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Facile resolution of racemic terbutaline and a study of molecular recognition through chiral supramolecules based on enantiodifferentiating self-assembly †

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An effective resolving agent, (2*S*,3*S*)-di-*O*-(*p*-toluoyl) tartaric acid (**4**), was screened using a 'family' approach to yield direct resolution of (*R*)-terbutaline (**1**) with high optical purity and yield. Molecular recognition was studied by X-ray crystallographic analyses of the single crystals of the pair of diastereomeric salts. The more-soluble salt formed a sheet supramolecular structure, and the less-soluble salt formed a columnar supramolecular structure by enantiodifferentiating self-assembly. The water molecule plays an important role during optical resolution, and makes the supramolecular structure of the less-soluble salt more thermodynamically stable than that of the more-soluble salt. Solvent system has little influence on the resolution.

Since development by Pasteur in 1853,[1] classical resolution has become an essential method for the preparation of the vast majority of chiral compounds. However, it is a bothersome task to search for an effective resolving agent during optical resolution. Many attempts have been made to develop a predictable technique for the choice and design of a suitable resolving agent, such as phase diagrams,[2] or differential scanning calorimetry (DSC).[3] Recently, Vries *et al.* reported a novel "family" approach to resolution,[4] which involves the addition of a family of structurally related resolving agents to a racemate; this provides a rapid and reliable method for the separation of enantiomers.[5] Terbutaline (**1**), 1-(3′,5′-dihydroxyphenyl)-2-(*tert*-butylamino)ethanol, is a β_2 – adrenergic receptor agonist for the treatment of asthma, bronchitis and emphysema. Compound (*R*)-**1** is about 200 times more potent as an adrenergic β_2 receptor stimulator than (*S*)-**1**.[6] In January 1996, the FDA announced that it would consider further incentives for the development of single isomer drugs,[7] owing to their better pharmacokinetic prosperity, safety, and tolerability. Racemic terbutaline has a well-established preparation method and is manufactured on a large scale, but there is not yet an efficient process for the preparation of single enantiomers. Although asymmetric synthesis is one way to obtain (*R*)-**1**,[8] it is difficult to prepare on a large scale. Moreover, literature research revealed that only the resolution of the *O*,*O*′,*N*-tribenzyl derivative of **1** has been achieved and the yield is very low.[6] In this paper, we report a facile and direct method for the resolution of racemic terbutaline (**1**). Meanwhile, the resolving agent, (2*S*,3*S*)-di-*O*-(*p*-toluoyl) tartaric acid, D-DTTA (**4**) was screened from a family group, which consisted of (2*S*, 3*S*)-tartaric acid (**2**), and (2*S*,3*S*)-di-*O*-benzoyl tartaric acid, *D*-DBTA (**3**) and **4** (Scheme 1).

It is well known that classical resolution depends on the different solubilities of diastereomeric salt pairs, which are ultimately due to significant differences between the molecular interactions within respective diastereomeric salts.[9] Thus, over the last decade, many groups have studied the crystal structures of pairs of diastereomeric salts to clarify the mechanism of chiral discrimination.[10] In 1988, Arnett and co-workers, through the study of the relationships between structures and energies of association of diastereomeric salts, found that the largest differences in thermochemical properties could be reasonably related to differences in hydrogen bonding schemes in their crystals.[11] By X-ray crystallographic analyses of a pair of diastereomeric salts, Saigo and co-workers[12] revealed that the high resolution efficiency of 2-arylglycolic acid arose from the formation of a supramolecular sheet assembled by the characteristic columnar hydrogen bonded network. In fact, hydrogen bonded supramolecules have also attracted much attention,[13] for example, in the field of nonlinear optical (NLO) materials[13b] and molecular recognition and self-assembly.[14] Moreover, to our knowledge, relatively few studies have probed the crystal structures of pairs of diastereomeric salts of tartrates to gain insight into recognition mechanisms.[15,16] In order to elucidate chiral discrimination, we studied the crystal structures of the less-soluble salt, which consists of (*R*)-**1** and **4**, and the more-soluble salt, which consists of (*S*)-**1** and **4**, by X-ray crystallographic analyses. Both (*R*)-**1** and (*S*)-**1** form stable supramolecular assemblies with **4** by hydrogen bonding. Herein, we will investigate the supramolecular structure of both the less- and the more-soluble salts and the relationships between structure and molecular recognition to understand why the salt of the matched (*R*)-**1** and **4** crystallized preferentially during the resolution.

Results and discussion

Resolution of terbutaline (1)

Since tartaric acid **2**, and its diaryl carboxylate derivatives **3** and **4** are among the most widely used chiral acids for the resolution of racemic amines,[2a] such as *N*,*O*,*O*′-tribenzyl terbutaline,[6] we first explored a mixed group of **2**, **3** and **4** as resolving agents. The mixture of resolving agents was added to a solution of equimolar amounts of *rac*-**1** in acetone, and the precipitate was analyzed by ^{1}H NMR and HPLC, which showed that the diastereomeric salt is composed of **1**, **3** and **4**, and does not contain **2**. (*R*)-**1** was obtained with 55% efficiency and 88% enantiomeric excess (Table 1, entry 1). The resolving efficiency of **3** or **4** individually was not as good as that of a mixture of **3** and **4** (Table 1, entries 2, 3, and 5), and this demonstrated that **3** and **4** could have a good cooperative effect during the

† Electronic supplementary information (ESI) available: 1) ^{1}H and ^{13}C NMR analyses of (*R*)-**1**·**4** and (*S*)-**1**·**4**; 2) ORTEP views and stacking structures of crystals **5**, **7** and **8**; 3) DSC and TG analyses of the more- and less-soluble salts. See http://www.rsc.org/suppdata/ob/b2/b211327a/

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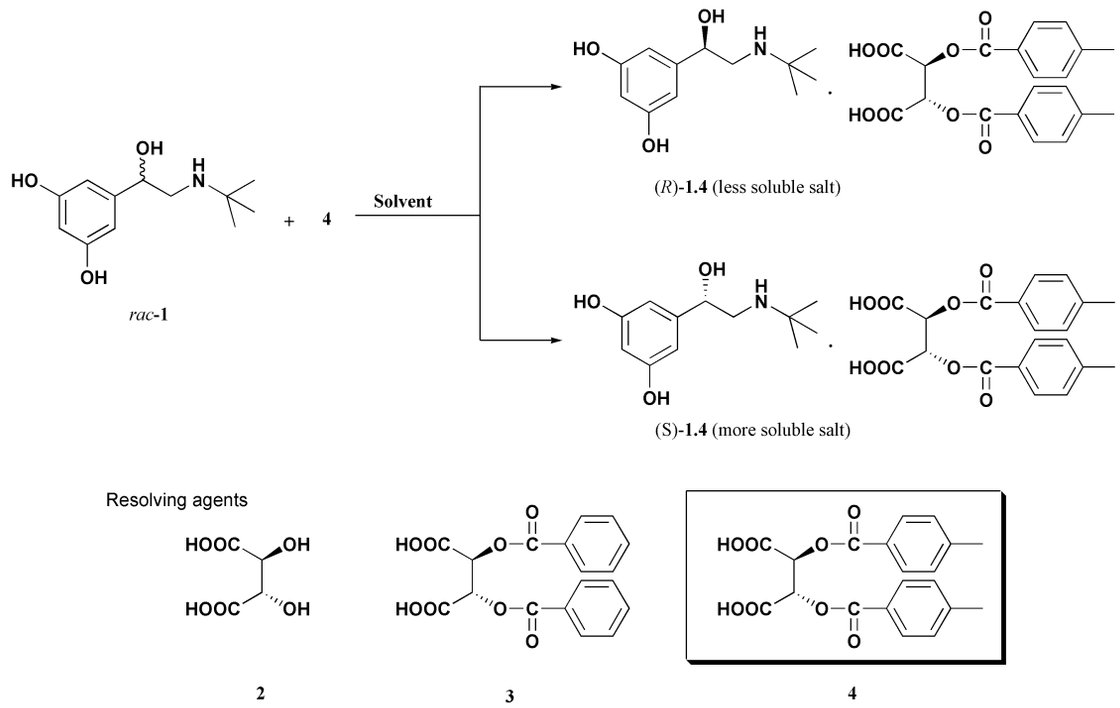

Resolving agents

2 3 4

Scheme 1 The resolution of racemic terbutaline (**1**).

Table 1 Results of resolution of *rac*-**1** by **3** and **4**

Entry	1 : 3 : 4 [a]	ee (%) [b]	Yield (%)	Eff. (%) [c]	3 : 4 [d]
1	— [e]	87.5	62.7 [f]	54.9	—
2	1 : 1 : 0	71.0	63.1 [f]	44.8	—
3	1 : 0 : 1	37.0	126.7 [f]	46.9	—
4	2 : 0 : 1	5.6	trace	—	—
5	2 : 1 : 1	74.6	89.9 [f]	67.0	1 : 3
6	— [g]	97.9	70.0	—	1 : 8
7	— [h]	99.8	86.5	—	1 : 40

[a] The initial molar ratio of *rac*-**1**, **3** and **4**. [b] In all experiments, (*R*)-**1** was obtained and the enantiomeric purity was determined by HPLC. [c] Resolving efficiency, defined as a product of the yield of the diastereomeric salt and the ee of the liberated **1**. [d] The molar ratio of **3** and **4** in the precipitated salts, and also the molar ratio of **1** and **3** + **4** remained as 1 : 1 in the salt. [e] A mixture of **2**, **3**, and **4** was used for the resolution of *rac*-**1** in a ratio of 1 : 1 : 1 : 3, but ^{1}H NMR analysis showed that **2** was not present in the precipitated salts. [f] The yield of (*R*)-**1** based on half the initial amount of *rac*-**1**. [g] Recrystallization from the mixed salt of entry 5. [h] Recrystallization from the mixed salt of entry 6.

resolution of *rac*-**1**. Nonetheless, after two recrystallizations of the less-soluble salt, **4** became the major component in the mixed salt, in which the molar ratio of **3** and **4** changed from 1 : 3 to 1 : 40 (Table 1, entries 5 and 7), and obviously, **4** has better chiral recognition of **1** than **3** does. Thus, by this "family" approach, we have successfully screened an effective resolving agent, **4**.

Furthermore, in order to improve the resolving efficiency, several solvents, such as methanol, ethanol, acetone and dichloromethane were surveyed and a mixed solvent of methanol and acetone was found to be an excellent solvent system, in which the less-soluble salt consists of (*R*)-**1**, **4** and water in a ratio of 1 : 1 : 1. Thus, utilizing **4** as a resolving agent, enantiomerically pure (*R*)-**1** was prepared with >99% ee in 77% yield,[17] the typical resolution procedure is described in the experimental section.

Crystal structures of diastereomeric salts

For exploring the chiral recognition ability of resolving agent **4** to terbutaline (**1**), a diastereomeric salt, (*S*)-**1**·**4** was prepared by combining equimolar amounts of (*S*)-**1** and **4** in methanol and dichloromethane and ^{1}H NMR and elemental analyses demonstrated that the more-soluble salt consists of (*S*)-**1** and **4** in a ratio of 1 : 1. Single crystals of **5** (more-soluble salt) and **7** (less-soluble salt) were obtained from a mixed solvent of methanol and dichloromethane, respectively. Moreover, two other single crystals of **6** (more-soluble salt) and **8** (less-soluble salt) were obtained from a mixed solvent of methanol and acetone. X-Ray crystallographic studies showed that identical crystals **5** and **6** from two solvent systems contain equimolar quantities of (*S*)-**1** and **4**, but crystal **7** includes another acetone molecule compared with crystal **8**, which consisted of (*R*)-**1**, **4** and water in the same ratio of 1 : 1 : 1 with the precipitated salt from the resolution process. The pertinent crystallographic data of the crystals **5**, **6**, **7**, and **8** are summarized in Table 2.[18] Thus, only crystal structures of **5**, **7**, and **8** will be discussed in this paper.

It is interesting that both diastereomeric salts form well-defined, and extremely ordered supramolecular structures *via* hydrogen bonded networks (Figs. 1 and 2). A dramatic difference between their crystal structures is that the more-soluble salt forms a sheet supramolecular structure (Figs. 1A and 1B), but both crystals **7** and **8** prepared from the less-soluble salt exist in a columnar supramolecular motif (Figs. 2A and 2B), in which (*R*)-**1**, **4** and water construct a columnar supramolecular structure *via* a hydrogen bonded network. The formation of the supramolecular structure is not dependent on the crystallizing solvent system. In fact, the different supramolecular structures of the pair of diastereomeric salts are determined by different hydrogen bonding relationships (Table 3). In both sheet and columnar supramolecules, two carboxylate groups of D-DTTA (**4**) point in opposite directions (*anti* conformation), and furthermore are interlinked by hydrogen bonds to self-assemble into ribbon structures along the *a* axis (Figs. 1C and 2C), which has been observed in the crystal structures of salts of **4** and other amines.[16,19,20] In the more-soluble salt, (*S*)-**1** molecules are incorporated between the parallel ribbon supramolecules by six hydrogen bonds (Table 3) to construct a sheet hydrogen bonded network (Figs. 1A and 1B), while in the less-soluble salt, (*R*)-**1** molecules are incorporated in a perpendicular manner between the opposite ribbon supramolecules by eight hydrogen bonds (Table 3) to construct

Table 2 Crystallographic data collection and structural refinement information[a]

Crystal No.	**5**	**6**	**7**	**8**
Configuration	(*S*)-**1**	(*S*)-**1**	(*R*)-**1**	(*R*)-**1**
Salt type[b]	M	M	L	L
Formula	$(C_{12}H_{20}NO_3)^+$ $(C_{20}H_{17}O_8)^-$	$(C_{12}H_{20}NO_3)^+$ $(C_{20}H_{17}O_8)^-$	$(C_{12}H_{20}NO_3)^+$ $(C_{20}H_{17}O_8)^-\cdot H_2O$	$(C_{12}H_{20}NO_3)^+$ $(C_{20}H_{17}O_8)^-\cdot H_2O\cdot C_3H_6O$
Formula weight	611.63	611.63	629.64	687.72
Z	2	2	4	4
Specimen size/mm	0.48 × 0.48 × 0.20	0.52 × 0.48 × 0.24	0.48 × 0.30 × 0.22	0.58 × 0.52 × 0.32
Crystal system	Monoclinic	Monoclinic	Orthorhombic	Orthorhombic
Space group	*P*2(1)	*P*2(1)	*P*2(1)2(1)2(1)	*P*2(1)2(1)2(1)
a/Å	7.506(1)	7.512(1)	7.917(2)	7.810(1)
b/Å	18.714(3)	18.733(4)	19.736(5)	21.431(4)
c/Å	11.590(2)	11.599(2)	21.320(5)	21.948(3)
α (°)	90.00	90.00	90.00	90.00
β (°)	103.03(1)	103.10(1)	90.00	90.00
γ (°)	90.00	90.00	90.00	90.00
V/Å^3	1586.1(4)	1589.8(5)	3331.2(14)	3673.6(10)
ρ_{calcd}/g cm^{-3}	1.281	1.278	1.255	1.243
μ/mm^{-1}	0.097	0.097	0.096	0.095
Radiation	Mo $K_{\alpha 1}$	Mo $K_{\alpha 1}$	Mo $K_{\alpha 1}$	Mo $K_{\alpha 1}$
Wavelength/Å	0.71073	0.71073	0.71073	0.71073
Scan mode	ω	ω	ω	ω
F(000)	648	648	1336	1464
$2\theta_{max}$	56.00	50.00	53.50	53.00
Reflections collected	4378	3225	4353	4670
Observed reflections ($I > 2\sigma(I)$)	2765	2882	1673	2544
No. of parameters	407	407	419	470
R^c, wR^d	0.0450, 0.1061	0.0418, 0.1003	0.0495, 0.0759	0.0464, 0.0990
Goodness of fit	0.925	0.944	0.796	0.862
Δ(*ρ*)max., min./e Å^{-3}	0.592, −0.163	0.575, −0.136	0.173, −0.177	0.238, −0.250

[a] **5** and **7** were obtained from MeOH–CH_2Cl_2, respectively; **6** and **8** were obtained from MeOH–acetone, respectively. [b] M = more-soluble salt; L = less-soluble salt. [c] $R = (|Fo| - |Fc|)/|Fo|$. [d] $wR = \{\Sigma[w(Fo^2 - Fc^2)^2]/\Sigma[w(Fo^2)^2]\}^{1/2}$.

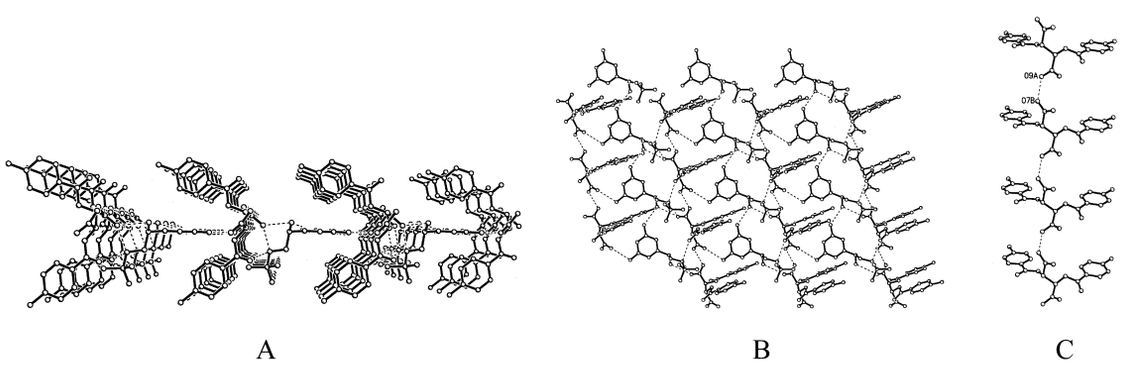

Fig. 1 Crystal structures of the more-soluble salt from crystal **5**. Supramolecular sheet, top view (A) and side view (B) down the *a* axis; Ribbon structure of D-DTTA molecules in the diastereomeric salts (C). All H-bonds are represented by dotted lines.

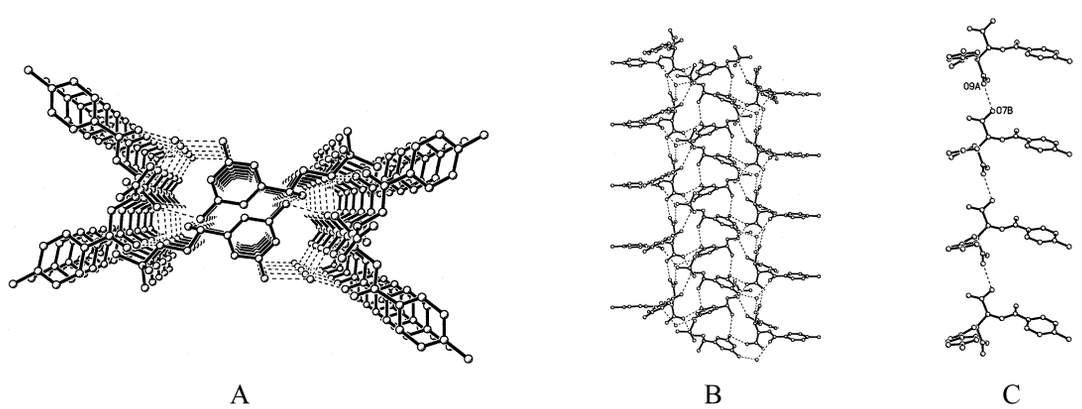

Fig. 2 Crystal structures of less-soluble salt from crystal **8**. Supramolecular column, top view (A) and side view (B) down the *a* axis; Ribbon structure of D-DTTA molecules in the diastereomeric salts (C). All H-bonds are represented by dotted lines.

a columnar hydrogen bonded network (Figs. 2A and 2B). Both ammonium ions of (*S*)- and (*R*)-**1** hold two DTTA molecules by salt-bridge hydrogen bonds[19] in a similar manner in the sheet and columnar supramolecules, respectively (Fig. 3). In the sheet supramolecule, the hydroxyl group on the stereogenic carbon of (*S*)-**1** forms a bridge hydrogen bond with the carboxylate group of D-DTTA (**4**) and the phenol group of the neighboring (*S*)-**1** molecule (Fig. 3A). In the columnar supra-

Table 3 Hydrogen bonded distances (Å) and angles (°) of crystals **5**, **7** and **8**

Crystal No.	**5**		Crystal No.	**7**		**8**	
D–H ··· A[a]	Distance D ··· A	Angle D–H–A	D–H ··· A[a]	Distance D ··· A	Angle D–H–A	Distance D ··· A	Angle D–H–A
N–H ··· O_{11}	2.896(4)	154.9	N–H ··· O_8	2.832(5)	162.4	2.844(4)	169(4)
N–H ··· O_6	2.963(4)	168.3	N–H ··· O_5	3.055(5)	160.3	3.037(5)	164(4)
O_1–H ··· O_8	2.778(3)	171.1	O_1–H ··· O_{12}	2.677(6)	170.9	2.767(4)	178.1
O_2–H ··· O_3	2.825(4)	146.0	O_2–H ··· O_8	2.727(4)	169.0	2.695(3)	175.4
O_3–H ··· O_6	2.928(3)	138.8	O_3–H ··· O_2	2.830(6)	145.8	2.871(5)	149.2
O_7–H ··· O_9	2.480(3)	168.2	O_7–H ··· O_9	2.471(5)	166.3	2.479(4)	168.3
			O_{12}–H ··· O_{11}	2.854(6)	174(5)	2.905(5)	160(6)
			O_{12}–H ··· O_6	2.835(7)	150(7)	2.944(5)	172(7)

[a] D: donor; A: acceptor.

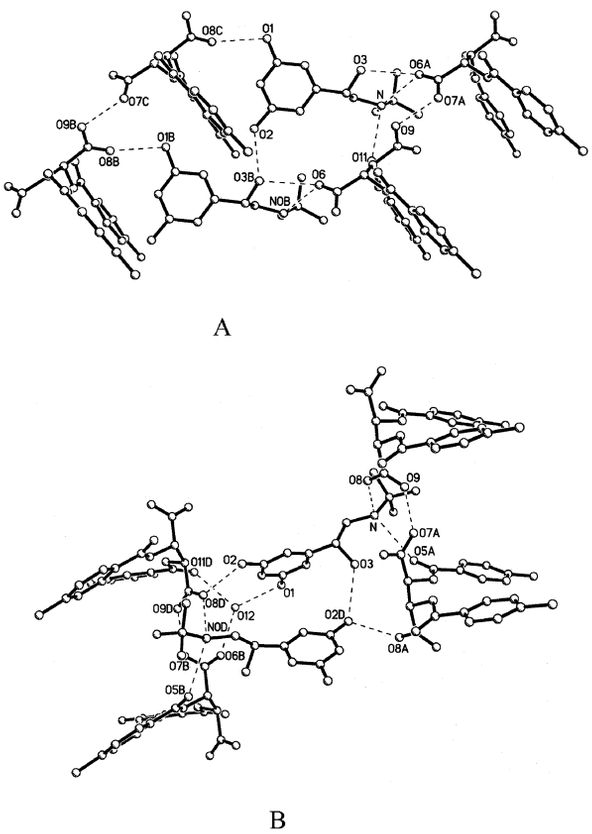

Fig. 3 The hydrogen bonding relationships of supramolecules in the more (A) and less (B) soluble salts of crystals **5** and **8**, respectively.

molecule however, the hydroxyl group on stereogenic carbon of (*R*)-**1** only formed a hydrogen bond with the phenol group of the neighboring (*R*)-**1** molecule and by this hydrogen bonding (Fig. 3B), (*R*)-**1** molecules self-assemble to construct a right-handed helicate structure (Fig. 2B). These imply that the success of the resolution is not determined by the presence of interactions between the groups on the chiral center of **4** and the enantiomers of **1**.[9,10b] Moreover, it is noticeable that in the less-soluble salt, (*R*)-**1** and **4** assembled with the aid of water to make the columnar supramolecular structure, in which a water molecule contributes to the formation of three hydrogen bonds and greater thermodynamic stability of the columnar supramolecule.[21] Differential scanning calorimetry (DSC) analyses[22] demonstrated that there are large differences between the heats of fusion of the more- and less-soluble salts (66.2 kJ mol^{-1} and 98.0 kJ mol^{-1}, respectively). In the less-soluble salt, there are two DSC curves and the first curve is relative to the loss of a water molecule, which was determined by thermogravimetric measurements (TG).[23,24] The energy of loss of a water molecule (ΔH = 53.6 kJ mol^{-1}) is higher than the enthalpy of fusion (44.4 kJ mol^{-1}) of the crystal without incorporated water, and this implies that the water molecule is important for the formation of more thermodynamically stable salts and efficient resolution, which is in agreement with Saigo's,[21a] Larsen's[21b] and Kozma's[23] results, and contrary to Wynberg's[24] and Valente's[25] results.

The above results showed that the formation of supramolecular structures is not dependent on the crystallizing solvent system. Moreover, solvent systems have little influence on the resolution of *rac*-**1**.[24] When *rac*-**1** was resolved from two solvent systems, the enantiomeric purity of (*R*)-**1** (86.4% ee) and yield (74.6%) of the crystals collected from the first crystallization in methanol–dichloromethane are consistent with those in methanol–acetone (87.4% ee and 73.1% yield, respectively), and no acetone molecule was detected by ^{1}H NMR analysis of the precipitated salts from methanol–acetone. Furthermore, the powder X-ray diffraction analysis also showed that the precipitated salts possess the same crystal structure as the salt recrystallized from methanol–acetone (Fig. 4). Thus, we conclude that the quite different supramolecular structures of the

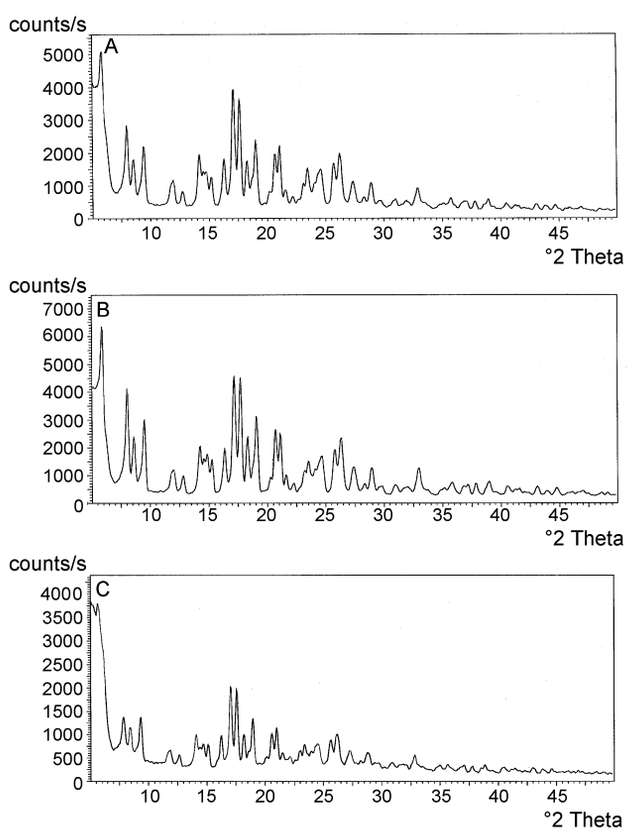

Fig. 4 Powder X-ray diffraction patterns for the salt (R)-**1**·**4**. Crystals collected from the resolution process in MeOH–CH_2Cl_2 (A) and in MeOH–acetone (B), and a single recrystallization in MeOH–acetone with (*R*)-**1**>99% ee (C).

pair of diastereomeric salts originate from the molecular chiral recognition between **4** and the enantiomer of *rac*-**1**, and contribute to the chiral discrimination of the diastereomeric salts and the effective resolution of *rac*-**1**.

Conclusion

A facile method for the direct resolution of terbutaline (**1**) has been established. The effective resolving agent **4** was quickly found by a "family" approach[4] and enantiomerically pure (*R*)-**1** was prepared with >99% ee in 77% overall yield. The four crystals of the diastereomeric salts were obtained from two solvent systems. X-Ray crystallographic studies demonstrated that the less-soluble salt pair forms a columnar supramolecular structure through a hydrogen bonded network, in which a water molecule contributes to the formation of two additional hydrogen bonds,[21] while the more-soluble salt pair forms a sheet supramolecular structure. The formation of supramolecules is independent of the crystallizing solvent system. These different supramolecular structures originate from the enantiodifferentiating self-assembly between **4** and the enantiomer of *rac*-**1** and contribute to crystal stability and effective resolution. It is of interest to point out that nature has selected among its many three-dimensional arrays of molecular shapes, the helix and the β-sheet as part of its mechanisms for recognition in life processes.[26] The resolution process is a simple model for recognition which plays an important role in biological systems and the preferred "biological answer" is the crystallization of one of the diastereomeric salts.[27]

Experimental

General

^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker (300 or 400 MHz) spectrometer, unless otherwise noted. Chemical shifts of ^{1}H NMR were expressed in ppm with the residual signal of DMSO as an internal standard (δ = 2.5 ppm), and chemical shifts of ^{13}C NMR were expressed in ppm with the residual signal of DMSO as an internal standard (δ = 39.8 ppm). IR spectra were measured with a NICOLET 200SXV FTIR spectrometer. Powder X-ray diffraction patterns were measured with a Philips Analytical system (X'Pert Graphics & Identify), using CoK_α radiation. Melting points were determined on digital melting point apparatus and are uncorrected. Differential scanning calorimetry (DSC) was measured with a Perkin-Elmer DSC7 system. Optical rotations are given in 10^{-1} deg cm^2 g^{-1} and were measured with a Perkin-Elmer polarimeter 341. Liquid chromatographic analysis was conducted on a Beckman-110 instrument equipped with model 168 detectors as an ultra violet light (280 nm).

Optical resolution of 1-(3′,5′-dihydroxyphenyl)-2-(*tert*-butylamino)ethanol (1)

The sulfate of 1-(3′,5′-dihydroxyphenyl)-2-(*tert*-butylamino)-ethanol (**1**) (20.0 g, 73 mmol) was dissolved in a solution of K_2CO_3 (15 g) in water (15 mL) and then extracted with ethyl acetate (70 mL × 4). The organic phase was dried over Na_2SO_4. After the solvent was removed, the free base of terbutaline was obtained as a solid, which was applied to the next resolution process as soon as possible. The solid was added to a solution of **4** (28.2 g, 73 mmol) in methanol (48 mL) and acetone (308 mL).[28] The mixture was heated to reflux for 2 h and then allowed to cool to room temperature. The resulting colorless crystals were collected by filtration and recrystallized twice. 21.5 g (76.8% and 99.0% ee) of the salt of (*R*)-**1** and **4** was obtained (Found: C, 60.76; N, 2.62; H, 6.26. $C_{32}H_{39}NO_{12}$ requires C, 61.04; N, 2.22; H, 6.24%); mp 165.8–167.0 °C; $[\alpha]_D^{20}$ +78.8 (*c* 0.8 in MeOH); ν_{max}(KBr)/cm^{-1} 3559, 3409, 1710, 1609, 1272, 1176, 1109 and 760; δ_H(300 MHz; DMSO) 1.20 (9H, s, *t*-Bu), 2.36 (6H, s, 2 × *p*-Me), 2.71 (1H, t, *J* = 11.7 Hz, NCH), 2.94 (1H, d, *J* = 12.0 Hz, NCH), 4.65 (1H, d, *J* = 9.6 Hz, OCH), 5.64 (2H, s, 2 × OCH, DTTA), 6.14 (1H, s, Ar), 6.24 (2H, s, Ar), 7.30 (4H, d, *J* =8.1 Hz, 2 × Ar, DTTA) and 7.83 (4H, d, *J* = 7.8 Hz, 2 × Ar, DTTA); δ_C(75 MHz, DMSO) 21.6, 25.2, 48.5, 56.0, 69.1, 73.1, 102.0, 104.2, 127.3, 129.6, 129.7, 144.1, 144.5, 158.8, 165.4 and 169.1. The enantiomeric purity of (*R*)-**1** in the diastereomeric salts was determined by HPLC on a SUMICHIRAL OA-4900 column with *n*-hexane–dichloromethane–methanol–trifluoroacetic acid (240 : 140 : 20 : 1) as eluent, flow rate 1.0 ml min^{-1}, t_D-*DTTA*= 5.32 min, *tS* = 14.97 min, *tR* = 17.08 min.

Preparation of salt (*S*)-1·4

To a solution of equimolar quantities of (*S*)-**1** (>99% ee) and **4** in methanol was added dichloromethane. The resulting crystals, salts of (*S*)-**1·4** were collected by filtration (Found: C, 62.84; N, 2.63; H, 6.14. $C_{32}H_{37}NO_{11}$ requires C, 62.84; N, 2.29; H, 6.10%); mp 193.0–195.0 °C; $[\alpha]_D^{20}$ −41.6 (*c* 0.8 in MeOH); ν_{max}(KBr)/cm^{-1} 3391, 1721, 1692, 1609, 1269, 1152, 1104, and 760; δ_H(400 MHz; DMSO; Me_4Si) 1.20 (9H, s, *t*-Bu), 2.36 (6H, s, 2 × *p*-Me), 2.71 (1H, t, *J* = 11.2 Hz, NCH), 2.92 (1H, d, *J* = 10.8 Hz, NCH), 4.66 (1H, t, *J* = 8.4, 2.0 Hz, OCH), 5.64 (2H, s, 2 × OCH, DTTA), 6.13 (1H, t, *J* = 2.4, 1.6 Hz, Ar), 6.23 (2H, d, *J* = 2.0 Hz, Ar), 7.29 (4H, d, *J* = 8.0 Hz, 2 × Ar, DTTA), 7.84 (4H, d, *J* = 8.4 Hz, 2 × Ar, DTTA) and 9.28 (br s, PhOH); δ_C(75 MHz; DMSO) 21.6, 25.2, 48.6, 56.0, 68.9, 73.2, 102.0, 104.2, 127.4, 129.6, 129.7, 144.1, 144.5, 158.7, 165.4 and 169.1.

Growth of single crystals

Single crystals **5** and **7** were obtained from methanol–dichloromethane, whereas **6** and **8** were obtained from methanol–acetone.

Crystallographic analysis

The X-ray diffraction measurements for crystals **5**, **6**, **7** and **8** were performed on a Siemens P4 automatic four-circle diffractometer using graphite monochromatic MoK_α radiation (λ = 0.71073 Å) at 295 K (**5**), 295 K (**6**), 295 K (**7**) and 291 K (**8**). Intensity data were collected in the variable ω scan mode. The structures were solved with direct methods by using SHELXL-97 and refined by full-matrix least-square calculation on F∧2∧ with SHELXL-97.[29] Calculations were performed on a PII-350 computer with the Siemens SHELXTL program package.[30]

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