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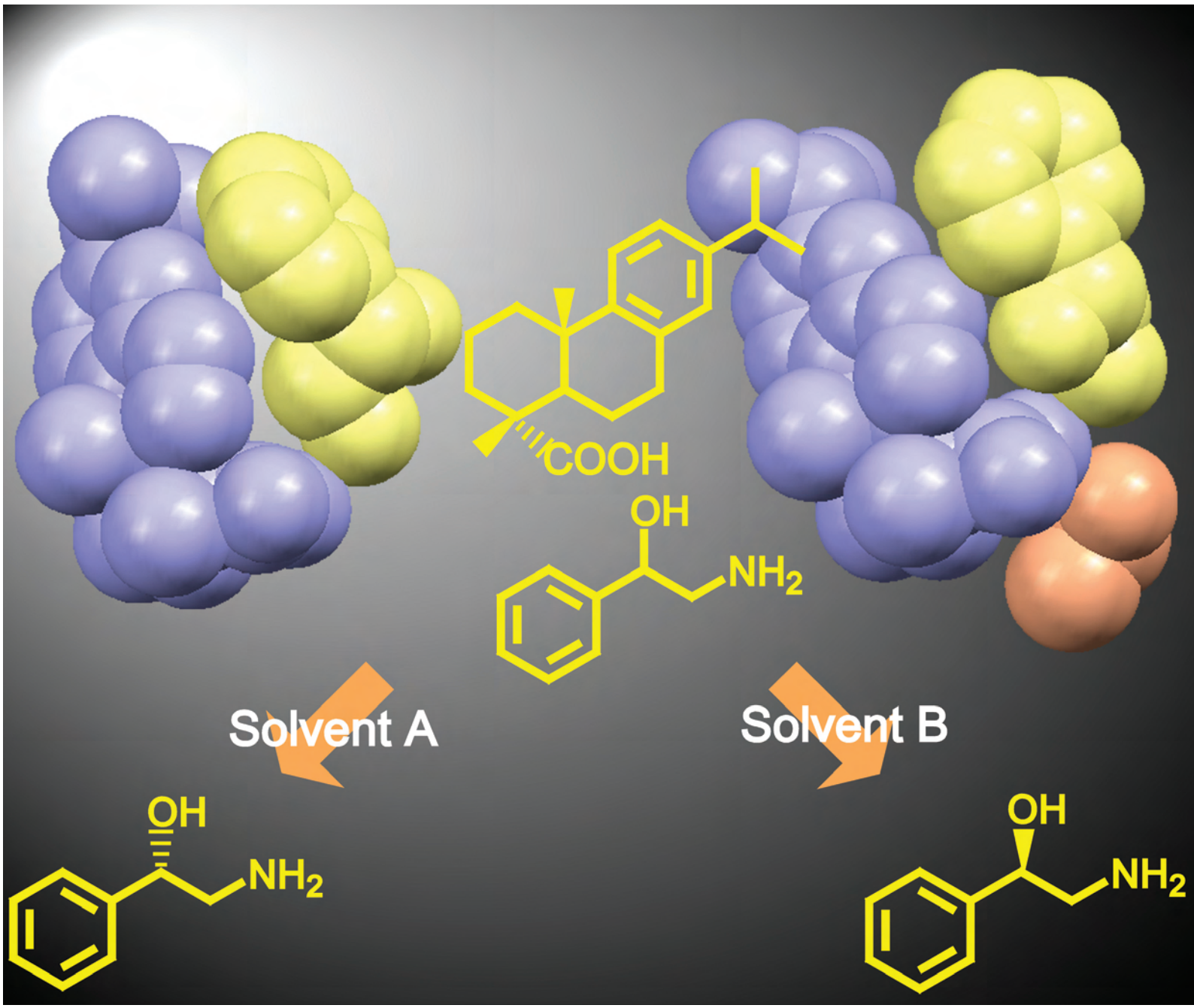

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FULL PAPER
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Solvent control of optical resolution of 2-amino-1-phenylethanol using dehydroabietic acid†‡

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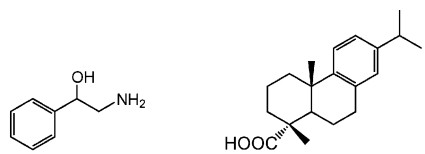
The optical resolution of 2-amino-1-phenylethanol (2-APE) by the solvent switch method was investigated using dehydroabietic acid (DAA), a natural chiral acid obtained as one of the main components of disproportionated rosin. The solvent dependency of optical rotation measurements of 2-APE, DAA and the diastereomeric salts suggested solvent control of optical resolution. Both (*R*)- and (*S*)-2-APE were resolved, as the first success for aminoalcohols, only by changing the resolving solvents: (*S*)-2-APE was obtained in high optical purity by a single crystallization operation with polar solvents ($\varepsilon > 50$), whereas the efficiency was lower for (*R*)-2-APE using less polar solvents ($20 < \varepsilon < 40$). The results were compared and discussed with reference to the crystal structures of the diastereomeric salts.

Introduction

Preparation of enantiomerically pure compounds is becoming increasingly important for various industries and has been widely studied.[1] Optical resolution by the diastereomeric salt formation method remains one of the most useful methods for obtaining a target chiral substrate, especially on an industrial scale.[2,3] In order to separate both enantiomers of a target racemate, the method usually requires both enantiomers of a resolving agent. Thus, most resolving agents derived from natural products are expected to resolve either enantiomer of a racemate.

Sakai *et al.* recently reported a new technique, the dielectrically controlled optical resolution (DCR) method, as a practical and convenient diastereomeric salt formation method.[4] This method allows both enantiomers of a racemate to precipitate as their less soluble salts using a single enantiomer of a resolving agent. So far, however, only limited amine–acid systems are known as successful examples,[4] because the controlling factors of the DCR phenomenon are as yet unclear. It is thus interesting and important to apply the DCR method to other kinds of chiral compounds and to investigate the effect of solvents from not only an industrial but also an academic viewpoint. In a previous paper, we reported that optical rotation study of diastereomeric salts provides an instant and simple clue to the combination of possible amine–carboxylic acids for DCR.[5]

Chiral 1,2-aminoalcohols are seen in many natural and pharmaceutical products[6] and are well known to be useful as chiral ligands for asymmetric synthesis.[7] 2-Amino-1-phenylethanol,[8,9] 2-APE **1** (Fig. 1), is an important basic skeleton in many adrenergic drugs.[10] We recently reported the optical resolution of **1** with dehydroabietic acid, DAA **2**, obtained as a single enantiomer from disproportionated rosin[11], by the conventional diastereomeric salt formation method.[12] In this study, we tried to resolve both enantiomers of **1** as less soluble salts with **2** through inspection of the relationship between solvent dependency of optical rotation and the DCR phenomenon. We also investigated single crystals of the diastereomeric salts and discuss the resolution data.



2-Amino-1-phenylethanol **1** Dehydroabietic acid **2**

Fig. 1 Structures of 2-amino-1-phenylethanol (2-APE, **1**) and dehydroabietic acid (DAA, **2**).

Results and discussion

Optical rotation measurement

The optical rotation of **1**, **2**, the diastereomeric salts and the chiral salts with achiral compounds, AcOH for **1** and 2-$PrNH_2$ and 2-aminoethanol for **2**, was investigated. The solvents used to control the polarity included $CHCl_3$, 2-PrOH, EtOH, MeOH, and water. All optical rotation data were presented as molar rotations [ϕ] for comparison between compounds of different molecular weights. The values of the dielectric constants of mixed solvents were calculated as the weighted average of the mixture components.

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† Electronic supplementary information (ESI) available: Solvent dependency of (*R*)-, (*S*)-**1** and the chiral salt (Fig. S1), **2** and the chiral salt (Fig. S2), and diastereomeric salts of (*R*)-**1/2**, (*S*)-**1/2** (1 : 1) and (*S*)-**1/2** (1 : 2) (Fig. S3); hydrogen bonding data (Tables S1–S3, Fig. S4–S6) for the crystals of (*R*)-**1/2**, (*S*)-**1/2** and (*S*)-**1/2** (1 : 2). See DOI: 10.1039/b717071h

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2-APE, DAA and achiral salts

The [ϕ] values of **1** decreased with the increase of ε,[4a] and some solvent dependency ($\Delta[\phi] = 77$) was observed (Fig. S1). Large solvent dependency was expected to be the result of conformational change due to the flexible structure.[13,14] The molar rotation of chiral (*R*)-**1**/AcOH salt was determined in order to study the effect of salt formation. A much smaller change ($\Delta[\phi] = 14$) was observed, although the solvent dependency was similar to that of the free amine, **1**. These results demonstrated that salt formation with small and achiral acids decreases the solvent dependency of the conformational change to a large extent.[5,13a]

The solvent dependency of **2** and its chiral salt was evaluated (Fig. S2). The resolving agent **2** showed a large [ϕ] but the solvent dependency, slightly concave to the axis, was much smaller ($\Delta[\phi] = 21$) than that of **1**. This result seems reasonable considering the rigid fused three-ring structure of **2**.[15] However, a much larger solvent dependency ($\Delta[\phi] = 78$), convex to the axis, was observed for the chiral salt with 2-aminoethanol, 2-AE. Salt formation seemed to induce a chiral nature around the flexible 2-AE.

In a previous study, either acids or amines showed a large solvent dependency of [ϕ] for DCR-successful systems while their counterparts did not.[5] Corresponding results were obtained for **1** and **2** ($\Delta[\phi]_2 > \Delta[\phi]_1$). The optical rotation data for the chiral salts also showed a difference between **1**/AcOH and **2**/2-AE. The present behaviour appeared to be similar for the DCR-successful system 1-phenyl-2-(4-methylphenyl)ethylamine/mandelic acid (PTE/MA),[5] even though the solvent dependencies of the amine and the acid were opposite.

2-APE/DAA

The optical rotation properties of the (1 : 1) diastereomeric salts of **1** and **2** were examined in various solvents and the results are shown in Fig. 2. The difference in optical rotation values of the diastereomeric salts was large ($[\phi]_{(R)\text{-}1/2}$–$[\phi]_{(S)\text{-}1/2}$ = 126–166). On the other hand, both diastereomeric salts showed a change of [ϕ] in the range of $\varepsilon < 10$ ($\Delta[\phi] = 61$ for (*S*)-**1/2** and $\Delta[\phi] = 53$ for (*R*)-**1/2**) while almost constant [ϕ] was obtained for higher ε ($\varepsilon > 18$). Again the results appeared similar to the behavior of the previous system[5] and the present system was therefore considered to be a new example of the DCR phenomenon.

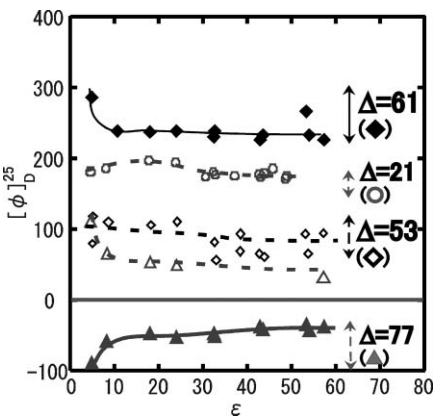

Fig. 2 Solvent dependence of molar rotation of (*R*)- and (*S*)-**1**, **2**, and the diastereomeric salts (*R*)-**1/2** and (*S*)-**1/2**. (*R*)-**1** (▲), (*S*)-**1** (△), **2** (○), (*R*)-**1/2** (◇), (*S*)-**1/2** (◆).

Optical resolution of 2-APE with DAA

Optical resolution of **1** with **2** was carried out in various solvents, mostly alcohol–water mixtures up to $\varepsilon = 63$, because of the low solubility of **2** in water. The data summarized in Table 1 and Fig. 3 are the results of a single crystallization in each solvent. It was clearly shown that both (*S*)- and (*R*)-**1** were obtained as less soluble salts depending on the solvents. This is the first report of the DCR phenomenon for an aminoalcohol. The use of **2**, easily obtained from a natural compound, should be an economical advantage from an industrial standpoint.

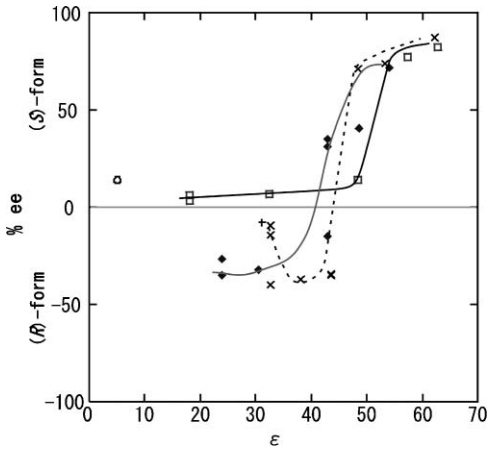

Fig. 3 Relationship between the enantiomeric excess of the less soluble diastereomeric salt and the dielectric constant (ε) of the solvent used in the resolution. 2-PrOH–H_2O (□), EtOH–H_2O (◆), MeOH–H_2O (×), chloroform (○), 90% MeOH–2-PrOH (+).

A clear feature seen in Fig. 3 is the tendency that the (*S*)-**1** rich salt is obtained in higher purity as the water content increases. For example, 25% 2-PrOH ($\varepsilon = 60$) gave (*S*)-**1/2** salt of high optical purity, 82% ee, at high efficiency (49.7%). The optical purity increased to the highest level of 87% ee with 35% MeOH ($\varepsilon = 59.7$) but with lower efficiency. On the other hand, in the middle ε range ($25 < \varepsilon < 40$), the less soluble diastereomeric salt gave a (*R*)-**1**-rich salt of 40% optical purity. The solvent dependency appears to be similar to that of PTE/MA.[4a]

As a second feature, a large solvent effect was observed; both EtOH and MeOH gave (*R*)-**2**-rich salt as the less soluble salt and (*S*)-**1**-rich salt with increase of water content. However, a linear change was seen for EtOH–water mixtures while for MeOH–water mixtures the change was very sharp at approximately $\varepsilon = 45$. On the other hand, from 2-PrOH–H_2O mixtures, only the (*S*)-**1**-rich salts were obtained over the entire ε range studied. Therefore, the resolution may be the effect of 'solvent switch'.[4b,c]

It should be mentioned here that NMR analysis showed that most of the (*S*)-**1/2** salt resolved had the (1 : 2) composition. Only from a 25% 2-PrOH solution was the (1 : 1) salt obtained, but slow recrystallization from the same solvent yielded the (1 : 2) salts. These results suggest that the (*S*)-**1/2** (1 : 2) salt is more stable than the (1 : 1) salt. On the other hand, (*R*)-**1** was always resolved as the (*R*)-**1/2** (1 : 1) salt. As far as we know, such an optical resolution has not been observed for the DCR phenomenon and further investigation is needed to rationalize the cause.

The solvent dependency of the optical rotation for the (1 : 2) salt species in various solvents was almost the same as that of the

Table 1 Resolution of (*RS*)-**1** with **2** in various solvents

Solvent Composition[a]	ε	Solvent volume[b] ml g^{-1}	Yield[c] (%)	$[a]_D^{25}$	op[d] (% ee)	Absolute config.	Resolution efficiency[e]
2-PrOH	18.0	12.5	16.3	36.2	5.9	*S*	1.9
2-PrOH	18.0	13.0	8.9	35.1	3.3	*S*	0.6
76% 2-PrOH	32.5	6.8	3.9	37.7	6.7	*S*	0.5
44% 2-PrOH	48.4	6.5	18.8	41.4	14.0	*S*	5.3
34% 2-PrOH	57.4	13.8	13.7	57.4	77.5	*S*	21.2
25% 2-PrOH	62.9	12.7	13.9	37.1	82.0	*S*	22.8
EtOH	24.0	12.9	8.4	—	34.8	*R*	5.9
EtOH	24.0	4.9	7.8	44.3	26.9	*R*	4.2
88% EtOH	30.6	6.8	4.3	28.9	32.4	*R*	2.8
65% EtOH	43.0	3.4	3.5	51.7	31.1	*S*	2.2
65% EtOH	43.0	6.5	22.6	39.9	15.1	*R*	6.8
65% EtOH	43.0	6.6	10.6	40.7	35.1	*S*	7.4
54% EtOH	48.7	9.2	6.4	44.0	40.6	*S*	5.2
44% EtOH	54.1	32.0	9.9	52.8	71.5	*S*	14.2
MeOH	32.6	12.5	20.4	29.2	39.8	*R*	16.2
MeOH	32.6	4.4	17.9	32.9	14.2	*R*	5.1
MeOH	32.6	10.2	16.5	38.0	9.3	*R*	3.1
88% MeOH	38.2	9.7	20.7	31.2	37.4	*R*	15.5
76% MeOH	43.5	12.7	4.0	35.8	34.7	*R*	2.7
76% MeOH	43.5	6.8	20.1	35.8	34.7	*R*	13.9
65% MeOH	48.5	13.4	11.1	52.5	71.1	*S*	15.8
54% MeOH	53.3	13.0	6.5	53.3	74.0	*S*	9.6
35% MeOH	62.2	107.7	18.5	60.6	87.0	*S*	32.2
Chloroform	5.0	6.4	4.6	46.2	13.8	*S*	1.3
90% MeOH–2-PrOH	31.1	6.4	9.1	32.9	7.5	*R*	1.4

[a] wt%. [b] *vs.* (*RS*)-**1**/(*S*)-**2**. [c] Based on (*RS*)-**1**. [d] Optical purity (op) determined by chiral HPLC analysis using CHIRALCEL OD-H. [e] Yield × 2 × op/100.

(1 : 1) salt species (Fig. S3). As a result, an optical rotation study of the (1 : 1) amine–acid salt combination would be effective for estimation of the DCR phenomenon.

Crystal structure analysis‡

Kinbara *et al.*[16] studied the crystal structures of diastereomeric salts which were effectively resolved by a diastereomeric salt formation method, and showed that the hydrogen-bond network forming a 2_1-column and van der Waals interactions are important for a less soluble crystal. Recently, Sakai *et al.* have shown a crystal structure difference in the hydrogen-bond network due to a water molecule in one of the diastereomeric salts[4a,c] to which the DCR method is applicable. In this study, structural analysis for the DCR phenomenon was also pursued with the present diastereomeric system, **1/2**.

As is well known, the X-ray analysis provides the relative stereochemistry, between **1** and **2** in the present system, but it is useful enough to obtain information on the hydrogen-bond network The crystals used for this study were independently grown in suitable solvents with commercially available and optically pure (*R*)- and (*S*)-**1** and natural compound **2** ((1*R*,4a*S*,10a*R*)-1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethyl-7-(1-methylethyl)-1-phenanthrenecarboxylic acid),[17] the structure of which was also analyzed previously.[15]

(*R*)-2-APE/DAA

Single crystals of (*R*)-**1/2** were prepared from AcOEt solution after salt formation in EtOH. As shown in Fig. 4, the crystals include EtOH, drawn by a ball-and-stick model, between **1** and **2**. Three components connect with each other through hydrogen bonding to form the 2_1-column along the *b* axis. This is the first structure resolved by the DCR method that contains alcohol, not water, in the diastereomeric salt.[4]

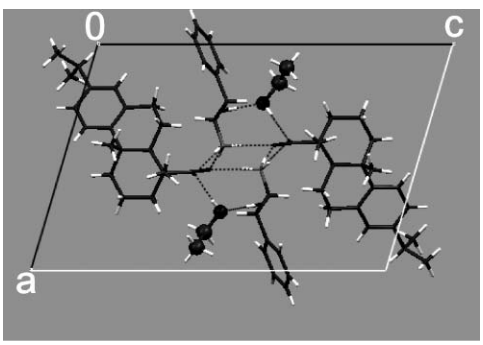

Fig. 4 Crystal structure of (*R*)-**1/2**.

(*S*)-2-APE/DAA (1 : 2) salt

The crystal formed the 2_1-column of $P2_12_12_1$ along the *a* axis and included no solvent (Fig. 5). However one **2** molecule, drawn by a ball-and-stick model, connects **1** and another **2**, so that it plays the same role as that of EtOH in the hydrogen-bond network of the (*R*)-**1/2** salt. The (1 : 2) salt consists of more hydrogen bonds than the (1 : 1) salt described below, making the crystal more stable after slow crystallization.

(*S*)-2-APE/DAA (1 : 1) salt

The single crystal of the (*S*)-**1/2** (1 : 1) salt was also obtained and analyzed. The crystal structure showed the 2_1-column expanding

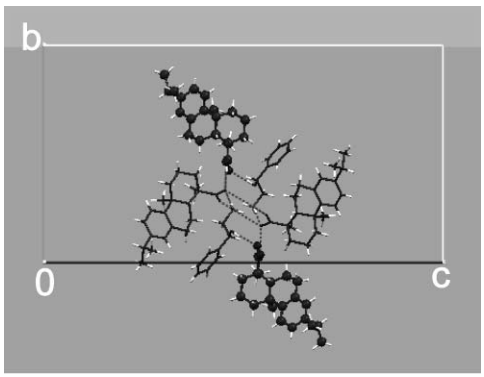

Fig. 5 Crystal structure of (*S*)-**1**/2(**2**).

a one-dimensional network along the *b* axis in the same way as (*R*)-2-APE/DAA (1 : 1), but no solvent was included (Fig. 6). The $P2_1$ structure with less hydrogen bonds seemed less stable than the (1 : 2) salt.

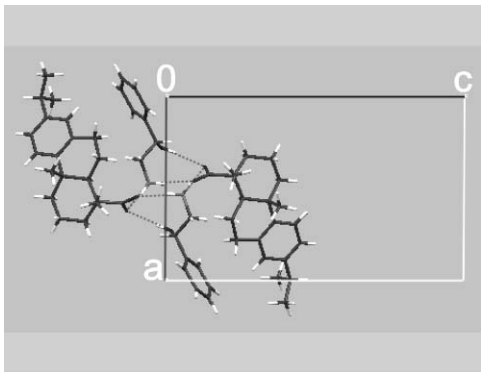

Fig. 6 Crystal structure of (*S*)-**1/2**.

Comparison of diastereomeric (*R*)-1/2 (1 : 1) and (*S*)-1/2 (1 : 2) salts

The stability of the diastereomeric crystals of (*R*)-**1/2** (1 : 1) salt and (*S*)-**1/2** (1 : 2) salt appears to be almost the same, because the arrangements of the molecules and the number of hydrogen bonds are quite similar (Tables S1 & S2). The largest difference is the hydrogen bonding between the hydroxyl group of **1** and the carbonyl group of **2** found in the (*S*)-**1/2** salt, but not in (*R*)-**1/2**. In (*R*)-**1/2**, the O–O length between the OH of **1** and C=O of **2** is 4.78 Å (O3–O2), and that of the corresponding groups in (*S*)-**1/2** (1 : 2) is 3.59 Å (O1–O2). These are a little too long to form a normal hydrogen bond. As a result, EtOH is included in (*R*)-**1/2** to fill the space between the acid and amine [EtOH $\cdots$ (R^2)COOH (**2**): 2.71 Å (O4–O2); EtO(H) $\cdots$ HO(R^1) (**1**): 2.71 Å (O4–O3)].

In the case of (*S*)-**1/2** (1 : 2), the second **2** connects **1** and **2** through hydrogen bonds with the hydroxyl group of the first **2** [(R^2CO)OH (1st **2**) $\cdots$ (R^2)CO(OH) (2nd **2**): 2.58 Å (O2–O5)] and with the hydroxyl group of **1** [(HO)OC(R^2) (2nd **2**) $\cdots$ HOR^1 ((*S*)-**1**): 2.70 Å (O4–O1)] (Tables S1–S3). The comparison of crystal structures indicates features common to the present system and previous ones:[4a,c,d,5,18] the diastereomeric salts contained a third component, that is, EtOH for (*R*)-**1/2** and H_2O[4a,c] as previously reported. The third molecule seems to be important to fill the space due to the chirality difference between the diastereomeric salts or due to conformational change.

Relationship between the DCR phenomenon and optical rotation, and the crystal structures of diastereomeric salts

The racemate **1** showed significant solvent dependency of optical rotation while the resolving agent **2** showed little in the present system. Between the two diastereomeric salts, (*R*)-**1/2** (1 : 1) and (*S*)-**1/2** (1 : 1), the optical rotation values were largely different (Fig. 2). The combination of the structural rigidity and flexibility of a resolving agent and a racemate seems to cause the difference in [ϕ]. This result corresponds to the previous systems for which the DCR phenomenon was observed.[4a,c,5]

The comparison of the crystal structures of the diastereomeric salts showed a clear difference in the hydrogen-bond network. Both diastereomeric salts contained a third component, that is, EtOH for (*R*)-**1/2** or a second **2** for (*S*)-**1/2** (1 : 2) in the present system. The third molecule is necessary to fill the space due to the large structural difference between the diastereomeric salts. Such a difference has not been observed before since one of the two diastereomeric salts contained H_2O for all previous systems.[4a,c]

For the DCR phenomenon, the contribution or incorporation of a solvent molecule through hydrogen bonding appears necessary. As a result, solvent or polarity dependence of [ϕ] can be a quick and easy probe for the DCR phenomenon, providing information to aid in the selection of resolving agents and solvent systems.

Experimental

General

Optically pure (*R*)- and (*S*)-2-amino-1-phenylethanol (**1**) were used without further purification. ^{1}H NMR spectra were recorded in $CDCl_3$ at 400 MHz (Bruker DRX400, Molecular Analysis and Life Science Center (MALS) of Saitama University). Chemical shifts are expressed in parts per million (ppm) relative to $(CH_3)_4Si$ and coupling constants in Hertz (Hz). Single crystal X-ray analysis was performed on a CCD system (Bruker Smart Apex, MALS). Specific rotations were measured with a polarimeter (JASCO DIP-370) and the optical rotation value reported was the mean of at least three measurements. HPLC analysis was performed at rt. Melting points are reported uncorrected.

Optical rotation measurement

The solution (10 mL) of a salt, an acid, or an amine was prepared at a concentration of 0.1 g per 100 mL (*c* 0.1) with a solvent incubated in a thermostatted bath at 25.0 ± 0.2 °C for 1 h. Optical rotation was measured using a water-jacketed cell by the Na D line at 25.0 ± 0.2 °C.[19] A solvent mixture was prepared by mixing two kinds of solvents in a certain weight ratio at 25.0 °C. The ε value of the mixed solvent was calculated as the weighted average of the mixture components based on the following equation: $\varepsilon_{(mix)} = (wt\%_{(solvent\ 1)} \times \varepsilon_{(solvent\ 1)}) + (wt\%_{(solvent\ 2)} \times \varepsilon_{(solvent\ 2)})$, where $\varepsilon_{(solvent)}$ is the dielectric constant at 20 °C of a pure solvent.[4a]

Purification of 1

Dehydroabietic acid (**2**) supplied in ~75% purity (Arakawa Chemical Ind., Ltd.) was purified according to the literature.[12] $[\alpha]_D^{20}$ 62.5 (*c* 2.0, 95% ethanol)

Preparation of 2-PrNH$_2$/2, 2-AE/2, (*R*)-1/AcOH and (*S*)-1/AcOH salts

After dissolving **2** (1.0 mmol) in methanol (10 mL), 2-PrNH$_2$ or 2-AE (1.0 mmol) was added. After concentration, the residue was recrystallized from ethanol to obtain 2-PrNH$_2$/**2** and 2-AE/**2** salts. In the same way, (*R*)-**1**/AcOH and (*S*)-**1**/AcOH salts were prepared from (*R*)- or (*S*)-**1** (1.0 mmol) and AcOH (1.0 mmol), respectively.

Preparation of optically pure (*R*)-1/2 salt

Commercially available (*R*)-**1** (137.2 mg, 1.0 mmol) and **2** (300.4 mg, 1.0 mmol) were dissolved in ethanol (10 ml), and the solvent was removed under reduced pressure to afford the salt (*R*)-**1/2**. Mp 160.0–161.5 °C, $[\alpha]_D^{20}$ 13.5 (*c* 0.1, methanol), ^{1}H NMR (400 MHz, CD$_3$OD): δ = 7.42–7.35 (m, 4H), 7.32–7.26 (m, 1H), 7.13 (d, J = 8.1 Hz, 1H), 6.92 (d, J = 8.1 Hz, 1H), 6.82 (s, 1H), 4.80 (dd, J = 9.2, 3.6 Hz, 1H), 3.04 (dd, J = 12.9, 3.6 Hz, 1H), 2.96–2.72 (m, 4H), 2.30 (d, J = 13.1 Hz, 1H), 2.20 (dd, J = 12.4, 2.3 Hz, 1H), 1.89–1.41 (m, 7H), 1.22 (s, 3H), 1.19 (br, 3H × 3).

Preparation of optically pure (*S*)-1/2 (1 : 2) salt

The optically pure (*S*)-**1/2** (1 : 2) salt was prepared by recrystallization of the (*S*)-**1/2** (1 : 1) salt resolved from 35% 2-PrOH. Mp 164.5–165.5 °C, $[\alpha]_D^{20}$ 61.6 (*c* 0.1, methanol), ^{1}H NMR (400 MHz, CD$_3$OD): δ = 7.42–7.35 (m, 4H), 7.33 (m, 1H), 7.14 (d, J = 8.1 Hz, 1H), 6.93 (dd, J = 2.8, 7.1 Hz, 2H), 6.83 (s, 2H), 4.81 (d, J = 4.0 Hz, 2H), 3.07 (dd, J = 12.5, 3.6 Hz, 8H), 2.32 (d, J = 10.6 Hz, 2H), 2.18 (dd, J = 12.2, 2.2 Hz, 2H), 1.87–1.4 (m, 14H), 1.24 (s, 6H), 1.19 (d, J = 4.0 Hz, 12H), 1.18 (s, 6H).

Preparation of optically pure (*S*)-1/2 (1 : 1) salt

The (*S*)-**1/2** (1 : 1) salt was prepared from (*S*)-**1** (137.2 mg, 1.0 mmol) and **2** (300.4 mg, 1.0 mmol) by the same procedure as for (*R*)-**1/2**. Mp 154.5–156.0 °C, $[\alpha]_D^{20}$ 82.5 (*c* 0.1, methanol), ^{1}H NMR (400 MHz, CD$_3$OD): δ = 7.42–7.37 (m, 4H), 7.32–7.30 (m, 1H), 7.14 (d, J = 8.1 Hz, 1H), 6.92 (d, J = 8.1 Hz, 1H), 6.82 (s, 1H), 4.85 (d, J = 8.8 Hz, 1H), 3.09 (d, J = 8.2 Hz, 1H), 2.97–2.84 (m, 4H), 2.30 (d, J = 12.6 Hz, 1H), 2.21 (d, J = 12.2 Hz, 1H), 1.88–1.43 (m, 7H), 1.23 (s, 3H), 1.19 (br, 3H × 3).

Optical resolution of 2-APE with DAA

(*RS*)-**1** (137.2 mg, 1.0 mmol) and **2** (300.4 mg, 1.0 mmol) were dissolved in EtOH (20 mL). After concentration, the residue was recrystallized from various solvents. The conventional recrystallization procedure is as follows: MeOH (5.5 mL) solution of (*RS*)-**1/2** salt was warmed to 80 °C to give a clear solution. Cooling to room temperature, the resulting crystals were separated and washed with MeOH to afford the (*R*)-**1/2** (1 : 1) salt (89.3 mg, 0.204 mmol, 20.4%, 39.8% de).

Recrystallization from 25% 2-PrOH gave the (*S*)-**1/2** (1 : 1) salt (60.9 mg, 0.139 mmol, 13.9%, 82.0% de).

Optical purity determination

The optical purity of **1** was determined from its *N*-dinitrophenyl derivative by chiral HPLC analysis.[5] Chiral HPLC analysis was performed using CHIRALCEL OD-H (ϕ 4.6 mm × 250 mm, detection wavelength: 254 nm, flow rate: 0.4 ml min^{-1}, eluent: 50% 2-PrOH in hexane).

Crystal structure analysis of (*R*)-APE/DAA, and (*S*)-APE/DAA (1 : 2 & 1 : 1) salts

It should be mentioned that the X-ray analyses established the relative stereochemistry to compare the hydrogen-bond networks in the diastereomeric salts prepared from optically pure **1** and **2** [(1*R*,4a*S*,10a*R*)-1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethyl-7-(1-methylethyl)-1-phenanthrenecarboxylic acid].[11,17]

The pure diastereomeric salts, (*R*)-**1/2** and (*S*)-**1/2** (1 : 1), described above, were used for the preparation of the crystals for X-ray analysis. Single crystals of both (*R*)-**1/2** and (*S*)-**1/2** (1 : 1) were obtained by recrystallization from AcOEt solution while that of (*S*)-**1/2** (1 : 2) was from the CH$_3$CN solution of (*S*)-**1/2** (1 : 1). X-Ray intensities were measured up to $2\theta_{max}$ = 55.0° using graphite-monochromated MoKα radiation (λ = 0.71069 Å). The crystal structure was determined by direct methods with SHELXS97 and refined by the full-matrix least-squares method using SHELXL97.[20]

(*R*)-1/2

$C_{30}H_{45}NO_4$; formula weight 483.67; monoclinic; $P2_1$; a = 12.595(3) Å, b = 6.1165(12) Å, c = 18.862(4) Å, β = 106.42(3)°, V = 1393.8(5) Å^3 (123(2) K), Z = 2, D_{calcd} = 1.152 g cm^{-3}, μ (MoKα) = 0.075 mm^{-1}, $R1$ = 0.0672 and w$R2$ = 0.1642 for 7017 observed reflections with $I > 2\sigma$ with 3349 unique reflections. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center: deposition number CCDC 655808.‡

(*S*)-1/2 (1 : 2)

$C_{48}H_{67}NO_5$; formula weight 738.03; orthorhombic; $P2_12_12_1$; a = 6.3023(8) Å, b = 19.070(2) Å, c = 35.095(4) Å, V = 4218.0(9) Å^3 (123(2) K), Z = 4, D_{calcd} = 1.162 g cm^{-3}, μ (MoKα) = 0.074 mm^{-1}, $R1$ = 0.0927 and w$R2$ = 0.1999 for 29325 observed reflections with $I > 2\sigma$ with 5487 unique reflections. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center: deposition number CCDC 655810.‡

(*S*)-1/2 (1 : 1)

$C_{28}H_{39}NO_3$; formula weight 437.60; monoclinic; $P2_1$; a = 10.981(2) Å, b = 6.1913(12) Å, c = 17.850(4) Å, β = 90.37(3)°, V = 1213.5(4) Å^3 (123(2) K), Z = 2, D_{calcd} = 1.198 g cm^{-3}, μ (MoKα) = 0.076 mm^{-1}, $R1$ = 0.0536 and w$R2$ = 0.1332 for 8383 observed reflections with $I > 2\sigma$ with 3042 unique reflections. Crystallographic data have been deposited with Cambridge Crystallographic Data Center: deposition number CCDC 655809.‡

Conclusions

Both enantiomers of 2-amino-1-phenylethanol **1** were efficiently resolved using dehydroabietic acid **2**, a natural chiral acid. The solvent dependency of [ϕ] of **1**, **2**, and their diastereomeric salts indicated that this was feasible. It was demonstrated, not only from the resolution results but also from the single crystal X-ray analysis of the diastereomeric salts, that optical rotation measurements were effective for screening the DCR phenomenon. This is the first successful application of the DCR method or solvent switch to an aminoalcohol. The present system is a good example to show the versatility of the method from an industrial viewpoint considering that **2** is an inexpensive compound easily obtained from rosin.

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