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Efficient resolution of venlafaxine and mechanism study via X-ray crystallography

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Abstract

Numbers of resolving factors were investigated to improve resolution of venlafaxine **1**. An effective resolving agent, O,O′-di-p-toluoyl-(R, R)-tartaric acid **2**, was screened using similar method of 'Dutch resolution' from tartaric acid derivatives. The resolution efficiency was up to 88.4%, when the ratio of rac-**1** and **2** was 1:0.8 in THF with little water (10:1 v/v). Enantiomerically pure venlafaxine was prepared with 99.1% ee in 82.2% yield. The chiral resolution mechanism was first explained through X-ray crystallographic study. One diastereomeric salt with well solubility forms a columnar supramolecular structure as the acidic salt (R)-**1**·**2**, while the other diastereomeric salt with less solubility forms a multilayered sandwich supramolecular structure by enantiodifferentiation self-assembly as the neutral salt 2(S)-**1**·**2**. The water molecules play a key role in the optical resolution, as indicated by the special structures of the diastereomeric salts.

KEYWORDS

acidic salt, diastereomeric salt, neutral salt, optical resolution, resolution mechanism, supramolecular structure, venlafaxine

1 | INTRODUCTION

1-[2(Dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol (Venlafaxine, **1)** is an antidepressant that inhibits the reuptake of both norepinephrine and serotonin. Because of its unique neuropharmacological activity, it is used to treat anxiety, panic disorder, and major depressive disorder, with the name of Effexor. Pharmaceutical **1** contains two enantiomers which exhibit different pharmacological effects[1,2] and metabolic process.[3] The (*S*)-**1** inhibits primarily the serotonin reuptake, while the (*R*)-**1** inhibits both serotonin and norepinephrine reuptake. So, the efficient and convenient separation of enantiomers of **1** is important for its medical applications. Currently, the following general methods have been reported: (1) asymmetric catalytic synthesis;[4,5] (2) enzymatic resolution;[6,7] (3) chromatographic resolution;[8-10] and (4) diastereomeric salt resolution.[11,12] Methods 1 to 3 are limitedly used in large-scale production, due to complicated operation, low catalyst recovery, high cost, and the special equipment. Thus, resolution via diastereomeric salt is still the major method for preparation of chiral isomers, especially when the racemate is available.

Although classical resolution has been the most widely used in laboratory and industry, the selection and optimization of resolution process are still based on a large number of experiments. In 1990, enantiomerically pure **1** was prepared by classical resolution in 68% yield,[12] and it was pity that the chiral resolution mechanism and the optimizing process were not reported. During the last

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decade, it has been proved that the resolution was greatly influenced by many factors, such as resolution agent and solvent.[13-15] Notably, the efficient ratio between the chiral host and guest compounds is different in using tartaric acid acyl derivatives as resolving agent.[16] It is known that the classical resolution depends on the different solubility of diastereomeric salt pairs and the solubility is determined by the supramolecular structures of respective diastereomeric salts.[17] With the development of crystallography, the crystal structures of diastereomeric salts are convictive proof in the mechanism research of chiral resolution.[13,18-21]

In this work, the optimized yield of enantiomerically pure **1** was increased from 68% to 82.2%, and the resolution mechanism was first explained via the diastereomeric crystal structures. Each factor was discussed during the resolution of **1** (Scheme 1) with the analogues of tartaric acid **2** to **4**, and single factor experiments were carried out to determine the most effective resolving condition.

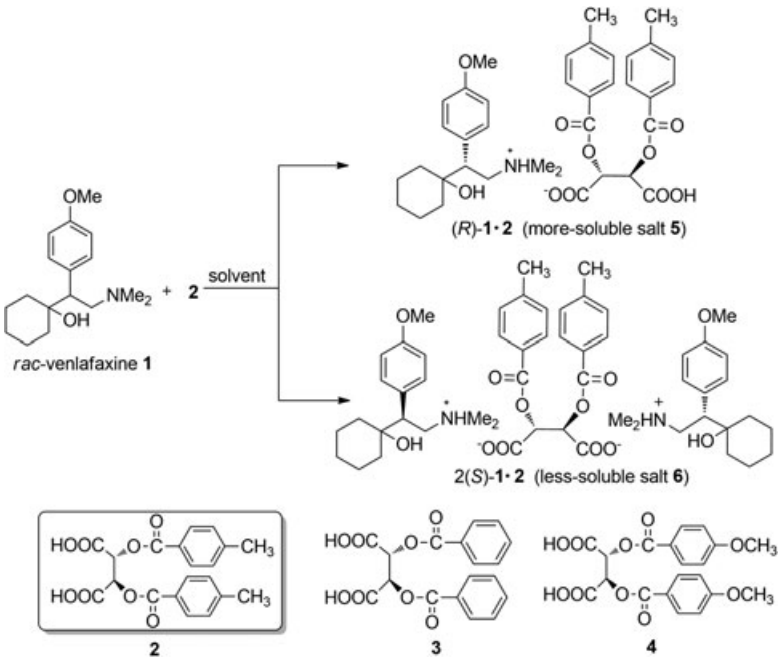
2 | MATERIALS AND METHODS

2.1 | General

Racemic venlafaxine hydrochloride was purchased from commercial resource and used without further purification. The resolving agents O,O′-di-p-toluoyl-(*R, R*)-tartaric acid **2** ((*R,R*)-DTTA), O,O′-dibenzoyl-(*R,R*)-tartaric acid **3**, and O,O′-di-p-anisoyl-(*R,R*)-tartaric acid **4** were commercially available or prepared in our laboratory. All chemicals and solvents were analytically pure and used directly without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer. ^{1}H NMR and ^{13}C NMR chemical shifts are expressed in ppm with the residual signal of DMSO-d_6 or D_2O as an internal standard. Melting points were determined with a digital melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet MX-1 spectrometer by the KBr method. Optical rotations were measured on Rudolph AUTOPOL IV automatic polarimeter. The enantiomeric excess value of **1** was determined by HPLC analysis using an Agilent-1100 instrument equipped with Chiralpak AD-H column (4.6 × 250 mm). The mobile phase was hexane/ethanol (90:10) with 0.2% triethylamine, and flow rate was 0.7 mL/min under detection wavelength of 274 nm. Retention time: *(R)*-**1** 7.2 minutes, *(S)*-**1** 10.3 minutes.

2.2 | Resolution of 1

The venlafaxine hydrochloride (31.292 g, 100 mmol) was added to the solution of NaOH (120 mL, 1 mol/L). The solution was stirred in several minutes and then extracted with ethyl acetate (150 mL×4). The organic layer was combined and washed with water (100 mL×2). The organic phase was dried over anhydrous $MgSO_4$, filtered, and the solvent evaporated. The free base of venlafaxine (27.435 g, 98.9%) was obtained as a white solid. Mp: 74–76°C; ^{1}H NMR (400 MHz, DMSO-d_6, δ):7.09 (d, J = 8.6 Hz, 2H), 6.79 (d, J =8.6 Hz, 2H), 5.21 (s, 1H), 3.71 (s, 3H), 2.95–2.92 (m, 1H), 2.77–2.74 (m, 1H), 2.43–2.38 (m, 1H), 2.12 (s, 6H), 1.57–1.29 (m, 7H), 1.15–0.88 (m, 3H) ppm.



SCHEME 1 Resolution pathway of racemic **1**

The racemic venlafaxine (5.548 g, 20 mmol) was added to a solution of **2** (6.182 g, 16 mmol) in THF (34 mL). The mixture was stirred and refluxed for 30 minutes. A little water (3.4 mL) was added dropwise into the mixture. The solution was refluxed for another 30 minutes and then cooled to room temperature slowly. The resulting colorless crystals were afforded by filtration and recrystallized twice in hydrous THF. The enantiomeric pure neutral salt 2(*S*)-**1**·**2** was obtained as a colorless solid (4.458 g). Mp:125–127 °C; $[\alpha]^{25}_{D} = -44.4$ (c = 1.07 in EtOH); ^{1}H NMR (400 MHz, DMSO-d_6, δ):7.83 (d, *J* = 7.9 Hz, 4H), 7.31 (d, *J* = 7.9 Hz, 4H), 7.12 (d, *J* = 8.3 Hz, 4H), 6.82 (d, *J* = 8.3 Hz, 4H), 5.61 (s, 2H), 3.72 (s, 6H), 3.60 (bs, 2H), 3.32–3.29 (m, 2H), 2.96–2.93 (m, 2H), 2.86–2.83 (m, 2H), 2.35 (s, 15H), 1.75 (bs, 3H), 1.55–1.22 (m, 14H), 1.11–0.89 (m, 6H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6, δ):168.4, 164.9, 157.9, 143.6, 132.0, 130.3, 129.3, 129.2, 127.1, 113.2, 79.2, 72.1, 67.0, 59.0, 54.9, 50.8, 43.9, 36.5, 33.0, 25.4, 25.1, 21.3, 21.2, 21.1 ppm; IR (KBr): γ = 3868.6, 3749.3, 3429.8, 2922.2, 1905.6, 1713.2, 1631.6, 1512.7, 1384.1, 1278.2, 1109.3, 908.4, 843.8, 760.7, 677.3, 634.2, 547.7, 517.5, 487.1, 455.6, 436.5, 419.0 cm^{-1}.

The salt was added to 1 N NaOH and stirred in several minutes. The free base was extracted with ethyl acetate (40 mL×4). The organic layer was combined, washed with water, dried over anhydrous $MgSO_4$, and evaporated to a crystalline residue (*S*)-**1** (2.279 g, 82.2% yield and 99.1% ee). Mp:103–104 °C; $[\alpha]^{25}_{D} = +30.9$ (c = 1.07 in EtOH). The (*S*)-**1** was treated with 1 N HCl/ethyl acetate and then concentrated. The precipitated solid (*S*)-**1**·HCl was obtained as a white solid (2.547 g). Mp: 243–244 °C; $[\alpha]^{25}_{D} = -23.5$ (c = 0.98 in H_2O); ^{1}H NMR (400 MHz, D_2O, *δ*):7.32 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 3.80 (s, 3H), 3.72 (t, *J* = 12.6 Hz, 1H), 3.57 (dd, *J* = 13.1 Hz and 3.8 Hz, 1H), 3.07 (dd, *J* = 12.0 Hz and 3.8 Hz, 1H), 2.80 (s, 3H), 2.76 (s, 3H), 1.68–1.65 (m, 1H), 1.48–1.21 (m, 9H) ppm.

2.3 | Preparation of (*R*)-1·2 salt

In the method described above, (*R*)-**1** (>99.0%ee) was obtained from *rac*-**1** as a colorless solid by using *(S, S)*-DTTA. Equimolar quantities of (*R*)-**1** and **2** dissolved in THF. After the organic solvent concentrated in vacuum, the resulting crystals were collected by filtration, and the enantiomeric pure salt of (*R*)-**1** and **2** was obtained. Mp:122–123 °C; $[\alpha]^{25}_{D} = -67.4$ (c = 1.01 in EtOH); ^{1}H NMR (400 MHz, DMSO-d_6, δ):7.83 (d, *J* = 8.0 Hz, 4H), 7.32 (d, *J* = 8.0 Hz, 4H), 7.17 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.64 (s, 2H), 3.74 (s, 3H), 3.53–3.49 (m, 1H), 3.35–3.29 (m, 1H), 2.94–2.91 (m, 1H), 2.52 (s, 6H), 2.50 (s, 1H), 2.33 (s, 6H), 1.54–1.23 (m, 6H), 1.19–0.91 (m, 4H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6, δ):168.1, 164.8, 158.2, 143.8, 130.8, 130.5, 129.3, 129.2, 126.8, 113.5, 79.2, 72.0, 71.7, 58.2, 54.9, 50.3, 43.2, 36.2, 33.1, 25.3, 21.3, 21.2, 21.0 ppm; IR (KBr): γ = 3571.7, 3413.7, 3067.3, 2928.4, 2860.1, 2842.8, 1704.6, 1611.0, 1514.4, 1470.9, 1409.2, 1339.5, 1273.2, 1176.0, 1109.0, 903.3, 846.0, 816.4, 773.5, 750.3, 695.4, 579.6, 543.9, 514.0, 470.3, 440.8, 417.2 cm^{-1}.

2.4 | Growth of single crystals and crystallographic analysis

Using (*R*)-**1**·**2** salt **5** in Section 2.3 and the enantiomeric pure neutral salt 2(*S*)-**1**·**2** **6** in Section 2.2 as raw material, single crystal of **5** was obtained in isopropyl alcohol, and single crystal of **6** was obtained in aqueous THF. The powder X-ray diffraction pattern of **5** obtained in aqueous THF is similar with that obtained in ^{i}PrOH. It showed that the precipitated salts of (*R*)-**1**·**2** in aqueous THF or ^{i}PrOH possess the same formation of supramolecular structure.[17] Powder X-ray diffraction was performed on a Siemens D5005 diffractometer with filtered Cu-Kα radiation (λ = 1.5418 Å) at 40 kV and 30 mA. Diffraction patterns were collected from 3° to 45° with a step size of 2° min^{-1}. Single-crystal X-ray diffraction data of **5** and **6** were collected on a Bruker Smart 1000 CCD diffractometer equipped with a graphite-monochromatic MoKα radiation (λ = 0.71073 Å) at room temperature. The empirical absorption corrections were applied using the SADABS program.[22] All calculations were performed using the SHELXTL-97 system of computer programs.[23] The crystal data of **5** and **6** have been uploaded to Cambridge Crystallographic Data Centre and the Cambridge Crystallographic Data Centre reference numbers are 1542851 and 1580285, respectively.

3 | RESULTS AND DISCUSSION

3.1 | Resolution of venlafaxine

It was reported that the *rac*-**1** could be resolved with (*R, R*)-DTTA **2** in ethyl acetate, through which enantiomerically pure **1** was prepared in 68% overall yield.[12] To improve the resolution efficiency, solvents of methanol, ethanol, isopropanol, acetone, dichloromethane, tetrahydrofuran, and ethyl acetate were first screened. The results show that acetone, tetrahydrofuran, and ethyl acetate lead to excellent resolution efficiency. The resolution efficiency is 76.8% in tetrahydrofuran (acetone 71.5%; ethyl acetate 62.8%). Further research revealed that small amount of water could greatly affect the efficiency. The better result for the resolution of **1** could be obtained in the solution of 90% tetrahydrofuran and 10% water, and the resolution efficiency can be up to 83.3%. (Table 1, entry 1)

TABLE 1 Results of resolution of *rac*-**1** in hydrous THF

Entry	1:2:3:4[a]	ee, %[b]	Yield, %[c]	Eff., %[d]
1	1:1:0:0	83.1	100.2	83.3
2	3:1:1:1	80.9	73.0	59.1 (5:2:3)[e]
3	-[f]	91.9	72.1[g]	- (12:2:5)[e]
4	1:0:1:0	-	Trace	-
5	1:0:0:1	53.7	66.8	35.9
6	1:0.9:0:0	85.3	99.8	85.1
7	1:0.8:0:0	88.9	99.4	88.4
8	-[h]	99.1	82.7[g] (82.2 overall yield)	-
9	1:0.7:0:0	90.1	97.8	88.1
10	1:0.6:0:0	88.8	92.8	82.4
11	1:0.5:0:0	80.6	89.4	72.1

[a]The initial molar ratio of *rac*-**1**, **2**, **3**, and **4**.

[b]In all experiments, (*S*)-**1** was obtained, and the enantiomeric purity was determined by HPLC.

[c]The yield of (*S*)-**1** based on half the initial amount of *rac*-**1.**

[d]Resolving efficiency, defined as a product of the yield and the ee of the liberated **1**.

[e]Molar ratio of **2**, **3**, and **4** in the precipitated salts.

[f]Recrystallization from the mixed salt of entry 2.

[g]The yield of recrystallization.

[h]Recrystallization from the salt of entry 7.

Resolving agent is another important factor affecting the resolution efficiency. Because **2**, **3**, and **4** are used widely for the resolution of racemic amines,[15,24] we choose these acids as resolving agents in this work.

In order to effectively screen the appropriate resolving agent, a 'family' approach similar to Dutch resolution[25] was developed involving a mixture of resolving agents. During the resolution with the mixture of resolving agents, the less soluble diastereomeric salt tends to contain more effective resolving agent.[13,17] So, the equimolar mixture of **2**, **3**, and **4** was added to a solution of *rac*-**1** in aqueous tetrahydrofuran. As a result, (*S*)-**1** was obtained with 73% yield and 80.9% enantiomeric excess (Table 1, entry 2). After recrystallization of the salt, **2** became the major component in the complex, in which the molar ratio of **2**, **3**, and **4** changed from 5:2:3 to 12:2:5 (Table 1, entry 2 and 3). The resolution was also studied with **2**, **3**, or **4** alone. The resolving efficiencies of **3** and **4** were lower than **2** (Table 1, entry 1, 4–5). It is difficult to precipitate out with **3** as resolving agent. So, compound **2** was proved to be the best resolving agent in the tartaric acid 'family'.

To further improve the resolving efficiency of **2**, resolving host-guest ratios were tested during the resolution of *rac*-**1**. We screened the ratio from 1:1 to 1:0.5, and the ratio of 1:0.8 was found to be the best (Table 1, entry 7). One half molar equivalent of **2** was used in literature,[12] which is different from this work. To explore the reason of the host-guest ratio, two optical pure diastereomeric salts were obtained and analyzed by ^{1}H NMR, respectively. According to the ^{1}H NMR records, the more-soluble salt **5** contains equal numbers of (*R*)-**1** and **2,** while the less-soluble salt **6** consists of (*S*)-**1** and **2** in a ratio of 2:1. Therefore, it can exactly explain why the ratio of 1:0.8 is the best. And it is derived that the salification is faster and more stable than the crystallization of diasteromeric salts during the resolution of **1**. Thus, with 0.8 equimolar **2** as a resolving agent, enantiomerically pure **1** was prepared from the racemate in 82.2% yield, the typical resolution procedure is described in Section 2.2.

3.2 | Crystal structures of diastereomeric salts

Different diastereomeric salts have different supramolecular structures and intermolecular interactions, which could discover the resolution mechanism effectively. As can be seen from the crystal structures of diastereomeric salts (Table 2), the more-soluble salt **5** forms a columnar supramolecular structure (Figure 1A,B), while the less-soluble salt **6** has multilayered sandwich supramolecular structure which is formed by the superimposition of venlafaxine molecular layer and DTTA molecular layer each other (Figure 2A,B).

In the multilayered sandwich structure, 1 DTTA molecule connects with four (*S*)-**1** molecules, and one (*S*)-**1** molecule directly links with two DTTA molecules (Figure 2B,C). So, the molar ratio of venlafaxine and DTTA is 2:1 in the less-soluble salt **6**, compared with the equal numbers of venlafaxine molecule and DTTA molecule in the more-soluble salt **5** (Figure 1A,B). As discussed in the previous sections, (*S*)-**1** forms neutral salt with half-quantity of **2,** and (*R*)-**1** unites with equal numbers of **2** to be acidic salt. Therefore, *rac*-**1** and **2** can react to form salt in the ratio of 4:3. It is reasonable that the mixture of *rac*-**1** and **2** consisting in the ratio of 1:0.8 is the most efficient in the chiral resolution (Table 1, entry 7).

In both sandwich and columnar supramolecules, the carboxylate groups of DTTA are point to the opposite directions (Figures 1C and 2C). In the more-soluble salt **5**, the carboxylate groups are interlinked by hydrogen bonds to self-assemble into ribbon structure along the b axis (Figure 1C), which is similar to another acidic salt of tartaric acid acyl derivatives.[13,17,26] In addition, the water molecules are found to be embedded into the ribbon structure and linked with upper and lower DTTA molecules as hydrogen bond donor. Meanwhile, the water molecules act as hydrogen bond acceptors to link with

TABLE 2 Crystallographic data collection and structural refinement information

Crystal No.	More-Soluble Salt 5	Less-Soluble Salt 6
Configuration	(*R*)-**1**	(*S*)-1
Formula	$2(C_{17}H_{28}NO_2)^+$ $2(C_{20}H_{17}O_8)^-$ $4.5(H_2O)^a$	$4(C_{17}H_{28}NO_2)^+$ $2(C_{20}H_{16}O_8)^{2-}$ $2(H_2O)$ (C_4H_8O)
Formula weight	1408.55	1990.41
Z	1	1
Crystal system	Monoclinic	Monoclinic
Space group	p21	C2
a/Å	14.296(2)	18.285(2)
b/Å	7.9189(12)	9.1147(10)
c/Å	17.427(3)	17.2500(19)
α (°)	90	90
β (°)	107.708(4)	97.9120(10)
γ (°)	90	90
V/Å^3	1879.4(5)	2847.6(5)
ρ_{calcd}/Mg m^{-3}	1.245	1.161
μ/mm^{-1}	0.093	0.082
Total reflections	15545	11488
Wavelength/Å	0.71073	0.71073
Unique reflections	8849 [R(int) = 0.0228]	5592 [R(int) = 0.0179]
F(000)	753	1072
θ_{max}	29.42	27.66

[a]In the structural final refinement, the position is occupied by the disordered H_2O molecule with 25% occupancy.

ammonium or hydroxyl of venlafaxine. So, (*R*)-**1** molecules connect with water at the joints of the DTTA ribbon. They are incorporated in a vertical way between the two opposite DTTA ribbons to construct the columnar supramolecules (Figure 1A,B).

In the neutral salt **6**, there is no obvious hydrogen bonding interactions between DTTA molecules. In fact, each DTTA molecule is connected to another nearby DTTA molecules via (*S*)-**1** molecules, which can form intermolecular hydrogen bonds with the carboxylate groups of DTTA (Figure 2C). The ammonium ion of (*S*)-**1** holds only one DTTA molecule by salt-bridge hydrogen bond, and the hydroxyl group of (*S*)-**1** forms the other hydrogen bond with the carboxylate group of another DTTA molecule. So, they form the multilayered sandwich supramolecular structure. The interlayer space of the sandwich supramolecule is 9.143 Å.

It is noted that the molecules of solvent are also found in the supramolecular structure of the less-soluble salt **6**. Although water does not work between (*S*)-**1** and **2**, it forms hydrogen bonds with two carboxylate groups on the same DTTA. The effect can influence spatial arrangement of DTTA to enhance the stability of the multilayered sandwich supramolecule. In the more-soluble salt **5**, there are 2 water molecules linked with upper and lower DTTA molecules to form ribbon structure (Figure 1C). So, water plays different roles in the formations of the diastereoisomeric supramolecular structure **5** and **6**, which explain its effect on improving the resolution efficiency of **1.** On the other hand, it is hinted that the amount of water participating in the formation of supramolecular structures influence on the tightness of **1** and **2** connection structure. Therefore, the acidic diastereomeric salt (*R*)-**1**·**2**·2H_2O reflects better solubility than the neutral diastereomeric salt 2(*S*)-**1**·**2**·H_2O. Besides, another water and tetrahydrofuran molecules, which are found between the supramolecular assemblies respectively (Table 2), have little contribution to the supramolecular structure.

To the best of our knowledge, it was the first report that the diastereomeric complexes respectively exist in form of acidic salt and neutral salt. In classical resolution, the difference of diastereomeric complexes depends on the supramolecular structures, and a more tightness diastereomeric complex formation is conducive to be

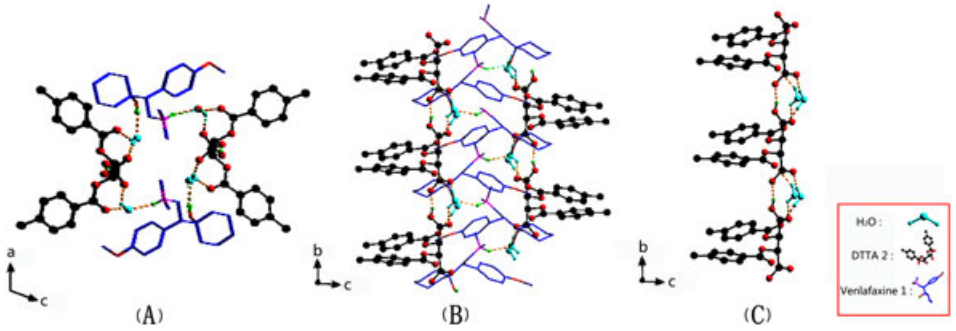


FIGURE 1 Supramolecular columnar structure in crystal structure of (*R*)-1·2. A, Top view and B, side view down the *b* axis; C, ribbon structure of (*R,R*)-DTTA molecules in the more soluble salt **5**

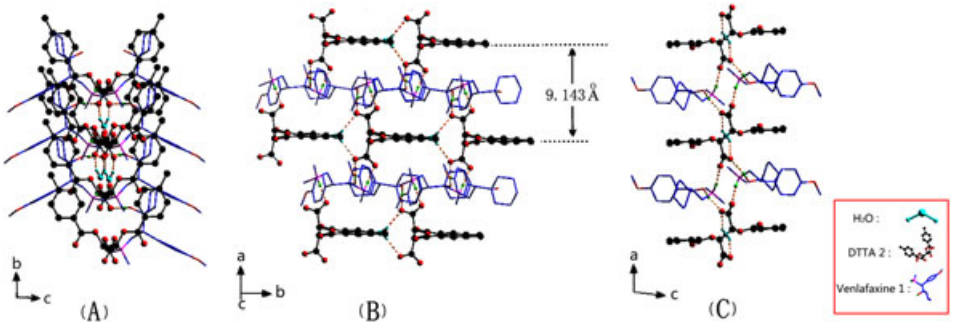


FIGURE 2 Supramolecular multilayered sandwich structure in crystal structure of 2(*S*)-**1**·**2.** A, Top view and B, side view down the *a* axis; C, the connection of (*S*)-**1** and (*R,R*)-DTTA molecules in the less-soluble salt **6**

precipitated out. After the structure of resolving agent was found to impact on the diastereomeric supramolecular structures via X-ray crystallography,[13] the solvent effect and amount of resolving agent are also confirmed to be vital factors by analyzing crystal structures of **5** and **6.** So, the comprehensive influence of the factors contributes to the chiral discrimination in resolving host-guest chemistry and the resolution efficiency.

4 | CONCLUSION

The direct resolution of venlafaxine **1** was investigated. The effective resolving agent **2** was confirmed by the 'family' approach from the tartaric acid derivates **2** to **4**, and resolution efficiency was best when the ratio of rac-**1** and **2** was 1:0.8 in THF with little water (10:1 v/v). These influent factors were substantiated in X-ray crystallographic studies, and the diastereomeric complexes were first found to be acidic salt and neutral salt respectively. The studies demonstrate that the acidic diastereomeric salt (*R*)-**1**·**2** with well solubility forms a columnar supramolecular structure, in which water molecule is a connection between (*R*)-**1** and **2,** while the neutral diastereomeric salt 2(*S*)-**1**·**2** with less solubility forms a multilayered sandwich supramolecular structure by direct interactions of (*S*)-**1** and **2**. In less-soluble supramolecular structure, water contributes to tighten the supramolecular structure by influencing spatial arrangement of **2**. These factors can greatly affect diastereomeric supramolecular structures and thus the resolution efficiency. Consequently, a slight change in these factors can make a big difference in chiral resolution.

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