white crystal. The crystals were collected by filtration and washed with 4°C mixture solvent (2 × 10 mL) to give optical pure (*1S, 4S)*-sertraline·(*S)*-MA (13.6 g, yield 91%). Melting point: 86.89–87.3°C (onset of DSC). ^{1}H NMR (d_6-DMSO/TMS), δ (ppm): 1.05 (*t*, 3H from ethanol CH_3), 1.84–2.07 (*m*, 4H), 2.53 (*s*, 3H), 3.44 (q, 2H, from ethanol CH_2), 4.02 (*t*, 1H), 4.12 (*d*, 1H), 4.70 (*s*, 1H), 6.735 (*d*, 1H), 7.17–7.24 (*m*, 4H), 7.27 (*m*, 2H), 7.375 (*m*, 2H), 7.455 (*d*, 1H), 7.48 (*d*, 1H) 7.56 (*d*, 1H).

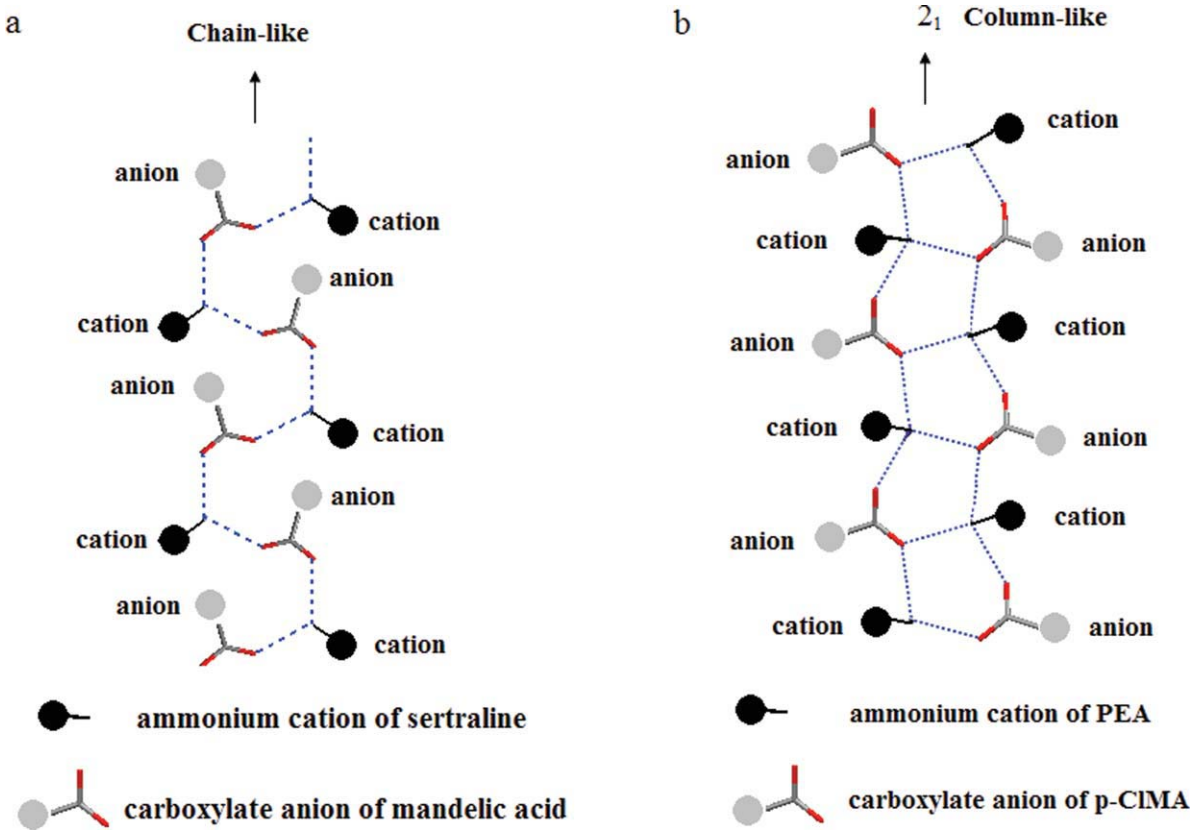

Fig. 5. Hydrogen-bonding network. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

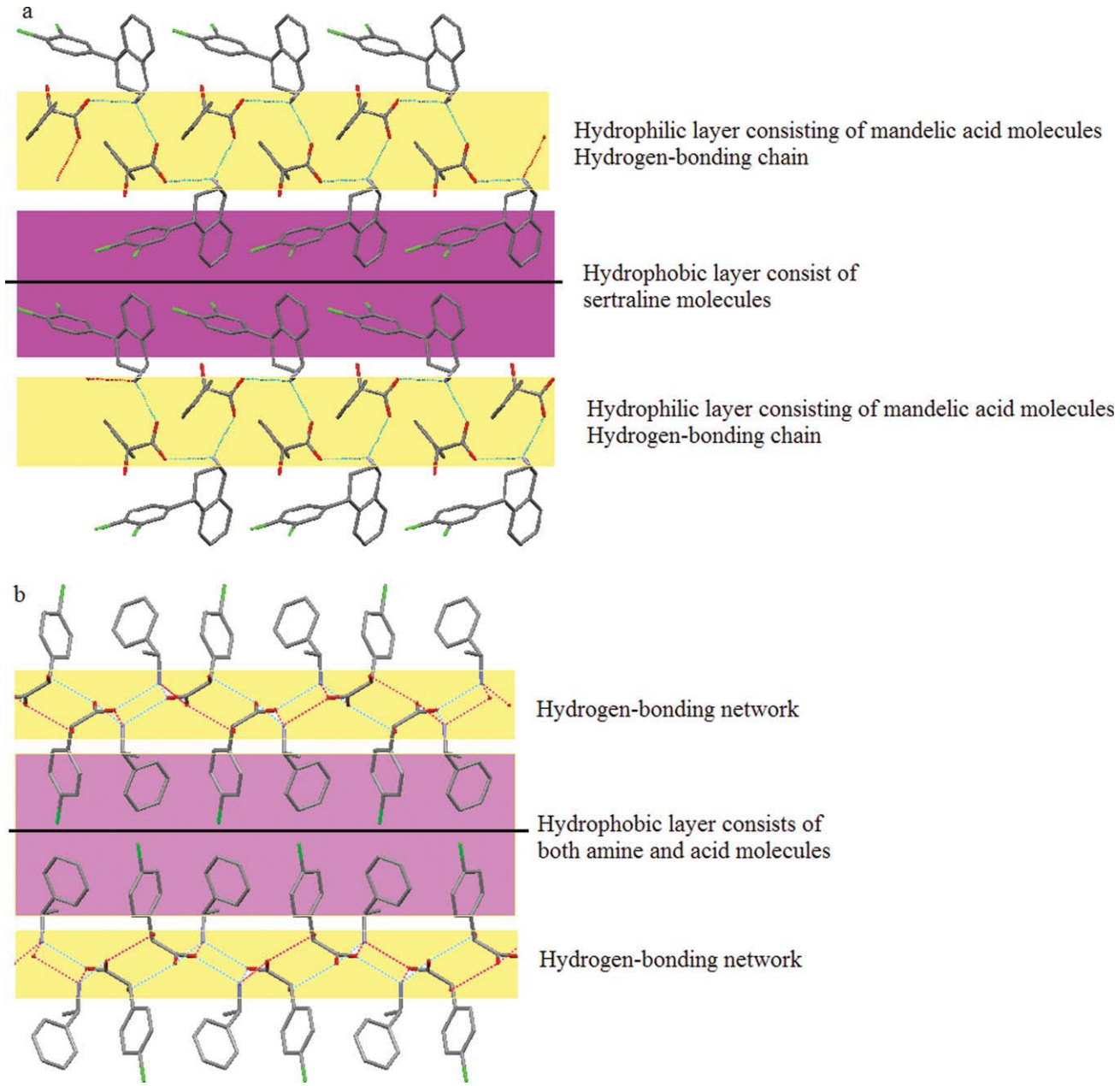

Fig. 6. Molecular layers packing in crystals. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

RESULTS AND DISCUSSION

Thermal Properties of Less and More Soluble Diastereomeric Salts

The standard less and more soluble salts of sertraline and mandelic acid were synthesized as described in the "Experimental" section. The thermal properties of the resulting salts were determined and are listed in Table 1.

As it can be seen, the melting point difference and the solubility difference are significant. The melting point of less soluble salt exceeds that of corresponding more soluble salt by >100°C. The solubility ratio of more soluble salt to less soluble salt in ethanol is 9:1, which is very large. Experimentally, it was also found that the more soluble salt resulted in an ethanolate. The ratio of incorporated solvent to sertraline mandelate was 1:3 based on thermal gravimetric analysis (TGA) and Nuclear Magnetic Resonance (NMR) analysis. The TGA trace of more soluble salt clearly showed 3.5% weight loss between 78 and 88°C. The NMR analysis indicated 3.2% ethanol existing in more soluble salt, which was consistent with TGA results. The differential scanning calorimetry (DSC) and TGA curves of more and less soluble salts are shown in Figures 2 and 3.

The comparison of the above thermal properties strongly suggests that the less soluble salt is much more stable than the more soluble salt. Consequently, excellent resolution efficiency is expected from such large stability difference.

Investigation of Chiral Discrimination Mechanism Based on Crystal Structure of Less Soluble Salt (1S, 4S)-Sertraline·(R)-Mandelic Acid

The large physicochemical property difference between the corresponding less and soluble salts is closely related to their crystal structures.

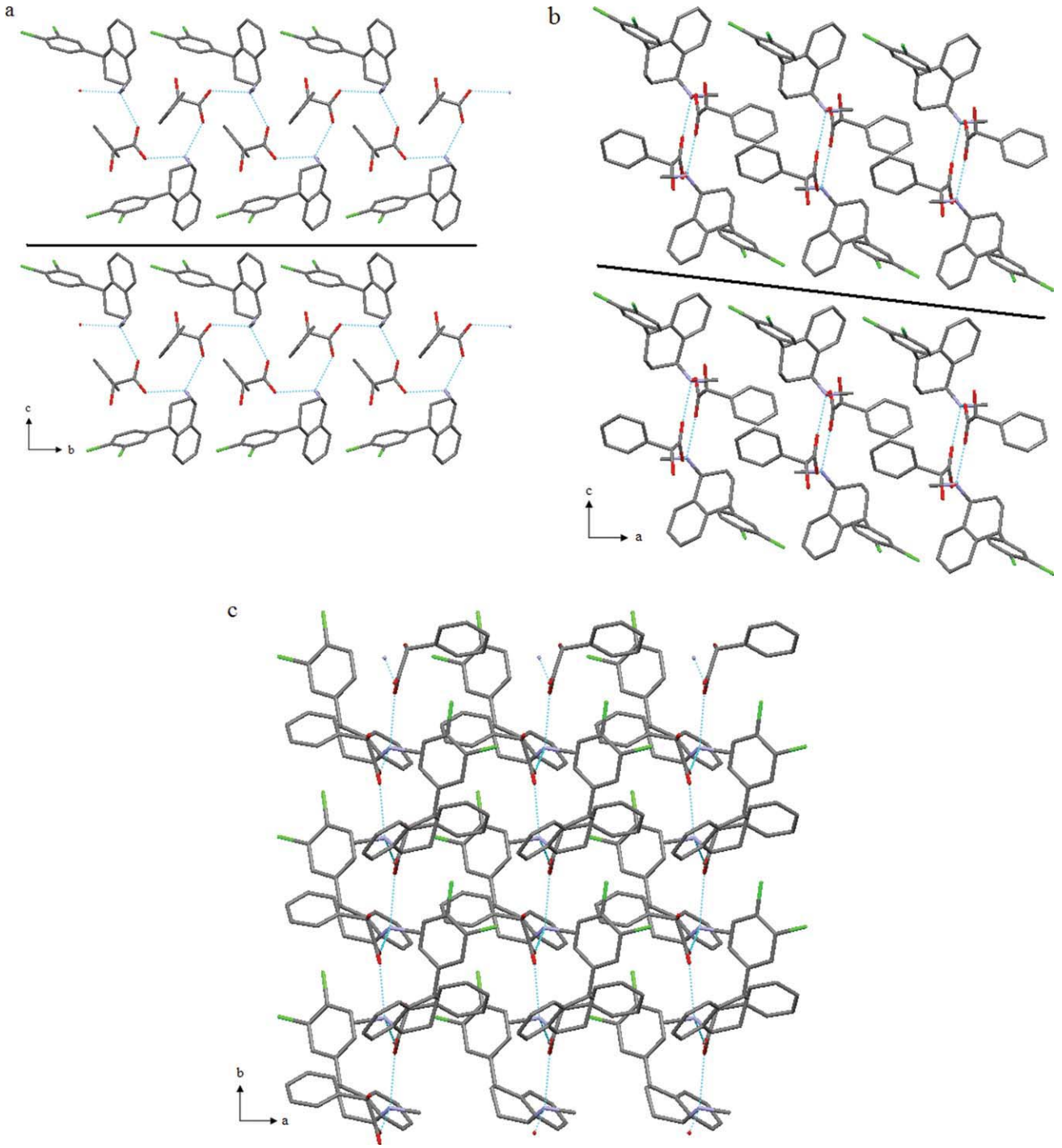

Fig. 7. Supramolecular packing of less soluble salt viewed from three axes. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The good quality single crystals of less soluble salt of (*1S, 4S)*-sertraline·(*R*)-mandelic acid were obtained for X-ray crystallographic analysis. The colorless needle-like crystals belong to monoclinic space group P1 2_1 1 and the unit cell contains two (*1S, 4S*)-sertraline cations and two (*R*)-mandelic acid anions. Figure 4 graphically illustrates the atomic-numbering schemes. Crystallographic lattice parameters and hydrogen bond geometry are summarized in Tables 2 and 3, respectively. Detailed crystal data are included in Supporting Information.

The less soluble salt presented a typical secondary amine and carboxylic acid salt structure containing sertraline ammonium cations and mandelic acid carboxylate anions, supported by electrostatic, hydrogen bond, and van der Waals interactions. The detailed structural features and non-bonded interactions are examined as follows:

Hydrogen-bonding network. The ammonium hydrogens of sertraline formed two hydrogen bonds with the carboxylate oxygens, one from neighboring mandelic acid molecules, another from the opposite mandelic acid molecule, namely N13-H13A. . .O22 (i) and N13-H13B-O21 as listed in Table 3. Sertraline and mandelic acid were connected head

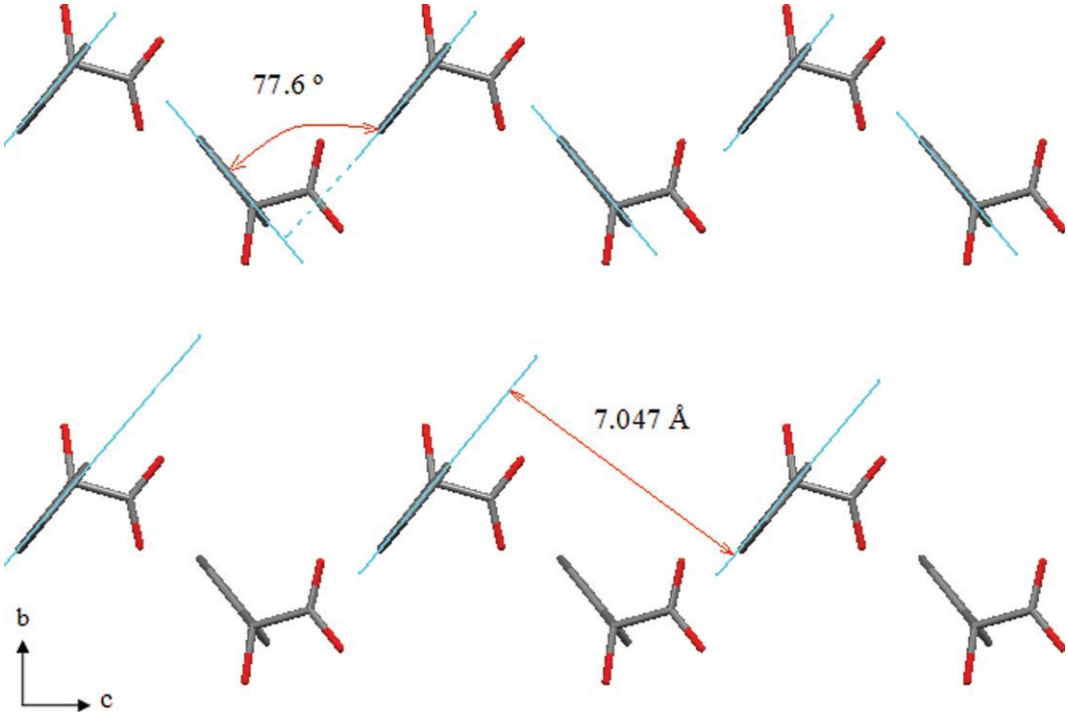

Fig. 8. Stacking of aromatic rings in hydrophilic region. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

to head alternatively to form a zigzag chain-like hydrogen-bonding network along the *b*-axis as shown in Figure 5a. To our surprise, the hydroxy group in mandelic acid was not involved in hydrogen bond formation in the case of sertraline mandelate.

This one-dimension pattern is quite different from the most commonly observed 2_1 columnar hydrogen-bonding network formed in primary amines and carboxylic acids, which is usually formed around a two-fold screw axis by ammonium hydrogens and carboxylate oxygens as shown in Figure 5b.[10,16] In the 2_1 columnar hydrogen-bonding network, there was also another hydrogen bond formed between hydroxy hydrogen and the carboxylate oxygen, which interlinked the two neighboring 2_1 columns to form a 2D hydrogen-bonding network extending throughout the crystal.[10]

Packing of hydrophobic layers. The molecules in less soluble salt assembled in a sandwich like structure illustrated in Figure 6a. The interesting observation was that the resolving agent mandelic acid molecules were close to each other and orientated along the *b*-axis to form the middle layer (hydrophilic layer) in sandwich. The larger sertraline molecules formed the outside two layers (hydrophobic layer) which were face to face and linked by hydrogen-bonding chain with the assistance of mandelic acid molecules. This is significantly different from the molecular packing mode in reported cases of amine and acid,[10–12,16,20–22,26–30] where the

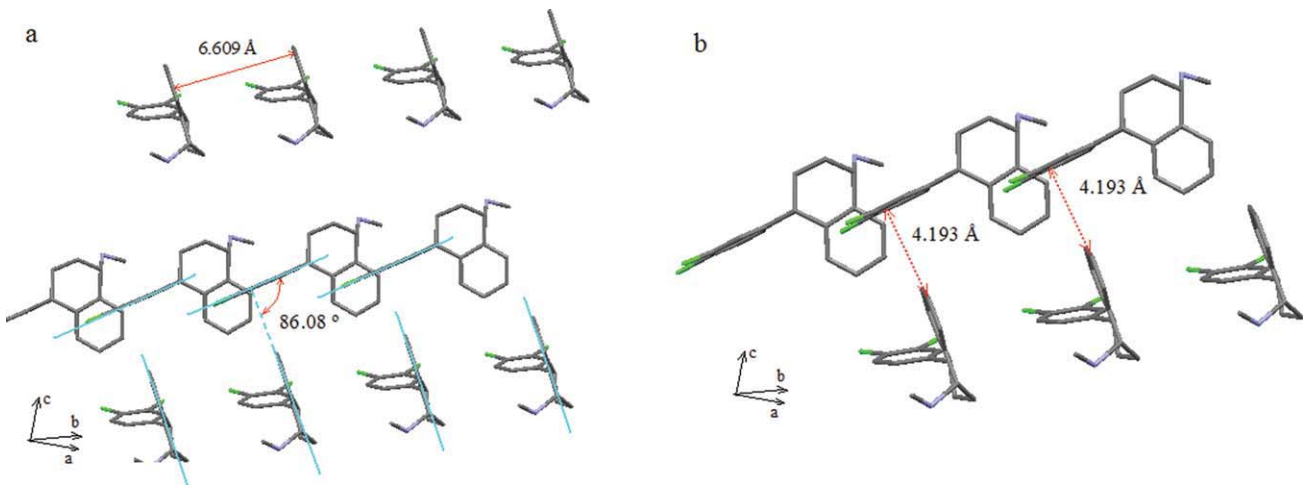

Fig. 9. (a) Stacking of aromatic rings (b) CH/Å interactions in hydrophobic region. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

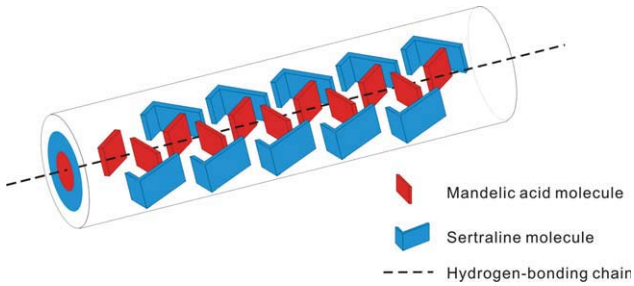

Fig. 10. Schematic orientation of molecules along the hydrogen-bonding chain. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

functional groups of amine and acid formed hydrogen-bonding layer, and the resolving agent like phenylethylamine and chiral recognized enantiomer chloromandelic acid coexisted in hydrophobic region as shown in Figure 6b.

The boundary surface of hydrophobic layers of the less soluble salt was planar and favorable to van der Waals interactions to realize a close packing. The detailed crystal packing patterns viewed long *a*-, *b*-, and *c*-axis respectively are depicted in Figure 7.

Stacking of Aromatic Groups, CH/π Interactions, and π/π Interaction

Examining the packing of aromatic groups of mandelic acids in hydrophilic region disclosed a T-shaped packing. The aromatic rings were orientated to be vertical to each other and the interplanar angle of aromatic rings was 77.6°. There was no strong CH/π interaction found in the region. Besides the T-shaped packing, the aromatic groups were arranged in parallel. The distance between π planes was 7.047Å, which was too far for attractive interactions to be taken into consideration. The packing mode of aromatic groups is depicted in Figure 8.

The packing of aromatic groups of sertraline in hydrophobic region also exhibited the T-shaped arrangement depicted in Figure 9a. The interplanar angle of aromatic groups from adjacent hydrophobic layers was 86.08°. Based on the definition of CH/π[34] as well as the consideration of measuring convenience, the CH/π interaction here was evaluated by the distance between C atom and π plane. There was one kind of CH/π interaction existing in the region. The CH/π interaction happened between CH located at C17 of one sertraline molecule and the ring of C2–C3–C5–C6–C7–C8 of adjacent sertraline molecule. The CH…π distance was 4.193Å, which was not very strong compared with 3.50–4.10Å in other cases of less soluble salt.[11,26,27,29] The aromatic groups of sertraline were also assembled to one another in parallel. The π…π distance was 6.609Å, which was not long enough either to consider the possible attractive forces between π planes. Figure 9b clearly shows CH/π interactions between sertraline molecules from the neighboring hydrophobic layers.

Summarizing the above crystal structure investigation, the less soluble salt of sertraline mandelate possesses most characteristic structural features that favor the stability of crystal, such as stable hydrogen-bonding pattern, planar boundary surface, and T-shaped aromatic group packing. However, the crystal structure of (*1S, 4S)*-sertraline·(*R*)-mandelic acid with these characteristic features was formed in different ways from the reported conventional less soluble salts.

First, a one-dimensional (1D) chain-like hydrogen-bonding network was observed. The chain extended infinitely along the *b*-axis, and the molecules were aligned around the chain by hydrogen bonds to form the backbone of structure shown in Figure 10. These parallel chains packed closely along *a*-axis and *c*-axis to form a compact crystal structure as shown in Figure 11. To the best of our knowledge, this kind of hydrogen-bonding pattern has not ever been reported in diastereomeric salts of mandelic acid and amine, or deeply hidden in literature. The mandelic acid and amine typically formed 2_1 columnar hydrogen-bonding networks. The newly found chain-like structure is assumed to be another stable hydrogen-bonding pattern in less soluble salts besides the well-known 2_1 column, closed globular cluster, and 2D sheet hydrogen-bonding networks.[16–21]

Second, the sandwich-like supramolecular packing in less soluble salt is novel. The resolving agent mandelic acid assembled in hydrophilic layer and sertraline molecules concentrated in hydrophobic region. It has been proposed that the hydrophobic boundary surface is expected to be planar, which is favorable to van der Waals interaction to realize close packing among the supramolecular layers.[16,23] Based on this consideration, it is widely accepted that the higher resolution efficiency will be achieved if the molecular lengths of racemate and resolving agent are identical. If difference in molecular length is one or more than one atoms determined by the method proposed by Sakai,[12] this difference can be compensated by incorporating protic solvent into diastereomeric salt to realize the planar boundary surface. The method is referred to as "space filler concept," which was successfully applied in the resolution of intermediate of doluxine using water as space filler.[35]

However, in the case of sertraline and mandelic acid, the difference in molecular length is five atoms, which is very large. The steric effect of big aromatic and six-membered rings hindered the mandelic acid to form the traditional hydrogen-bonding network as well as typical supramolecular packing mode. If both mandelic acid and sertraline were crowded into hydrophobic layer, there would be unavoidable large spaces in crystal, which would deteriorate the stability of crystal. The observed less soluble salt, sertraline mandel-

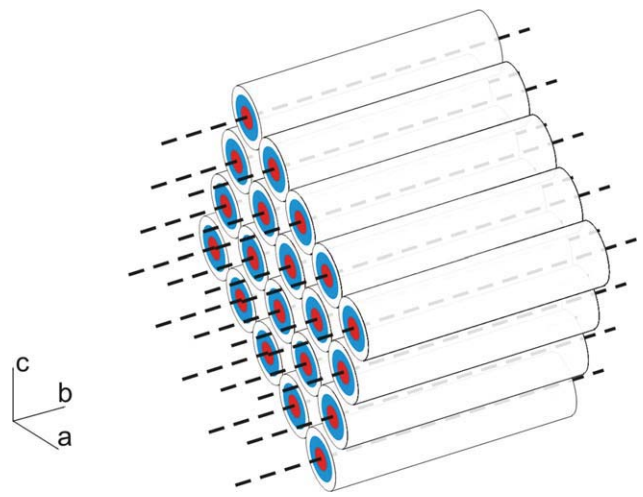

Fig. 11. Schematic diagram of superamolecular packing in less soluble salt. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

ate, adapted into a new more efficient packing mode. The small mandelic acid molecules were closely packed in core layer and surrounded by sertraline molecules. The chair-shape molecular structure of sertraline[36] allowed the head of sertraline fit into the void of mandelic acid layer through hydrogen bond formation. The tail part of sertraline molecules packed parallel to each other locating in external layer and resulted in a planar hydrophobic surface as shown in Figure 10. As shown in Figure 11, the hydrophilic layers are located in the center. The hydrophobic layers are packed layer by layer along both *c*-axis and *a*-axis to form a compact packing (The red and blue circles represent hydrophilic and hydrophobic regions, respectively). From the case study, we believe that the molecular arrangement is determined not only by the primary factor and hydrogen bond ability but also by the size and shape of molecular. The molecules tend to optimize the intermolecular interactions to realize a favorable packing. The observed structure provides the evidence that if the molecular length of raccemate is significantly larger than that of resolving agent, small resolving agent should be employed, which can possibly fit into the void of supramolecular layer formed by big molecules to realize the chiral recognition. Vice versa, namely, if the racemate is a small molecule, the commercial available resolving agent can be elongated or enlarged to increase the chiral discrimination ability.

Third, the herringbone arrangement (T-shaped) of aromatic groups has been universally identified in both hydrophobic and hydrophilic regions. This packing motif is believed to favor the stability of the crystal.[24,25,37] The CH/π interactions existing in neighboring hydrophobic layers also stabilize the less soluble salt.

Fourth, the solvent ethanol was incorporated into more soluble salt, which was a very rare case. It is generally believed, in diastereomeric resolution, that the solvents are more likely to be incorporated into less soluble salts and provide more hydrogen bond sites or fill space voids, which benefit the stability of less soluble salts.[12,38–40] We would argue that in the case of sertraline resolved by mandelic acid, the more soluble salt is a solvate with very high solubility and leads to excellent resolution. The similar phenomenon was observed in another system of lactic acid with 1-phenylethylamine, one equivalent water molecule was incorporated in the more soluble salt.[41] We believe, the fact that fewer examples of more soluble salt solvate have been observed does not mean it occurs less. It is more likely owing to the difficulty in crystallization of the more soluble salt due to its higher solubility. One safe conclusion can be made that the solvent's incorporation does play an important role in chiral discrimination besides its role as a medium to the diastereomeric salts crystallization. The incorporation of solvents can change the stability order among diastereomeric salts and their solvates, which is attributed to the polymorphism nature of diastereomeric salts. Unfortunately, we failed to get crystal structure of more soluble salt for the comparison with less soluble salt. The lower stability of more soluble salt cannot be interpreted concretely.

From the case study of less soluble salt of sertraline and mandelic acid, it can be concluded that the stable hydrogen-bonding pattern, herringbone-like arrangement of aromatic rings, and planar boundary surface in hydrophobic region are the three most important structural characteristics expected in less soluble salts. The existence and magnitude of hydrogen bond, CH/π interaction, and van der Waals interaction related to these characteristic structures determine the stability of diastereomeric salt. The hydrogen bond is not necessarily the dominant factor. The synergy and optimization of all three interactions will enhance the stability of salts and can lead to extremely high resolution efficiency. In most cases, these conditions cannot be completely matched, so moderate resolution efficiency is achieved. The less soluble salt of sertraline and mandelic acid match the three conditions, a new kind of stable hydrogen-bonding network, CH/π interaction, and a unique compact packing mode, which is a good template for the selection and design of resolving agent.

CONCLUSIONS

The diastereomeric resolution of sertraline by mandelic acid was investigated with respect to resolution mechanism. Systematic examination of the intermolecular interactions and packing features in crystal structure of less soluble salt (*1S, 4S)*-sertraline·(*R*)-mandelic acid, elucidated the high resolution efficiency in the system. A new 1D chain-like characteristic hydrogen-bonding network in diastereomeric salt formed between amine and carboxylic acid was disclosed for the first time. Novel sandwich supramolecular assembly was observed. The structure resulted from adapting the specific structures of racemate and resolving agent to realize T-shaped packing of aromatic groups as well as planar boundary surfaces. It is concluded that the stable hydrogen-bonding pattern, herringbone-like arrangement of aromatic rings, and planar boundary surface in hydrophobic region are the three most important structural characteristics. The existence and magnitude of hydrogen bonds, CH/π interaction, and van der Waals related to characteristic structures determine the stability of less soluble salt. It is common that the less soluble salt has one or two of three factors to offer moderate or high resolution efficiency. If less soluble salt possesses all three favorable structural features like sertraline mandelate, very high resolution efficiency is expected. Resolving agent could be selected and designed to favor the formation of diastereomeric salts with these structural features.

It was also found that solvent is not incorporated into the less soluble salt to stabilize the crystal. It existed, however in the more soluble salt. The effects of solvent on the stability of diastereomeric salt are more complicated than just providing more hydrogen bond sites or filling the space to realize the close packing of crystal as generally believed. Further investigation on the role of solvent in resolution is necessary.

ACKNOWLEDGMENTS

Authors are grateful to Apotex PharmaChem for providing free chemicals.

LITERATURE CITED

1. Caner H, Groner E, Levy L. Trends in the development of chiral drugs. Drug Discov Today 2004;9:105–110.
2. Rouhi AM. Chiral business. Chem Eng News 2003;81:45–55.
3. Dyer UC, Henderson DA, Mitchell MB. Application of automation and thermal analysis to resolving agent selection. Org Process Res Dev 1999;3:161–165.
4. Borghese A, Libert V, Zhang T, Alt CA. Efficient fast screening methodology for optical resolution agents: solvent effects are used to affect the efficiency of the resolution process. Org Process Res Dev 2004;8:532–534.
5. Ebber E, Ariaans A, Zwanenburg B, Bruggink A. Controlled design of resolution. Prediction of efficiency of resolution based on samples of arbitrary composition. Tetrahedron: Asymmetry 1998;9:2745–2753.

6. Leusen FJJ, Noordik JH, Karfunkel HR. Racemate resolution via crystallization of diastereomeric salts: thermodynamic considerations and molecular mechanics calculation. Tetrahedron 1993;49:5377–5396.
7. Leusen FJJ. Crystal structure prediction of diastereomeric salts: a step toward rationalization of racemate resolution. Cryst Growth Des 2003;3:189–192.
8. Karamertzanis PG, Price SL. Challenges of crystal structure prediction of diastereomeric salt Pairs. J Phys Chem B 2005;109:17134–17150.
9. Karamertzanis PG, Anandamanoharan PR, Fernandes P, Cains PW, Vickers M, Tocher DA, Florence AJ, Price SL. Toward the computational design of diastereomeric salt resolving agents: an experimental and computational study of 1-phenylethlammonium-2-phenylacetate derivatives. J Phys Chem B 2007;111:5326–5336.
10. Kinbara K. Design of resolving agents based on crystal engineering. Synlett 2005;5:732–743.
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.
12. Saika K, Sakurai R, Nohira H. New resolution technologies controlled by chiral discrimination mechanisms. In: Novel optical resolution technologies, Vol.269,Topics in Current Chemistry Series. 2007. p 199–231.
13. Saika K, Sakurai R, Hirayama N. Molecular mechanisms of dielectrically controlled resolution (DCR). In: Novel optical resolution technologies, Vol.269,Topics in Current Chemistry Series. 2007. p 233–271.
14. 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.
15. Bialonska A, Ciunik Z. Hydrophobic 'lock and key' recognition of N-4-nitrobenzoylamino acid by strychnine. Acta Cryst B 2006;62:1061–1070.
16. Kinbara K, Sakai K, Hashimoto Y, 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.
17. Liao J, 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 self-assembly. Org Biomol Chem 2003;1:1080–1085.
18. Kobayashi Y, Maeda J, Saigo K. Synthesis and chiral recognition ability of O-ethyl(2-naphthyl) phosphonothioic acid. Tetrahedron: Asymmetry 2006;17:1617–1621.
19. Kobayashi Y, Hiroaki H, Handa H, Maeda J, 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.
20. Kobayashi Y, Kokubo Y, Aisaka T, Saigo K. Hydrogen-bonding sheets in crystals for chirality recognition: synthesis and application of (2S,3S)-2,3-dihydroxy- and (2S,3S)-2,3-dibenzyloxy-1,4-bis(hydroxyamino)butanes. Tetrahedron: Asymmetry 2008;19:2536–2541.
21. Molins E, Miravitlles C, Lopez-Calahorra F, Castells J, Raventos J. Structure of (-)-1-phenylethylammonium hydrogen (+)-tartrate. Acta Crystallogr C 1989;45:104–106.
22. Kinbara K, Sakai K, Hashimoto Y, Nohira H, Saigo K. Design of resolving agents: p-substituted mandelic acid as resolving agents for 1-arylalkylamines. Tetrahedron: Asymmetry 1996;7:1539–1542.
23. Kodama K, Kobayashi Y, Saigo K. Role of the relative molecular length of the component in ternary inclusion crystals in the chiral recognition and assembly of supramolecular helical architectures. Cryst Growth Des 2007;7:935–939.
24. Desiraju GR, Steiner T. The weak hydrogen bond. New York: Oxford Press; 1999.
25. Nishio M. CH/π hydrogen bonds in crystals. CrystEngComm 2004;6:130–158.
26. 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.
27. Kobayashi Y, Kurasawa T, Kinbara K, Saigo K. Rational design of CH/π interaction sites in a basic resolving agent. J Org Chem 2004;69:7436–7441.
28. Wang ZH, Hirose T, Shitara H, Goto M, Nohira H. Structure and chiral recognition ability of endo-3-benzamidonorborn-5-ene-2-carboxylic acid. Bull Chem Soc Jpn 2005;78:880–885.
29. Suezawa H, Ishihara S, Umezawa Y, Tsuboyama S, Nishio M. The aromatic CH/π hydrogen bond as an important factor in determining the relative stability of diastereomeric salts relevant to enantiomeric resolution—a crystallographic database study. Eur J Org Chem 2004;23:4816–4822.
30. He Q, Gomaa H, Rohani S, Zhu J, Jennings M. Chiral discrimination in diastereomeric salts of chlorine-substituted mandelic acid and phenylethylamine. Chirality 2010;22:707–716.
31. Top 200 Brand Drugs by Units in 2007 (PDF). Drug topics. Available at:http://www.drugtopics.com/drugtopics/article/articleDetail.jsp?id=491207. Retrieved March 30, 2008.
32. Taber JP, Pfisterer DM, Colberg JC. A New and simplified process for preparing N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)- aphthalenylidene]-methanamine and a telescoped process for the synthesis of (1S-cis)-4-(3,4-dichlorophenol)-1,2,3,4-tetrahydro- N-methyl-1-naphthalenamine mandelate: key intermediates in the synthesis of sertraline hydrochloride. Org Process Res Dev 2004;8:385–388.
33. Quallich GJ. Development of the commercial process for Zoloft®/sertraline. Chirality 2005;17:S120–S126.
34. Nishio M, Hirota M, Umezawa Y. CH··· π interaction: evidence, nature, and consequences. Weinheim: Wiley-VCH; 1998.
35. Sakai K, Sakurai R, Yuzawa A, Kobayashi Y, Saigo K. Resolution of 3-(methylamino)-1-(2-thienyl)propan-1-ol, a new key intermediate for duloxetine, with *(S)*-mandelic acid. Tetrahedron: Asymmetry 2003;14:1631–1636.
36. He Q, Rohani S, Zhu J, Gomaa H. Sertraline racemate and enantiomer: solid-state characterization, binary phase diagram and crystal structures. Cryst Growth Des 2010;10:1633–1645.
37. Hunter CA, Sanders JKM. The nature of π-π Interactions. J Am Chem Soc 1990;112:5525–5534.
38. Kozma D, Novak C, Tomor K, Pokol G, Fogassy E. Mechanism of optical resolutions via diastereoisomeric salt formation. VII. Role of the solvents in the optical resolution of alpha-phenylethylamine by 2R, 3R-tartaric acid. J Therm Anal Calorim 2000;61:45–50.
39. Bialonska A, Ciunik Z. When in the presence of the strong hydrogen bonds, the weak hydrogen bonds gain an importance. Crystengcomm 2006;8:66–74.
40. Morimoto M, Yamakawa A, Katagiri H, Sakai K. Resolution of racemic 1-benzyl-5-oxo-3-pyrrolidinecarboxylic acid with enantiopure (S)-phenylalanine N-benzylamide via diastereomeric salt formation. Tetrahedron: Asymmetry 2007;18:2869–2875.
41. Langkilde A, Oddershede J, Larsen S. Salts of lactic acid and 1-phenylethylamine, their structures and relative stabilities. Acta Cryst B 2002;58:1044–1050.