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Optical Rotation Study on Solvent Dependence of Diastereomeric Salt Discrimination Properties

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The optical rotation properties have been studied for two diastereomeric salts of four kinds of amine–carboxylic acid salt systems, and the results have been compared among them and their chiral salts. The diastereomeric salts of 2-(4-methylphenyl)-1-phenylethylamine/mandelic acid (1-phenyl-2-(4-methylphenyl)ethylamine; PTE/MA) and α-amino-ε-caprolactam/*N*-tosylphenylalanine (ACL/TPA) exhibited relatively large differences in optical rotation values and solvent dependency. In contrast, the diastereomeric salts of α-methylbenzylamine/MA and piperazine-2-carboxylic acid *t*-butylamide/TPA possessed similar optical rotation behavior; the values and solvent dependency were almost identical. These results were discussed in relation to the dielectrically controlled resolution phenomenon for the formers, PTE/MA and ACL/TPA, and were also compared with the crystal structures.

The reliable preparation of enantiomerically pure compounds is important in areas such as the pharmaceutical and food industries. On an industrial scale, the most useful method for the preparation of single enantiomers remains separation by crystallization, and diastereomeric salt formation is the most widely used technique.[1]

We have an ongoing program involving optical resolution by diastereomeric salt formation[2] and have been studying molecular recognition between chiral acids and amines.[3] Optical rotation measurement is a typical method for determining the purity of a resolved amine or acid. We are interested in the optical rotation of diastereomeric salts because the resultant value provides the purity of the target amine or acid before decomposition of the salt.[3c] At the same time, optical rotation reflects the molecular conformation of chiral compounds in solution,[4–6] which is useful information for molecular recognition studies. However, no systematic study has been reported for amine–acid salts.

Recently, Sakai et al. proposed a new diastereomeric salt formation method, dielectrically controlled optical resolution (DCR), which separates both enantiomers of a target molecule as less-soluble salts using one enantiomer of the resolving agent while controlling the solvent dielectric constant, ε, to achieve optical resolution.[7,8] This method is practical and overcomes the economic and time constraints of the diastereomeric salt formation method.[1] The DCR phenomenon indicates a reversal in the solubility of the diastereomeric salts. Analysis of the structural and conformational features of diastereomeric salts in solution can provide a deeper understanding of the mechanism of molecular recognition.

In this study, we chose four kinds of salts, 2-(4-methylphenyl)-1-phenylethylamine (PTE, **2**)/mandelic acid (MA, **1**),[8] α-methylbenzylamine (MBA, **3**)/**1**, α-amino-ε-caprolactam (ACL, **5**)/*N*-tosylphenylalanine (TPA, **4**),[7] and piperazine-2-carboxylic acid *t*-butylamide (PBC, **6**)/**4**,[9] (Chart 1) and the optical rotation properties were characterized. The carboxylic acid **1** is the resolving agent for both **2** and **3**, and **4** is that for **5** and **6** in a conventional diastereomeric salt formation method. However, the DCR method can be applied to **2**/**1**[8] and **5**/**4**,[7] but not to **3**/**1** and **6**/**4**.[9b] The relation between their optical rotation behavior and DCR phenomena is discussed together with comparison of the crystal structures.

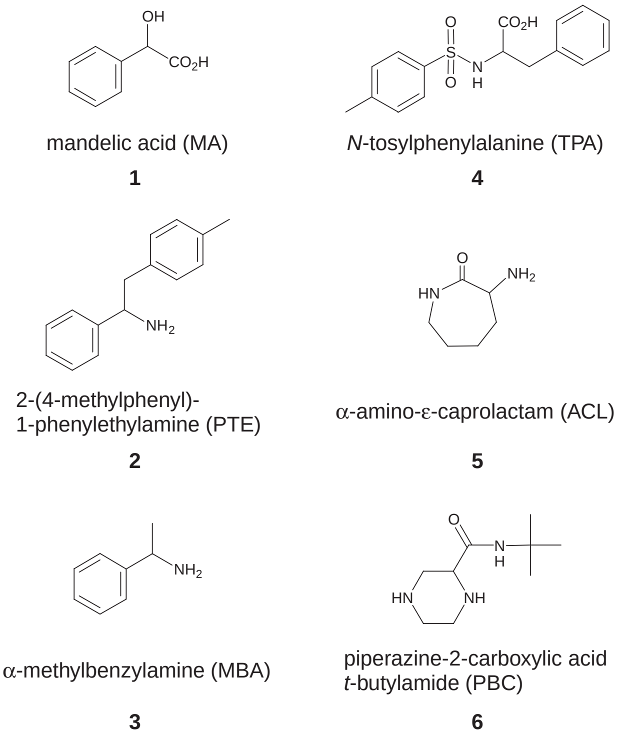
mandelic acid (MA)
1
N-tosylphenylalanine (TPA)
4
2-(4-methylphenyl)-1-phenylethylamine (PTE)
2
α-amino-ε-caprolactam (ACL)
5
α-methylbenzylamine (MBA)
3
piperazine-2-carboxylic acid *t*-butylamide (PBC)
6

Chart 1. Chiral carboxylic acids and amines used in the study.

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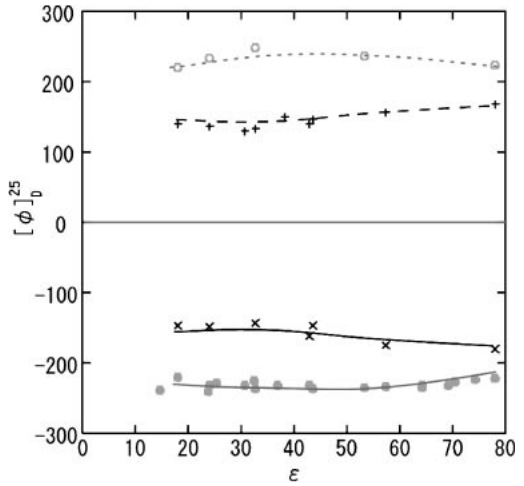

Fig. 1. Solvent dependence of molar rotation of the resolving agents ((*S*)- and (*R*)-(**1**)) and chiral salts with *i*-PrNH$_2$ (*i*-PrNH$_2$/(*R*)-**1** and *i*-PrNH$_2$/(*S*)-**1**). (*R*)-**1** (●), (*S*)-**1** (○), *i*-PrNH$_2$/(*R*)-**1** (×), and *i*-PrNH$_2$/(*S*)-**1** (+).

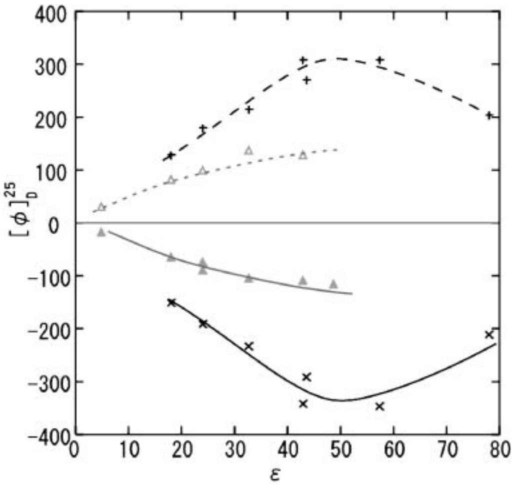

Fig. 2. Solvent dependence of molar rotation of the amines ((*R*)- and (*S*)-**2**), and chiral salts with CH$_3$CO$_2$H ((*R*)-**2**/CH$_3$CO$_2$H and (*S*)-**2**/CH$_3$CO$_2$H). (*R*)-**2** (▲), (*S*)-**2** (△), (*R*)-**2**/CH$_3$CO$_2$H (×), and (*S*)-**2**/CH$_3$CO$_2$H (+).

Results

Optical Rotation Measurement of Chiral Salts (Achiral Amine/Chiral Acid and Chiral Amine/Achiral Acid). Optical rotation provides structural information on chiral compounds in solution, even though the value is an average of all possible conformations.[4,6] In order to discuss the conformation and solvent dependency of the diastereomeric salts, the chiral salts, that is achiral amine/chiral acid and chiral amine/achiral acid, were investigated under controlled conditions. The chiral salts of **2**, **3**, **5**, and **6** were prepared with acetic acid, while those of **1** and **4** were prepared with isopropylamine (*i*-PrNH$_2$). The solvents used to control the polarity included MeOH, EtOH, *i*-PrOH, and water. All data are presented as molar rotation in the figures for comparison with those of the corresponding diastereomeric salts.

***i*-PrNH$_2$/MA (1):** The optical rotation was measured in various solvents and the results are summarized in Fig. 1, where molar rotation and the ε value of each solvent were used as the axis and the abscissa,[3,6–8] respectively. The optical rotation values were nearly constant and symmetrical ($[\phi] \approx \pm 230$) for (*S*)- and (*R*)-**1**.

The salts between *i*-PrNH$_2$ and (*R*)- and (*S*)-**1** were studied to examine the effect of salt formation. The optical rotation value largely decreased ($\Delta[\phi] \approx 40$–100) from the values obtained for (*R*)- and (*S*)-**1**, but the solvent dependency was similar to that of the free acids (The results contrast to those of *i*-PrNH$_2$/**4** are presented as Supporting Information.).

PTE (2)/CH$_3$CO$_2$H: The optical rotation of (*R*)- and (*S*)-**2** gradually increased up to $\varepsilon = 48$ ($\Delta[\phi] \approx 170$), as shown in Fig. 2, but measurements were limited due to its low solubility in polar solvents. The results for salts with CH$_3$CO$_2$H are also summarized in Fig. 2. Contrary to **2**, the optical rotation values of **2**/CH$_3$CO$_2$H increased. The solvent dependency was larger than that of the free amine, which indicates the conformation change of the salt is large, depending on the solvent polarity. The maximum values of the absolute values were observed at $\varepsilon \approx 50$.

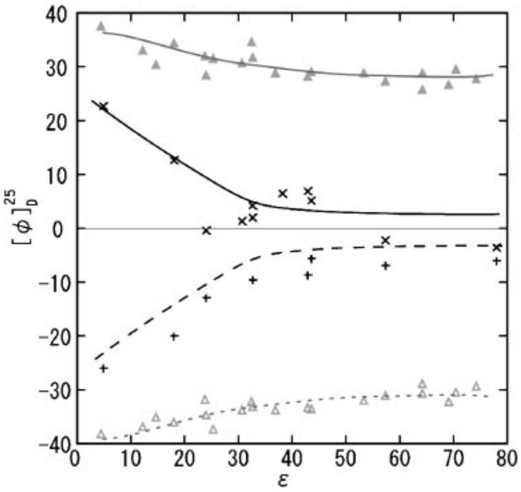

Fig. 3. Solvent dependence of molar rotation of the amines ((*R*)- and (*S*)-**3**) and chiral salts with CH$_3$CO$_2$H ((*R*)-**3**/CH$_3$CO$_2$H and (*S*)-**3**/CH$_3$CO$_2$H). (*R*)-**3** (▲), (*S*)-**3** (△), (*R*)-**3**/CH$_3$CO$_2$H (×), and (*S*)-**3**/CH$_3$CO$_2$H (+).

MBA (3)/CH$_3$CO$_2$H: For both enantiomers of **3**, more optical rotation measurements were performed using more mixed solvent systems of different ε values. Optical rotation for both enantiomers of **3** was measured more precisely than at the ε values for other amines and acids. As shown in Fig. 3, the values for (*R*)- and (*S*)-**3** correspond well with opposite signs; their solvent dependencies were weak. Optical rotation of the CH$_3$CO$_2$H salts drastically decreased ($\Delta[\phi] \approx 20$), then $[\phi]$ approached zero at higher polarity ($\varepsilon > 35$).

The optical rotation of (*S*)-**4**, (*R*)- and (*S*)-**5**, and (*R*)- and (*S*)-**6** was also studied with their *i*-PrNH$_2$ or CH$_3$CO$_2$H salts. The molar rotation values for *i*-PrNH$_2$/**4** were increased, which was different from *i*-PrNH$_2$/**1**. On the other hand, the absolute values of CH$_3$CO$_2$H salts for **5** and **6** were decreased, which was contrary to the results for **2** but correspondent to those of **3** (The data are available as Supporting Information.).

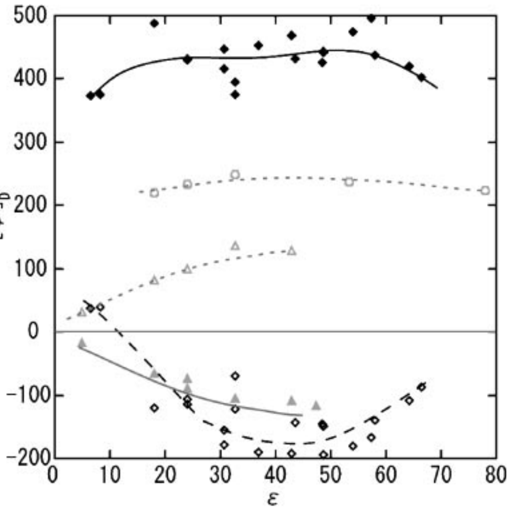

Fig. 4. Solvent dependence of molar rotation of the amines ((*R*)- and (*S*)-**2**), resolving agent (*S*)-**1**, and diastereomeric salts ((*R*)-**2**/(*S*)-**1** and (*S*)-**2**/(*S*)-**1**). (*R*)-**2** (▲), (*S*)-**2** (△), (*S*)-**1** (○), (*R*)-**2**/(*S*)-**1** (◇), and (*S*)-**2**/(*S*)-**1** (◆).

Table 1. Optical Rotation Changes for Each Salt and Differences between Diastereomeric Salts in Figs. 4–7

System	Diastereomeric salt	$\Delta[\phi]$	$\lvert[\phi]_{SS} - [\phi]_{RS}\rvert$
PTE (**2**)/MA (**1**)	(*S*)-**2**/(*S*)-**1**	122	330–670
	(*R*)-**2**/(*S*)-**1**	230	
MBA (**3**)/MA (**1**)	(*R*)-**3**/(*R*)-**1**	51	7–40[a)]
	(*S*)-**3**/(*R*)-**1**	88	
ACL (**5**)/TPA (**4**)	(*S*)-**5**/(*S*)-**4**	199	20–100
	(*R*)-**5**/(*S*)-**4**	174	
PBC (**6**)/TPA (**4**)	(*S*)-**6**/(*S*)-**4**	142	0–30
	(*R*)-**6**/(*S*)-**4**	135	

a) $\lvert[\phi]_{RR} - [\phi]_{SR}\rvert$.

Optical Rotation Measurement of Diastereomeric Salts (Chiral Amine/Chiral Acid). Optical rotation values for the diastereomeric salts of **2**/**1**, **3**/**1**, **5**/**4**, and **6**/**4** were determined in $CHCl_3$ as a less-polar solvent, in CH_3CN, MeOH, EtOH, *i*-PrOH, and water as polar solvents, and in mixtures of these solvents.

PTE (2)/MA (1): Results for the diastereomeric salts between (*R*)- and (*S*)-**2** and (*S*)-**1** are presented in Fig. 4. The optical rotation further changed from the chiral salt, **2**/CH_3CO_2H (Fig. 2), so that the change should be the effect of the chirality of **1**. The [ϕ] values for (*R*)-**2**/(*S*)-**1** and (*S*)-**2**/(*S*)-**1** were quite different, $\lvert[\phi]_{SS} - [\phi]_{RS}\rvert \approx$ 330–670, which are summarized in Table 1 along with the data for other salts. In addition, both diastereomeric salts showed substantial solvent dependency ($\Delta[\phi] \approx$ 122–230), which indicates the large conformation change of the salts as **2**/CH_3CO_2H (Fig. 2). Of the two salts, the change for (*S*)-**2**/(*S*)-**1** was a little smaller ($\Delta[\phi] = 122$).

MBA (3)/MA (1): The [ϕ] change of the diastereomeric salts of (*R*)-**3**/(*R*)-**1** and (*S*)-**3**/(*R*)-**1** is shown in Fig. 5. It is surprising that little difference was found between the diastereomeric salts[10] ($[\phi]_{RR} - [\phi]_{SR} \approx$ 7–40), which contrasted **2**/**1** in spite of the carboxylic acid being the same. This is the first reported observation for a diastereomeric salt. The solvent dependency means that the solvent effect on the conformation is very close for both diastereomeric salts. The [ϕ] values of (*R*)-**3**/(*R*)-**1** and (*S*)-**3**/(*R*)-**1** showed more change ($\Delta[\phi]_{RR} \approx 51$, $\Delta[\phi]_{SR} \approx 88$) than those of **3** and **1**. The optical resolution of **3** by **1** was repeatedly tried using various solvents, but the DCR phenomenon was not observed at all (Supporting Information).

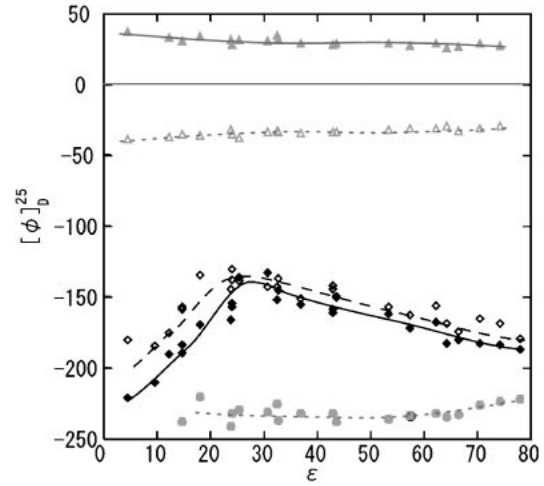

Fig. 5. Solvent dependence of molar rotation of the amines ((*R*)- and (*S*)-**3**), resolving agent (*R*)-**1**, and diastereomeric salts ((*R*)-**3**/(*R*)-**1** and (*S*)-**3**/(*R*)-**1**). (*R*)-**3** (▲), (*S*)-**3** (△), (*R*)-**1** (●), (*R*)-**3**/(*R*)-**1** (◇), and (*S*)-**3**/(*R*)-**1** (◆).

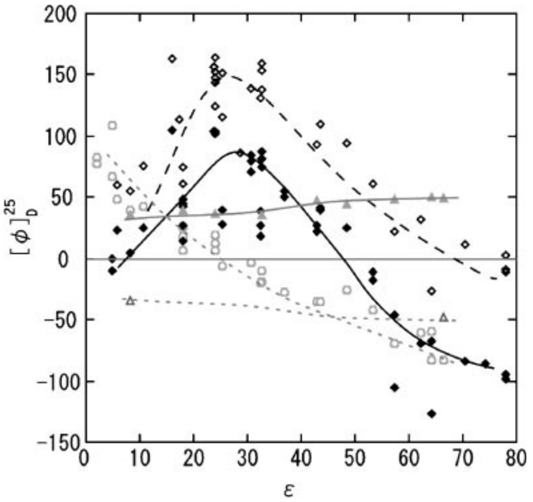

Fig. 6. Solvent dependence of molar rotation of the amines ((*R*)- and (*S*)-**5**), resolving agent (*S*)-**4**, and diastereomeric salts ((*R*)-**5**/(*S*)-**4** and (*S*)-**5**/(*S*)-**4**). (*R*)-**5** (▲), (*S*)-**5** (△), (*S*)-**4** (○), (*R*)-**5**/(*S*)-**4** (◇), and (*S*)-**5**/(*S*)-**4** (◆).

ACL (5)/TPA (4): The optical rotation values of both diastereomeric salts (*R*)-**5**/(*S*)-**4** and (*S*)-**5**/(*S*)-**4** increased to a maximum at $\varepsilon \approx$ 25–30, where the [ϕ] of **4** was almost zero, and then gradually decreased and changed sign (Fig. 6). Comparing with the result of **2**/**1**, the difference in [ϕ] of the diastereomeric salts, $[\phi]_{RS} - [\phi]_{SS}$, seems smaller but its value and $\Delta[\phi]_{RS}$ and $\Delta[\phi]_{SS}$ are still large as can be seen in Table 1, indicating that they behave differently in solution.

PBC (6)/TPA (4): Interestingly, both diastereomeric salts (*R*)-**6**/(*S*)-**4** and (*S*)-**6**/(*S*)-**4** had almost identical [ϕ] values in the whole range of the solvent polarity, just as seen for **3**/**1**

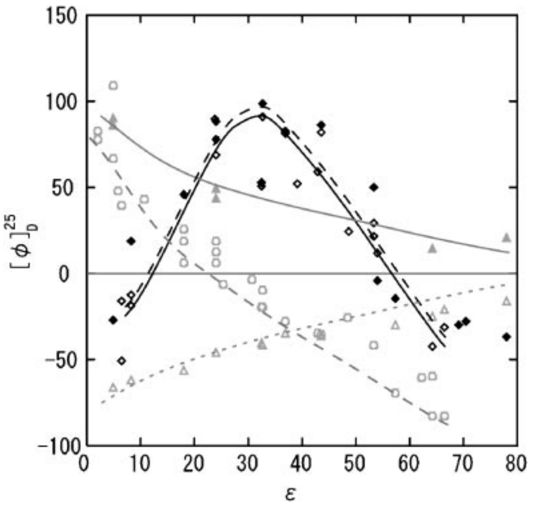

Fig. 7. Solvent dependence of molar rotation of the amines ((*R*)- and (*S*)-**6**), resolving agent (*S*)-**4**, and the diastereomeric salts ((*R*)-**6**/(*S*)-**4** and (*S*)-**6**/(*S*)-**4**). (*R*)-**6** (▲), (*S*)-**6** (△), (*S*)-**4** (○), (*R*)-**6**/(*S*)-**4** (◇), and (*S*)-**6**/(*S*)-**4** (◆).

(Fig. 7 and Fig. 5). The sign of optical rotation changed twice, at $\varepsilon \approx 10$ and 50–60, and had a maximum at $\varepsilon \approx 10$.

Discussion

Optical Rotation Changes by Chiral Salt Formation. Figures 1–3 show the following two effects on optical rotation by chiral salt formation: 1) The optical rotation values [ϕ] were changed by salt formation for all chiral amines and carboxylic acids. 2) The solvent dependency of a chiral amine or acid was similar to that of the corresponding salt with an achiral counterpart in spite of the change in the optical rotation values. The first effect is explained by the electric charge formation and the conformation change of a chiral molecule to that of its salt. The second effect, however, was unexpected and interesting because it indicates that the basic effect of the solvent polarity on an amine or acid is the same as that on its salt. The relative arrangement of the chiral moiety would be slightly affected by salt formation.

Optical Rotation and Structural Features of the Diastereomeric Salts. Comparison of Figs. 2 and 4, and Figs. 3 and 5 shows that substantial changes were caused by the diastereomeric salt formation, while the basic features look similar to those of the corresponding chiral salt. Apparently, the optical rotation of the parent amine or acid was further affected by the chirality of the pairing acid or amine.

The optical rotation measurements of **1** and **3**, shown in Figs. 1, 3, and 5, help to explain the combinations of a simple amine and carboxylic acid. The nearly constant [ϕ], regardless of chiral salt formation and solvent polarity, indicates that stable conformations do not depend on solvent because of their inflexible structures. The [ϕ] values of (*R*)-**3**/(*R*)-**1** and (*S*)-**3**/(*R*)-**1** were close but produced small $\Delta[\phi]$ in the entire ε range studied. A similar behavior was observed for **3**/CH_3CO_2H at $\varepsilon > 30$ (Fig. 3). These results indicate that conformational changes are limited due to simple and rigid substituents on the asymmetric carbons of **1** and **3**. Exactly, the same optical rotation behaviors were obtained for (*R*)-**6**/(*S*)-**4** and (*S*)-**6**/(*S*)-**4** in Fig. 7. The results suggest the relative solution properties of the diastereomeric salts resemble each other for **3**/**1** and **6**/**4** and, therefore, solubility reversal is unlikely, which corresponds with the optical resolution.

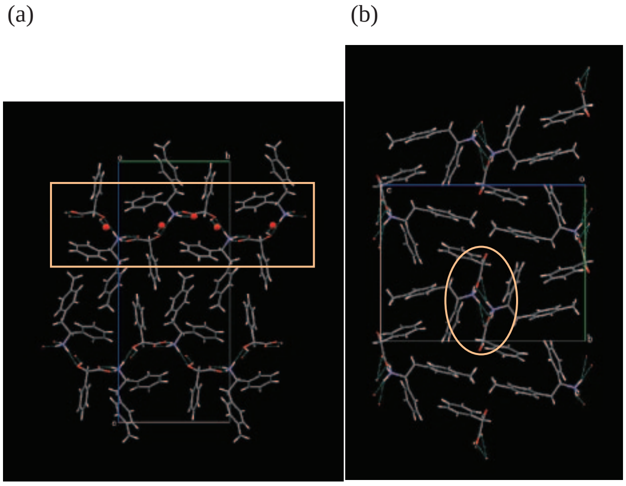

Fig. 8. Crystal packing of (a) (*S*)-**2**/(*S*)-**1**•H_2O[8] and (b) (*R*)-**2**/(*S*)-**1**.[8]

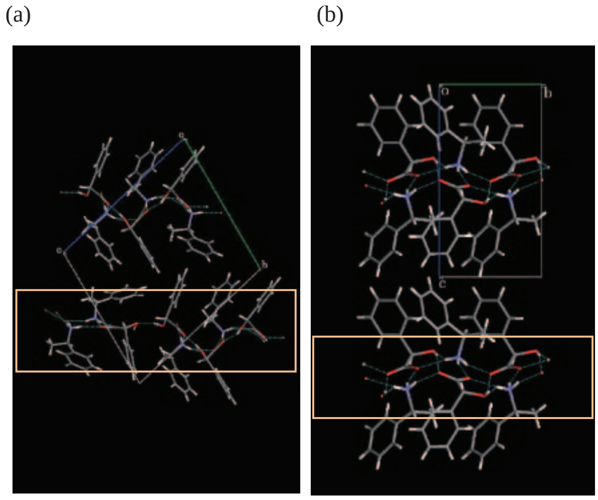

Fig. 9. Crystal packing of (a) (*S*)-**3**/(*R*)-**1**[14] and (b) (*R*)-**3**/(*R*)-**1**.[15]

In contrast, large differences in [ϕ] and solvent dependency were observed between (*R*)-**2**/(*S*)-**1** and (*S*)-**2**/(*S*)-**1** in Fig. 4 and, therefore, the solution properties of each salt are expected to be rather different. The results agree well with those of (*R*)-**5**/(*S*)-**4** and (*S*)-**5**/(*S*)-**4** shown in Fig. 6. Differences in both [ϕ] and solvent dependency between the diastereomeric salts should be essential for a reversal in solubility leading to the DCR phenomenon.[7,8] Thus, study of the solvent dependency of [ϕ] would provide a good instant clue for the selection of proper resolving agents for DCR.

Comparison with Crystal Structures. As optical resolution is the result of crystal growth from an appropriate solution, the crystal structure could reflect molecular structures in the solution. Therefore, it is interesting and useful to study the crystal structure of the diastereomeric salts and compare them with the optical rotation data mentioned above.

Figures 8 and 9[11] show the structures of **2**/**1**[8] and **3**/**1**,[11–13]

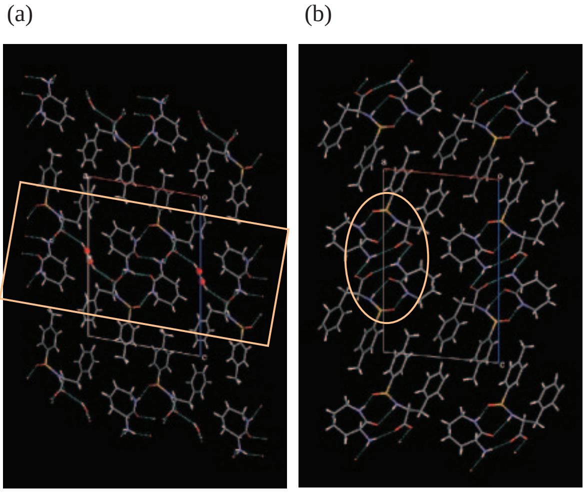

Fig. 10. Crystal packing of (a) (*S*)-**5**/(*S*)-**4**•H_2O[7b,16] and (b) (*R*)-**5**/(*S*)-**4**.[7b,16]

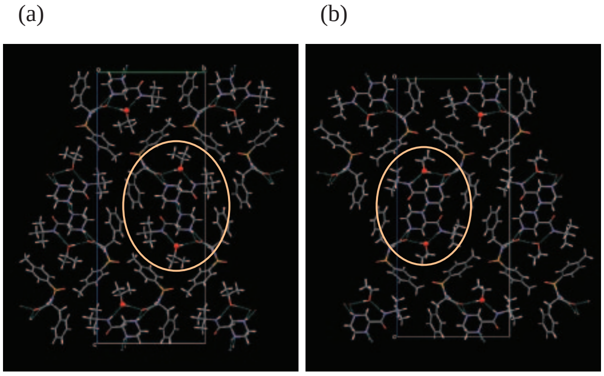

Fig. 11. Crystal packing of (a) (*S*)-**6**/(*S*)-**4**•*i*-PrOH and (b) (*R*)-**6**/(*S*)-**4**•EtOH.

respectively. A large difference exists in the structures of the diastereomeric salts of **2**/**1**: (*S*)-**2**/(*S*)-**1** forms a hydrogen-bonding layer involving water molecules in the network (Fig. 8a), whereas (*R*)-**2**/(*S*)-**1** forms a cluster of two amines and two acids without solvent molecules (Fig. 8b). In contrast, although the molecular arrangement of the diastereomeric salts of **3**/**1** (Fig. 9) are somewhat different, the hydrogen bonds form layers in both crystals. Two kinds of crystal systems, $P2_1$[11] (Fig. 9b) and $P2_12_12_1$,[13] have been reported for the less-soluble salts, but the basic feature of the hydrogen bonding is quite similar.

The crystal structures of diastereomeric salts of **5**/**4**[7b,16] and **6**/**4** are shown in Figs. 10 and 11, respectively. Both molecular arrangements of the diastereomeric **5**/**4** look similar. However, the hydrogen-bonding network is established by incorporating water molecules in (*S*)-**5**/(*S*)-**4** (Fig. 10a), while two amines and two acids form a closed network hydrogen-bonded without any solvent in (*R*)-**5**/(*S*)-**4** (Fig. 10b). On the other hand, the diastereomeric salts of **6**/**4** form similar crystal structures, with hydrogen bonding forming a small cluster from two amines and two acids plus two solvent molecules, *i*-PrOH (Fig. 11a) or EtOH (Fig. 11b).

A clear difference in the hydrogen-bonding systems was observed between the diastereomeric salts **2**/**1** and **5**/**4**, but quite a similarity was seen for **3**/**1** and **6**/**4**. Considering DCR is possible for the former two salts while not for the latter, the result corresponds qualitatively well with optical rotation measurement.

Conclusion

Measurement of the optical rotation of four chiral amine/chiral carboxylic acid salts in various solvents revealed two types of solvent dependency: one involving differences in optical rotation behavior and the other, observed for the first time, involving very similar behavior between the diastereomeric salts. The former was observed for the systems **2**/**1** and **5**/**4**, for which a new diastereomeric salt formation method, DCR, was applicable.[7,8] In contrast, the latter was observed for **3**/**1** and **6**/**4**, for which only a conventional diastereomeric salt formation method was applied. Crystal structure analysis seemed supportive of much easier optical rotation study; that is, the applicability of DCR was well related to differences in the hydrogen-bonding networks. For **2**/**1** and **5**/**4**, a large difference was observed between the diastereomeric salts, while quite a similarity was observed for **3**/**1** and **6**/**4**. Thus, optical rotation study of diastereomeric salts provides an instant and simple clue to the choice of possible amine–carboxylic acid combinations for DCR.

Experimental

Most of the diastereomeric salts studied, (*S*)-2-(4-methylphenyl)-1-phenylethylamine (**2**)/(*S*)-mandelic acid (**1**), (*R*)-**2**/(*S*)-**1**, (*RS*)-α-methylbenzylamine (**3**)/(*R*)-**1**, and (*S*)-**3**/(*R*)-**1**, (*S*)-α-amino-ε-caprolactam (**5**)/(*S*)-*N*-tosylphenylalanine (**4**), (*R*)-**5**/(*S*)-**4**, (*S*)-piperazine-2-carboxylic acid *t*-butylamide (**6**)/(*S*)-**4**, (*R*)-**6**/*N*-tosyl-(*S*)-alanine (TA), were supplied in >99% purity by Yamakawa Chemical Industry Co., and were used as received. The diastereomeric salt (*R*)-**6**/(*S*)-**4** was prepared from (*R*)-**6**/(*S*)-TA as described below. ^{1}H NMR spectra were recorded on a Bruker DRX400 spectrometer at the Molecular Analysis and Life Science (MALS) Center of Saitama University. Chemical shifts are internally referenced to the TMS signal (0 ppm) and *J* values are recorded in Hz. Single-crystal X-ray analysis was performed on a Brucker SMART CCD system (MALS Center). Melting points were determined with a Mitamura Riken Kogyo MEL-TEMP instrument and recorded in uncorrected form. Optical rotations were measured on a JASCO DIP-370 polarimeter. High-performance liquid chromatography was performed on a JASCO Intelligent HPLC system 900 equipped with a JASCO CD-1594 detector at rt.

(*R*)- and (*S*)-5.[17] Diastereomerically pure (*R*)-**5**/HCl (56.0 mg, 0.340 mmol) was neutralized with 8 M aqueous NaOH (5 mL), and extracted with dichloromethane. The organic layer was dried with anhyd. Na_2SO_4 and concentrated under reduced pressure to give (*R*)-**5** (41.0 mg, 0.319 mmol, 93.8%). Optically pure (*S*)-**5** was prepared from diastereomerically pure (*S*)-**5**/(*S*)-**4** by the same procedure.

(*R*)- and (*S*)-6.[9] Optically pure (*R*)-**6** was obtained from (*R*)-**6**/(*S*)-TA according to the following procedure. To an aqueous solution (1 mL) of the diastereomeric salt (434.3 mg, 1.01 mmol) was added 6 M aqueous HCl (1 mL), and the mixture was kept at 60 °C for 30 min. After cooling to 0 °C, TA was separated by filtration, and the filtrate neutralized with 6 M aqueous NaOH (0.7 mL) and concentrated under reduced pressure. To the concentrated solution, 6 M aqueous NaOH (0.55 mL) was added. The basic aqueous solution was extracted with *i*-PrOH (10 mL × 3), and the alcoholic solution was washed with 10% aqueous NaCl (10 mL), then evaporated under reduced pressure. Toluene (4 mL) was added to the residue, and the solution was stirred at 60 °C for 30 min. The hot solution was filtered and the filtrate concentrated under reduced pressure to give (*R*)-**6** (160.8 mg, 0.869 mmol, 86.0%). Optically pure (*S*)-**6** was prepared from diastereomerically pure (*S*)-**6**/(*S*)-**4** by the same procedure.

(*R*)- and (*S*)-2.[18] Diastereomerically pure (*R*)-**2**/(*S*)-**1** (202.53 mg, 0.557 mmol) was dissolved in 6 M aqueous NaOH (10 mL), and then extracted with three portions of 10 mL ether. The organic layer was washed with brine (5 mL), and dried with anhyd. Na_2SO_4. The ether solution was concentrated under reduced pressure to give (*R*)-**2** (110.7 mg, 0.524 mmol, 94.1%). Optically pure (*S*)-**2** was prepared from diastereomerically pure (*S*)-**2**/(*S*)-**1** by the same procedure.

(*R*)-6/(*S*)-4. In MeOH (10 mL), (*R*)-**6** (160.8 mg, 0.869 mmol), and (*S*)-**4** (277.7 mg, 0.869 mmol) were dissolved, and the solvent was removed under reduced pressure to afford the salt. (*R*)-**6**/(*S*)-**4**: mp 102–105 °C; $[\alpha]_D^{25}$ 19.5 (MeOH, *c* 0.1); IR (KBr) cm^{-1}: 3351, 3270, 1679, 1667, 1579, 1391, 1366, 1155; ^1H NMR (400 MHz, CD_3OD): δ 7.59 (d, $J = 8.0$ Hz, 2H), 7.25 (d, $J = 8.0$ Hz, 2H), 7.17–7.14 (m, 5H), 3.79 (dd, $J = 5.2$, 6.8 Hz, 1H), 3.49 (dd, $J = 3.2$, 9.6 Hz, 1H), 3.23 (dd, $J = 3.2$, 12.8 Hz, 1H), 3.10–2.99 (m, 3H), 2.96–2.89 (m, 4H), 2.38 (s, 3H), 1.34 (s, 9H).

Optical Purity Determination. The optical purity of α-methylbenzylamine (**3**) was determined on its acetylated derivative by chiral HPLC analysis. To a stirred solution of **3** (8.0 mg, 0.066 mmol) in dry THF was added Et_3N (6.68 mg, 0.066 mmol) in dry THF at rt under a nitrogen atmosphere. Acetic anhydride (6.74 mg, 0.066 mmol) in dry THF was added dropwise to the mixture, which was stirred for 30 min at the same temperature. The reaction mixture solvent was removed under reduced pressure. The residue was dissolved in EtOAc and washed with sat. aqueous $NaHCO_3$ and brine, and then dried with anhyd. Na_2SO_4. After concentration under reduced pressure, the residue was purified by preparative silica gel TLC (EtOAc) to give (8.8 mg, 0.054 mmol, 81.6%) as a white solid.

Chiral HPLC analysis was performed using CHIRALCEL AD-H (ϕ 4.6 mm × 250 mm, detection: UV at 254 nm, flow rate: 0.5 mL min^{-1}, eluent: 10% *i*-PrOH in hexane).

Optical Rotation Measurement. The solution (10 mL) of a salt, an acid, or an amine was prepared at a concentration of 0.1 g/100 mL (*c* 0.1) with a solvent incubated in a thermostated bath at 25.0 ± 0.2 °C for 1 h. The 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 and literatures: $\varepsilon_{(mix)} = (wt\,\%_{(solvent\ 1)} \times \varepsilon_{(solvent\ 1)}) + (wt\,\%_{(solvent\ 2)} \times \varepsilon_{(solvent\ 2)})$, where $\varepsilon_{(solvent)}$ is the dielectric constant at 20 °C of a pure solvent.[8]

Optical Resolution of 3 with (*R*)-1. A solution of (*RS*)-**3** (121.18 g, 1 mmol) and (*R*)-**1** (152.15 g, 1 mmol) in water (1.5 mL) was warmed to 100 °C to give a clear solution. The solution was cooled to room temperature and the resulting crystals were separated. The crystals were removed by filtration and washed with water to afford (*R*)-**3**/(*R*)-**1** salt (83.23 mg, 0.30 mmol, 60.9%).

The enantiomer of **3** was obtained by decomposing the separated diastereomeric salt by the following process: the diastereomeric salt (*R*)-**3**/(*R*)-**1** (20.0 mg, 0.073 mmol) was dissolved in 3 M aqueous NaOH (20 mL), and the oily organic layer was extracted with ether (20 mL × 3). The combined extract was washed with brine (20 mL), dried with anhyd. Na_2SO_4, and concentrated under reduced pressure to give (*R*)-**3**[10] (8.0 mg, 0.066 mmol, 90.5%, 99.9% ee).

Crystal Structure Analysis of (*R*)-6/(*S*)-4 and (*S*)-6/(*S*)-4. Single crystals of (*R*)-**6**/(*S*)-**4** and (*S*)-**6**/(*S*)-**4** were prepared by slow evaporation of the solvent from EtOH and an *i*-PrOH/H_2O (9:1) solution, respectively.

X-ray intensities were measured up to $2\theta_{max} = 55.0°$ using graphite-monochromated Mo Kα radiation ($\lambda = 0.71069$ Å). The crystal structure was solved by a direct method with SIR97[20] and refined by full-matrix least-squares using SHELX97.[21]

(*R*)-6/(*S*)-4•EtOH: $C_{27}H_{42}N_4O_6S$; formula weight 550.71; orthorhombic; $P2_12_12_1$ (#19); $a = 5.9245(8)$ Å, $b = 15.104(2)$ Å, $c = 34.762(5)$ Å, $V = 3110.7(7)$ Å^3 (296 K), $Z = 4$, $D_{calcd} = 1.176$ g cm^{-3}, μ(Mo Kα) $= 0.147$ mm^{-1}, $R = 0.0582$ and $Rw = 0.142$ for 7150 observed reflections with $I > 2\sigma$ from 3035 unique reflections. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC-285984.

(*S*)-6/(*S*)-4•*i*-PrOH: $C_{28}H_{44}N_4O_6S$; formula weight 564.73; orthorhombic; $P2_12_12_1$ (#19); $a = 5.6723(18)$ Å, $b = 14.453(2)$ Å, $c = 36.534(12)$ Å, $V = 2995.1(16)$ Å^3 (123 K), $Z = 4$, $D_{calcd} = 1.252$ g cm^{-3}, μ(Mo Kα) $= 0.154$ mm^{-1}, $R = 0.0687$ and $Rw = 0.1713$ for 6793 observed reflections with $I > 2\sigma$ from 5813 unique reflections. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC-285983. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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Supporting Information

Solvent dependences of molar rotation of (*S*)-(**4**), *i*-$PrNH_2$/(*S*)-**4**, (*R*)- and (*S*)-**5**, (*R*)-**5**/CH_3CO_2H, (*S*)-**5**/CH_3CO_2H, (*R*)- and (*S*)-**6**, (*R*)-**6**/CH_3CO_2H, (*S*)-**6**/CH_3CO_2H. Optical resolution data of **3** with (*R*)-**1** by changing solvent polarity. These materials are available free of charge on the web at http://www.csj.jp/journals/bcsj/.

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