Solvent-Induced Chirality Control in the Enantioseparation of 1-Phenylethylamine via Diastereomeric Salt Formation

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ABSTRACT Solvent-induced chirality control in the enantioseparation of 1-phenylethylamine **1** by *N*-(*p*-toluenesulfonyl)-(*S*)-phenylalanine **2** via diastereomeric salt formation was studied. (*S*)-**1**·(*S*)-**2** was preferentially crystallized as a less-soluble salt from aqueous alcohol, while (*R*)-**1**·(*S*)-**2** salt was mainly obtained by addition of solvents with a six-membered ring such as dioxane, cyclohexane, tetrahydropyran, and cyclohexene to 2-propanol. Further investigations were carried out from the viewpoints of molecular structures, optical rotation measurement, and X-ray crystallographic analyses. Crystallographic analyses have revealed that incorporation of the six-membered ring solvent molecule in (*R*)-**1**·(*S*)-**2** without hydrogen bonds changed the molecular conformation of (*S*)-**2** to stabilize the salt, which changed the selectivity of **1** in the enantioseparation. *Chirality 23:326–332, 2011.*

KEY WORDS: optical resolution; enantiomer; amino acids; solvent-switch method; X-ray crystallographic analysis; hydrogen-bonding network

INTRODUCTION

One of the most attractive methods to achieve enantioseparation of racemates into their enantiopure forms is a diastereomeric salt formation method with an enantiopure acidic/basic resolving agent.[1–3] This method enables us to obtain enantiopure compounds both in the laboratory and industrial scale because of the simple, economical, and reproducible operation. Recently, it has been reported that application of the mixture of structurally similar resolving agents can improve the enantioselectivity.[4] Although several researchers have been tried to clarify the chiral recognition mechanism from the viewpoint of phase diagrams, computational method, structural similarity, it is still difficult to predict an appropriate resolving agent for a racemate.[5–7] Therefore, it is necessary to apply several resolving agents to find a suitable combination by a trial-and-error approach, and a variety of new resolving agents have been developed to meet the demand.[8,9] For the design of new resolving agents, natural compounds are preferable candidates as inexpensive chiral sources.[10] Natural amino acid derivatives are one of the most widely used resolving agents because both acidic and basic resolving agents are easily accessible; however, only a single enantiomer is available from natural sources, and it is a drawback for efficiently obtaining both enantiomers from racemates.

Recently, Sakai et al. have reported an interesting enantioseparation method that both enantiomers are accessible from racemates using a single enantiomer as a resolving agent only by changing dielectric constants (ε) of the resolution solvents (dielectrically controlled resolution).[11–14] This method is especially advantageous for the naturally occurred resolving agents. In this method, a diastereomeric salt that is more-soluble in non-polar solvents can form hydrated (solvated) less-soluble salt crystals in polar solvents. This solvation phenomenon is dependent on the dielectric constant of the mixed solvents, which can inverse the relative stability of the less and more-soluble diastereomeric salts. Similar solvent-dependent switch of enantioselectivity has been reported in a resolution of diastereomeric 1-phenylethylamides of 1,1′-binaphthalene-2,2′-dicarboxylic acid[15] and enantioselective inclusion of 2-methylpiperidine with a chiral host compound.[16] In most cases, solvent molecules are included in the crystals by hydrogen bonds to switch the enantioselectivity.

Previously, we have also reported a solvent dependent enantioseparation of racemic 1-phenylethylamine **1** by a natural amino acid derivative, *N*-(*p*-toluenesulfonyl)-(*S*)-phenylalanine **2** (Fig. 1).[17] In this example, non-solvated diastereomeric salt (*S*)-**1**·(*S*)-**2** was preferably obtained from polar aqueous alcohols, on the other hand, 1,4-dioxane/alcohol mixed solvents afforded the solvated diastereomeric salt, (*R*)-**1**·(*S*)-**2**·dioxane as a less-soluble salt. Crystallographic analysis has revealed that incorporated dioxane molecules fill the void space and stabilize the (*R*)-**1**·(*S*)-**2** diastereomeric salt without any hydrogen-bonding interactions. In this example, no simple dependency was observed between ε and enantiomeric purity of resolved **1**. We have also showed the similar incorporation of cyclohexane in the diastereomeric salt (*R*)-**1**·(*S*)-**2**·cyclohexane from the X-ray crystallographic analysis. This observation strongly suggests that (*R*)-**1**·(*S*)-**2** can be solvated by solvents with a six-membered ring and cyclohexane, which is isostructural to dioxane, is a potential solvent

Crystallographic data for the structures reported in this article have been deposited with the Cambridge Crystallographic Data Centre.

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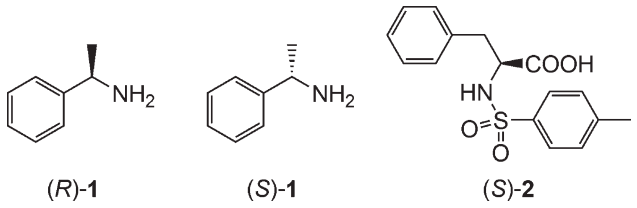

Fig. 1. Chemical structures of 1-phenylethylamine (**1**) and *N*-(*p*-toluenesulfonyl)-(*S*)-phenylalanine (**2**).

that the solvent switch method can be applied. In this study, we show the enantioseparation of *rac*-**1** by (*S*)-**2** in cyclohexane/2-propanol mixed solvents and clarify the mechanism of chirality control that depended on the shape and size of the solvent on the basis of X-ray crystallographic analyses of the diastereomeric salts.

MATERIALS AND METHODS

General

The measurement of ^{1}H NMR spectra was performed on Bruker DPX 200, AVANCE 300, and DRX 400 spectrometers (Molecular Analysis and Life Science Center, Saitama University). Melting temperatures were recorded on the MEL-TEMP melting point apparatus and are uncorrected. Optical rotation values were measured on the JASCO DIP-370 polarimeter. HPLC analyses were performed by using a JASCO Intelligent HPLC system 900.

Preparation of the Resolving Agents and the Diastereomeric Salts

Enantiopure resolving agents **2–4** were synthesized from the corresponding amino acids and arylsulfonyl chlorides and characterized according to the literatures. Enantiopure 1-phenylethylamines were kindly supplied by Yamakawa Chemical Industry Co.

***N*-(p-toluenesulfonyl)-(*S*)-phenylalanine (2).**[18] $[\alpha]_D^{25} = +2.10$ (*c* 1.00, MeOH, $T = 25^\circ$C); mp 168.0°C; IR(KBr) cm^{-1}: 3321, 3030, 1711, 1331, 1158; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.60 (d, $J = 8.2$ Hz, 2H), 7.26–7.05 (m, 7H), 5.00 (d, $J = 8.6$ Hz, 1H), 4.27–4.17 (m, 1H), 3.16–2.95 (m, 2H), 2.40 (s, 3H).

***N*-(p-toluenesulfonyl)-(*R*)-phenylglycine (3).**[19] $[\alpha]_D^{22} = -113.4$ (*c* 1.00, MeOH, $T = 22^\circ$C); mp 181.0–182.0°C; IR(KBr) cm^{-1}: 3591, 3293, 1725, 1600, 1460, 1344, 1326, 1290, 1258, 1210, 1167, 1091, 1069, 926, 899, 814, 725, 690, 594, 571, 533; ^{1}H NMR ($CDCl_3/CD_3OD$, 400 MHz): δ 7.61 (d, $J = 8.4$ Hz, 2H), 7.25–7.18 (m, 7H), 4.98 (s, 1H), 3.38 (s, 1H), 2.38 (s, 3H).

***N*-benzenesulfonyl-(*S*)-phenylalanine (4).**[20] $[\alpha]_D^{24} = +0.50$ (*c* 1.00, MeOH, $T = 24^\circ$C); mp 135.5°C; IR(KBr) cm^{-1}: 3342, 3173, 3061, 2967, 1735, 1697, 1447, 1376, 1347, 1294, 1171, 1109, 1093, 955, 835, 756, 720, 701, 688, 640, 586, 541; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72 (d, $J = 7.6$ Hz, 2H), 7.54 (t, $J = 7.2$ Hz, 1H), 7.44 (t, $J = 7.8$ Hz, 2H), 7.25–7.24 (m, 3H), 7.09–7.07 (m, 2H), 5.02 (d, $J = 8.8$ Hz, 1H), 4.28–4.22 (m, 1H), 3.11 (dd, $J_1 = 5.6$ Hz, $J_2 = 14$ Hz, 1H), 3.02 (dd, $J_1 = 6.4$ Hz, $J_2 = 14$ Hz, 1H).

Compound (*R*)-1·(*R*)-3. $[\alpha]_D^{24} = -105.7$ (*c* 1.00, MeOH, $T = 24^\circ$C); mp 185.0–186.0°C; IR(KBr) cm^{-1}: 3313, 1655, 1595, 1519, 1457, 1365, 1342, 1321, 1225, 1157, 1090, 1065, 921, 809, 729, 699, 667, 564, 546; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.64 (d, $J = 8.4$ Hz, 2H), 7.46–7.17 (m, 12H), 4.34 (q, $J = 6.9$ Hz, 1H), 4.16 (s, 1H), 2.39 (s, 3H), 1.45 (d, $J = 6.6$ Hz, 3H).

Compound (*S*)-1·(*R*)-3. $[\alpha]_D^{24} = -110.4$ (*c* 1.00, MeOH, $T = 24^\circ$C); mp 168.0–170.0°C; IR(KBr) cm^{-1}: 3316, 1648, 1583, 1496, 1456, 1376, 1358, 1344, 1325, 1231, 1159, 1090, 1063, 915, 896, 808, 777, 734, 718, 696, 669, 564, 548; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.64 (d, $J = 8.4$ Hz, 2H), 7.48–7.17 (m, 12H), 4.33 (q, $J = 6.6$ Hz, 1H), 4.20 (d, $J = 6.6$ Hz, 1H), 2.39 (s, 3H), 1.45 (d, $J = 6.6$ Hz, 3H).

Compound (*R*)-1·(*S*)-4. $[\alpha]_D^{24} = +23.8$ (*c* 1.00, MeOH, $T = 24^\circ$C); mp 150.0–152.0°C; IR(KBr) cm^{-1}: 3335, 1655, 1570, 1497, 1448, 1386, 1322, 1308, 1226, 1159, 1093, 969, 904, 753, 698, 687, 603, 588, 556; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.56 (d, $J = 7.5$ Hz, 2H), 7.47–7.42 (m, 1H), 7.32–7.27 (m, 7H), 7.13–7.11 (m, 3H), 7.04 (s, 2H), 4.10 (q, $J = 6.6$ Hz, 1H), 3.83 (dd, $J_1 = 5.1$ Hz, $J_2 = 6.9$ Hz, 1H), 3.00 (dd, $J_1 = 4.8$ Hz, $J_2 = 13.8$ Hz, 1H), 2.73 (dd, $J_1 = 7.5$ Hz, $J_2 = 13.8$ Hz, 1H), 1.44 (d, $J = 6.6$ Hz, 3H).

Compound (*S*)-1·(*S*)-4. $[\alpha]_D^{24} = +17.4$ (*c* 1.00, MeOH, $T = 24^\circ$C); mp 159.0–162.0°C; IR(KBr) cm^{-1}: 2930, 1559, 1449, 1398, 1324, 1163, 1093, 963, 905, 853, 751, 716, 700, 687, 587, 557, 488; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.74 (d, $J = 6.6$ Hz, 2H), 7.66–7.19 (m, 13H), 4.30 (q, $J = 6.6$ Hz, 1H), 3.46 (t, $J = 5.1$ Hz, 1H), 3.01 (dd, $J_1 = 5.1$ Hz, $J_2 = 13.5$ Hz, 1H), 2.93 (dd, $J_1 = 5.4$ Hz, $J_2 = 13.5$ Hz, 1H), 1.44 (d, $J = 6.6$ Hz, 3H).

Procedure of Enantioseparation via Diastereomeric Salt Formation

The general enantioseparation experiment was carried out as follows. Equimolar amounts of racemic 1-phenylethylamine **1** and *N*-(*p*-toluenesulfonyl)-(*S*)-phenylalanine **2** were dissolved in an appropriate solvent under a refluxed temperature. The solution was then left standing at room temperature to crystallize. The deposited crystals were filtered and washed with a small amount of solvent, followed by air drying. The obtained **1**·(*S*)-**2** salt crystals were subjected to acetylation by acetic anhydride in the presence of pyridine or triethylamine as a base. Acetyl amide of **1** was purified by preparative scale TLC, and its enantiomeric purity was determined by HPLC analysis using Chiralpak AD-H (Daicel Chemical Ind., eluent: 10% 2-propanol in hexane, flow rate: 0.5 ml/min, detection: UV 254 nm, retention time: $t_1 = 12$ min(*R*), $t_2 = 14$ min(*S*)).

Optical Rotation Measurement

The sample solutions for optical rotation measurement were prepared by mixing equimolar amounts of **1** and **2** in MeOH/dioxane or MeOH/water at a concentration of 1.0 g /100 ml (c 1.0). The water-jacketed cell was used to control the measurement temperature at 25.0°C. The dielectric constants ε of the mixed solvents were calculated as the weighted average of the mixture components.

X-Ray Crystallographic Analyses

X-ray crystallographic data were collected on a Bruker SMART APEX diffractometer with graphite monochromated Mo Kα radiation (Table 1). The crystal structures were determined by a direct method using

TABLE 1. Crystallographic data for the diastereomeric salts

	(*R*)-**1**·(*S*)-**2**	(*R*)-**1**·(*S*)-**2**·tetrahydropyran
Formula	$C_{24}H_{28}N_2O_4S$	$C_{29}H_{38}N_2O_5S$
FW	440.54	526.67
Temperature (K)	293	123
Crystal system	Monoclinic	Orthorhombic
Space group	$P2_1$	$P2_12_12_1$
a (Å)	13.184(2)	6.1431(12)
b (Å)	5.8641(10)	20.043(4)
c (Å)	15.511(3)	22.181(4)
β (°)	109.623(4)	90
V (Å^3)	1129.5(3)	2731.0(9)
Z	2	4
D_c (g/cm^3)	1.295	1.281
R	0.0536	0.0592
R_w	0.1340	0.1691
Measured reflns	6588	29767
Unique reflns	3780	6251
Observed refluns	3295	5661
Refluns used	3780	6251
parameters	298	352
Number CCDC	776840	776841

TABLE 2. Enantioseparation of *rac*-1 with (*S*)-2 in 2-propanol/cyclohexane mixed solvents

Entry	Solvent 2-propanol/ cyclohexane (v/v)	Solvent volume (ml/mmol of *rac*-**1**)	Initial salt (g)	Yield (g)[a]	Ee (%)[b]	Absolute configuration	Dielectric constant
1	100:0	4.2	0.440	0.154	68.4	*S*	19.9
2	90:10	5.7	0.929	0.351	28.3	*S*	18.1
3	80:20	7.0	0.899	0.221	48.0	*S*	16.4
4	70:30	6.5	0.458	0.145	46.9	*S*	14.6
5	60:40	8.0	0.436	0.138	69.1	*S*	12.8
6	50:50	11.0	0.451	0.173	33.3	*R*	11.0
7	40:60	13.0	0.446	0.165	24.0	*R*	9.2
8	30:70	42.0	0.458	0.144	35.0	*R*	7.4
9	20:80	65.0	0.454	0.147	34.5	*R*	5.6
10	10:90	144.0	0.447	0.137	53.7	*R*	3.8

[a]Material yield of the deposited diastereomeric salts.
[b]Determined by chiral HPLC analysis (Daicel Chiralpak AD-H) after derivatizing to its acetyl amide.

SIR97[21] and refined by the full-matrix least squares method using SHELXL-97.[22]

RESULTS AND DISCUSSION

Enantioseparation of rac-1 with (S)-2 in Cyclohexane/ 2-Propanol

First, we investigated the enantioseparation of *rac*-**1** with (*S*)-**2** in a mixed solvent of cyclohexane and 2-propanol with changing their mixing ratio by 10% based on their volume. Enantiopure (*S*)-**2** was synthesized from L-phenylalanine and *p*-toluenesulfonyl chloride according to the literature.[18] Both *rac*-**1** and (*S*)-**2** (1 or 2 mmol) were added in the crystallization solvents and dissolved at refluxed temperature, then left at room temperature to crystallize the salt. After the salt was separated and air-dried to measure the yield, **1** was derivatized to its acetyl amide before the determination of enantiomeric excess(ee) by chiral HPLC analysis. The results are summarized in Table 2. Although low solubility of the salt prevented crystallization from 100% cyclohexane, the salt of **1**·(*S*)-**2** was obtained as white solids for all the solvent systems examined. It was shown that (*S*)-**1**·(*S*)-**2** was obtained from the solvents with low cyclohexane content; on the other hand, an increase of cyclohexane ratio in the crystallization solvent changed the mainly obtained enantiomer of **1** from *S* to *R*-isomer. (*R*)-**1** was obtained from the solvents with more than 50% of cyclohexane ratio and 2-propanol/cyclohexane = 10:90 (v/v) gave (*R*)-**1** in the best selectivity. This chirality inversion is in accordance with the result performed in dioxane/2-propanol mixed solvents while only 25% of dioxane in 2-propanol changed the selectivity.[17] It is suggested that subtle difference of the molecular structures between dioxane and cyclohexane affect the stability of the diastereomeric salts and efficiency of the enantioseparation.

Enantioseparation of rac-1 with (S)-2 in Various Solvents with Five- or Six-Membered Ring Structures

Since the inversion of enantioselectivity by dioxane and cyclohexane appeared to be mainly due to incorporation of the solvent molecules in (*R*)-**1**·(*S*)-**2** salt, the phenomenon would be generally observed in the solvents with similar size and shape. Considering the structure of the crystallization solvents, we expected that tetrahydropyran (THP), cyclohexene, and tetrahydrofuran(THF) were also potential solvents to inverse the enantioselectivity of **1**. The results of enantioseparation of *rac*-**1** with (*S*)-**2** in a mixed solvent of 2-propanol/cyclic solvents = 10:90 (v/v) are summarized in Table 3. The ratio of the mixed solvents used was fixed to afford appropriate solubility and make comparisons with the result obtained for cyclohexane. THP is composed of a saturated six-membered ring like dioxane and cyclohexane. 2-Propanol/THP (10:90, v/v) afforded the diastereomeric salt incorporating THP with about 30 mol % inclusion ratio estimated from the ^{1}H NMR measurement. As we expected, the mainly obtained **1** was *R*-isomer (56.2% ee), and addition of THP to 2-propanol in the crystallization solvent has also changed the enantioselectivity of **1** from *S* to *R*. Cyclohexene has a similar but more rigid and planar structure than cyclohexane due to an unsaturated carbon–carbon bond in the six-membered ring. 2-Propanol/cyclohexene (10:90, v/v) also afforded (*R*)-**1** with 42.1% ee. On the other hand, (*S*)-**1** was mainly obtained from 2-propanol/THF (10:90, v/v), which is composed of one less carbon atom compared with THP. These results suggest that size and shape of the crystallization solvents are crucial factors to determine the enantioselectivity of **1** and that the solvents with a six-membered ring structure generally change the enantioselectivity of **1** from *S* to *R*.

TABLE 3. Enantioseparation of *rac*-1 with (*S*)-2 in 2-propanol/cyclic compound mixed solvents

Entry	Solvent (v/v)	Solvent volume (ml/mmol of *rac*-**1**)	Initial salt (g)	Yield (g)[a]	Ee (%)[b]	Absolute configuration
1	2-Propanol	4.2	0.440	0.154	68.4	*S*
2	2-Propanol/THP (10:90)	21.2	0.541	0.187	56.2	*R*
3	2-Propanol/cyclohexene (10:90)	120.8	0.091	0.024	42.1	*R*
4	2-Propanol/THF (10:90)	1.1	1.585	0.564	47.9	*S*

[a]Material yield of the deposited diastereomeric salts.
[b]Determined by chiral HPLC analysis (Daicel Chiralpak AD-H) after derivatizing to its acetyl amide.

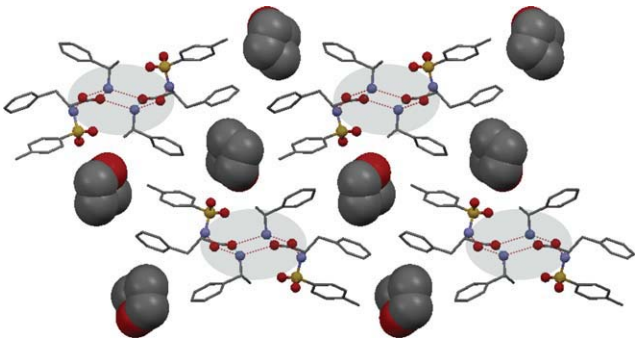

Fig. 2. Crystal structure of (*R*)-**1**·(*S*)-**2**·tetrahydropyran viewed from the columnar axis. The dotted lines and colored circles show hydrogen bonds and columnar structures, respectively. Hydrogen atoms are omitted for clarity. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

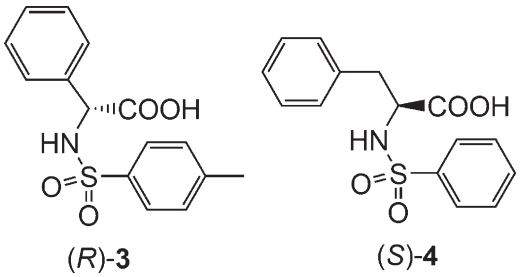

Fig. 3. Chemical structures of *N*-(*p*-toluenesulfonyl)-(*R*)-phenylglycine (**3**) and *N*-benzenesulfonyl-(*S*)-phenylalanine (**4**).

To know the reason of chirality inversion caused by the addition of THP, X-ray crystallographic analysis was performed for the single crystal of (*R*)-**1**·(*S*)-**2** prepared from THP/2-propanol (Fig. 2). As observed for the cases that dioxane and cyclohexane were included in (*R*)-**1**·(*S*)-**2**, THP molecules were included in the one dimensional void space to form (*R*)-**1**·(*S*)-**2**·THP ternary inclusion crystal. The molecular arrangements of (*R*)-**1** and (*S*)-**2** were quite similar to those of other inclusion crystals, and THP molecules were included without any hydrogen bonds. It was revealed that THP molecules also effectively filled the void space to stabilize the (*R*)-**1**·(*S*)-**2** diastereomeric salt and contributed to switch the enantioselectivity of **1**.

Structural Modification of the Resolving Agents

It was found that the solvents with a six-membered molecular structure were potential to switch the enantioselectivity of **1** resolved with (*S*)-**2**. In the next step, we investigated the effect of the structures of resolving agents. We prepared two structurally related resolving agents, *N*-(*p*-toluenesulfonyl)-(*R*)-phenylglycine(**3**) and *N*-benzenesulfonyl-(*S*)-phenylalanine(**4**), which have one less carbon atom compared with **2** (Fig. 3). Enantiopure **3** and **4** were synthesized from the corresponding amino acids and arylsulfonyl chlorides by the similar manner to (*S*)-**2**. The results of the enantioseparation of *rac*-**1** with (*S*)-**2**, (*R*)-**3** and (*S*)-**4** in 2-propanol and 2-propanol/cyclohexane = 10:90 (v/v) mixed solvent are summarized in Table 4. When (*R*)-**3** was used as a resolving agent, addition of cyclohexane to 2-propanol gave little difference in the enantioseparation, and the homochiral diastereomeric salt (*R*)-**1**·(*R*)-**3** was obtained as a less-soluble salt in the selectivities of 49.6% ee and 47.3% ee, respectively (entries 3 and 4). Similarly, **1**·(*S*)-**4** crystallized from 2-propanol and 2-propanol/cyclohexane (10:90, v/v) consistently afforded homochiral (*S*)-**1**·(*S*)-**4** as a less-soluble salt in 46.6% and 47.8% selectivities (entries 5 and 6). It was suggested that chirality inversion phenomenon was not observed by the addition of cyclohexane when (*R*)-**3** and (*S*)-**4** were applied as a resolving agent. This is in sharp contrast to the result that heterochiral diastereomeric salt (*R*)-**1**·(*S*)-**2** was crystallized from 2-propanol/cyclohexane = 10:90 (v/v) mixed solvent (entry 2).

It is well known that even a slight modification of the resolving agents can drastically change the enantioselectivity.[8,9] In this case, a decrease of only one carbon atom in the resolving agent has made it difficult to switch the enantioselectivity of **1** dependent on the solvents. We have reported that appropriate flexibility of the molecular conformation is seemed to play a key role to apply the solvent-induced chirality switch in the enantioseparation by changing the molecular conformation to include solvent molecules and form densely packed salt crystals.[23,24] As discussed below,[25–28] it is probable that **1**·(*R*)-**3** and **1**·(*S*)-**4** have similar hydrogen-bonding networks as **1**·(*S*)-**2**, however, slight differences such as more rigid structure of (*R*)-**3** and less bulky structure of (*S*)-**4** have changed the molecular packing in the salt crystals to prevent their heterochiral diastereomeric salts from incorporating cyclohexane molecules in the void space to switch the enantioselectivity.

Comparison of Crystal Structures of the Diastereomeric Salts: (R)-1·(S)-2, (S)-1·(S)-2, (R)-1·(S)-2·Solvent

To investigate the mechanism of this solvent dependent resolution system in detail, we compared the crystal structures of the three salt crystals, (*R*)-**1**·(*S*)-**2**, (*S*)-**1**·(*S*)-**2**,[17] and (*R*)-**1**·(*S*)-**2**·dioxane[17] (Fig. 4). The single crystal of

TABLE 4. Enantioseparation of *rac*-1 with (*S*)-2, (*R*)-3 and (*S*)-4 in a 2-propanol/cyclohexane mixed solvent

Entry	Resolving agents	Solvent 2-propanol/ cyclohexane (v/v)	Solvent volume (ml/mmol of *rac*-**1**)	Initial salt (g)	Yield (g)[a]	Ee (%)[b]	Absolute configuration	Homo/ hetero[c]
1	(*S*)-**2**	100:0	4.2	0.440	0.154	68.4	*S*	Homo
2	(*S*)-**2**	10:90	144.0	0.447	0.137	53.7	*R*	Hetero
3	(*R*)-**3**	100:0	8.8	0.289	0.086	49.6	*R*	Homo
4	(*R*)-**3**	10:90	312	0.274	0.099	47.3	*R*	Homo
5	(*S*)-**4**	100:0	3.7	0.115	0.017	46.6	*S*	Homo
6	(*S*)-**4**	10:90	63.2	0.081	0.030	47.8	*S*	Homo

[a]Material yield of the deposited diastereomeric salts.
[b]Determined by chiral HPLC analysis (Daicel Chiralpak AD-H) after derivatizing to its acetyl amide.
[c]Chirality of the resolving agents and **1** in the less-soluble diastereomeric salts.

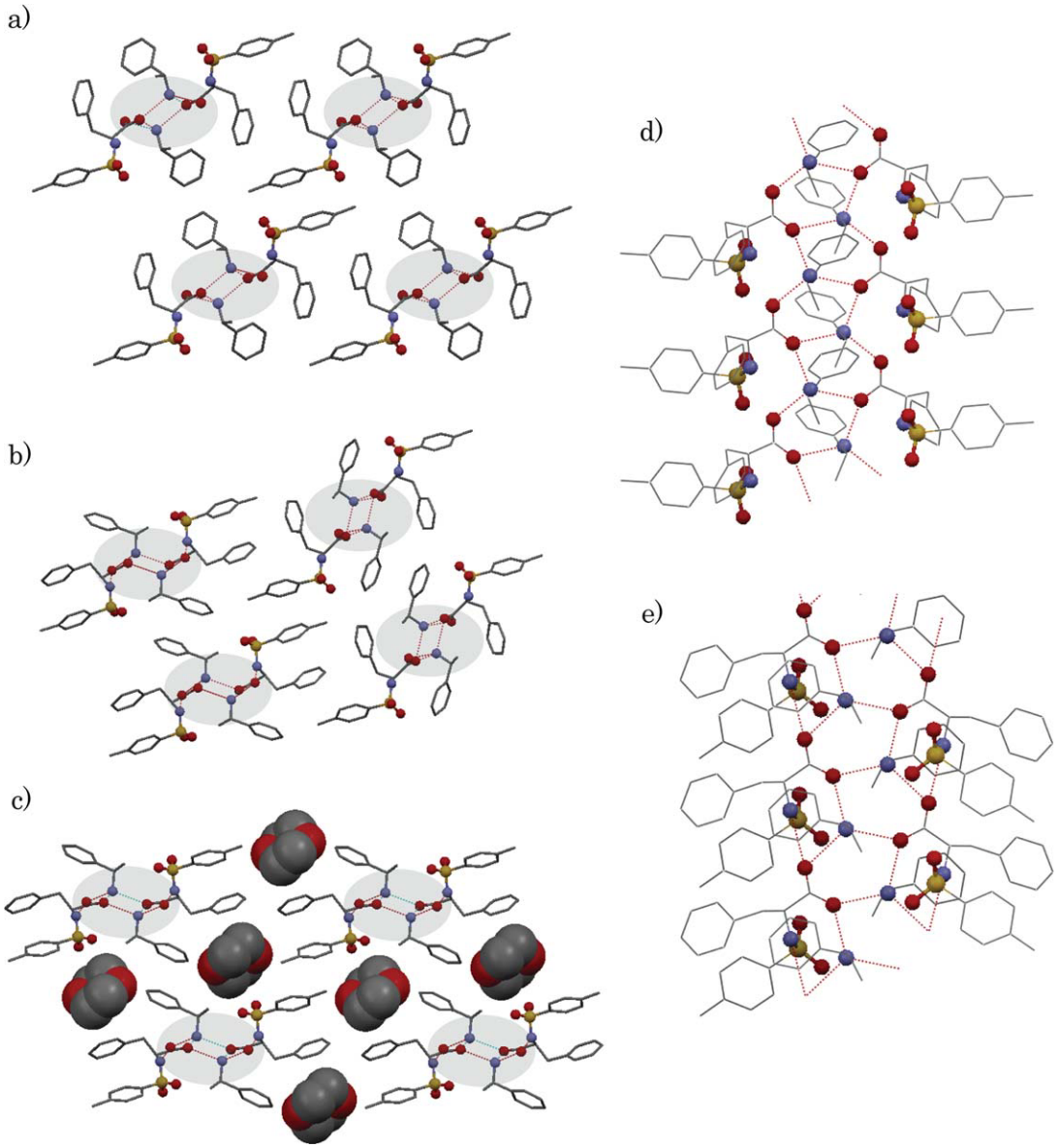

Fig. 4. Structures of the three diastereomeric salt crystals: (**a**) (*R*)-**1**·(*S*)-**2**, (**b**) (*S*)-**1**·(*S*)-**2**, (**c**) (*R*)-**1**·(*S*)-**2**·dioxane viewed from the columnar axis, respectively. Columnar hydrogen-bonding network of (**d**) (*R*)-**1**·(*S*)-**2**, (**e**) (*R*)-**1**·(*S*)-**2**·dioxane, respectively. The dotted lines and colored circles show hydrogen bonds and columnar structures, respectively. Hydrogen atoms are omitted for clarity. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

(*R*)-**1**·(*S*)-**2** was prepared by slow evaporation of the toluene/THF solution of (*R*)-**1**·(*S*)-**2**. Figure 4 shows that a one dimensional columnar hydrogen-bonding network is commonly constructed in the three salt crystals, which is an often observed supramolecular structure in primary ammonium-carboxylate salt crystals.[25–28] In (*R*)-**1**·(*S*)-**2**·dioxane, dioxane molecules were included in the void space formed between the columnar structures without any hydrogen-bonding interaction as mentioned above for (*R*)-**1**·(*S*)-**2**·THP (Fig. 4c).

One critical difference between these crystal structures is the molecular conformation of (*S*)-**2**. Three possible conformers of (*S*)-**2** are described in Figure 5. In general, *gauche-trans* conformation appears to be the most stable form because two bulky groups, phenyl and *p*-toluenesulfonyl amide groups adopt *trans*-position to avoid their steric repulsion. This is the case for the crystal of carboxylic acid (*S*)-**2** itself.[13] On the other hand, it is necessary for (*S*)-**2** to adopt *trans-gauche* or *gauche-gauche* conformation to maintain a columnar hydrogen-bonding network formed with primary amine **1**. These two conformations are commonly observed in the salts of (*S*)-**2** and other primary amines.[13] In (*R*)-**1**·(*S*)-**2**, (*S*)-**2** takes a *gauche-gauche* conformation and the columnar network was formed between the ammonium hydrogen atom of (*R*)-**1** and carboxylate oxygen atom of (*S*)-**2** (Fig. 4d). On the other hand, *trans-gauche* orientation is adopted in (*R*)-**1**·(*S*)-**2**·dioxane and the one dimensional columnar structure is maintained not only by the hydrogen bonds between the ammonium hydrogen atom of (*R*)-**1** and carboxylate oxygen atom of (*S*)-**2** but the additional hydrogen bond between carboxylate oxygen atom and amide hydrogen atom of (*S*)-**2** (Fig. 4e). It was found that this additional intermolecular hydrogen bond between (*S*)-**2**

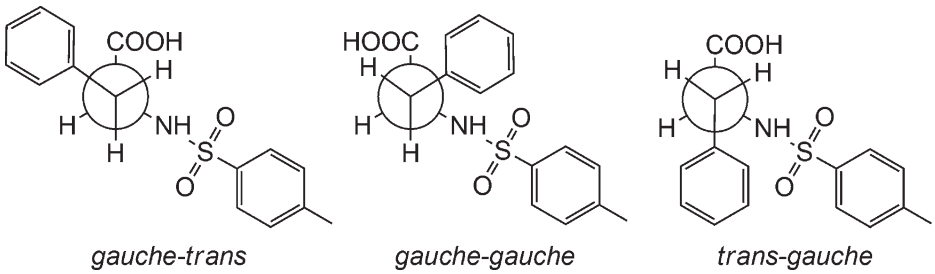

Fig. 5. Three possible conformers of (*S*)-**2**. The first designation denotes the relationship between phenyl and carboxylate groups, second one denotes that of phenyl and tosylamide groups.

molecules stabilized the columnar structure of (*R*)-**1**·(*S*)-**2**·dioxane.

In addition, *gauche-gauche* conformation of (*S*)-**2** appears to be disadvantageous for efficient packing of columns than that with *trans-gauche* conformation. Viewed from the columnar axis of (*R*)-**1**·(*S*)-**2**, the orientation of two aromatic rings of *gauche-gauche* (*S*)-**2** is almost perpendicular and packed less densely (Fig. 4a); on the other hand, parallel orientation is observed in *trans-gauche* (*S*)-**2,** and more dense and efficient packing of columnar structures was achieved for (*R*)-**1**·(*S*)-**2**·dioxane (Fig. 4c). In (*S*)-**1**·(*S*)-**2** diastereomeric salt, (*S*)-**2** takes both *gauche-gauche* and *trans-gauche* conformations and shows conformational isomorphism (Fig. 4b). One column is constructed from (*S*)-**2** with *gauche-gauche* conformation, and the other column is constructed from (*S*)-**2** with *trans-gauche* conformation. These conformational differences may reflect the order of the stability of the three salts ((*R*)-**1**·(*S*)-**2**·dioxane > (*S*)-**1**·(*S*)-**2** > (*R*)-**1**·(*S*)-**2**). In the presence of an appropriate solvent as a space filler, (*R*)-**1**·(*S*)-**2**·solvent ternary crystals become favorable than (*S*)-**1**·(*S*)-**2** and the enantioselectivity of **1** has changed from *S* to *R*. The crystals obtained from cyclohexane and THP are isostructural to (*R*)-**1**·(*S*)-**2**·dioxane, except for the alignment of the columns: parallel alignment for the dioxane inclusion crystal (space group: $P2_1$) and antiparallel alignment for the other two inclusion crystals (space group: $P2_12_12_1$). This subtle difference is seemed to be caused by the presence of two oxygen atoms; however, it has little effect on the stability of the inclusion crystals and results of enantioseparation.

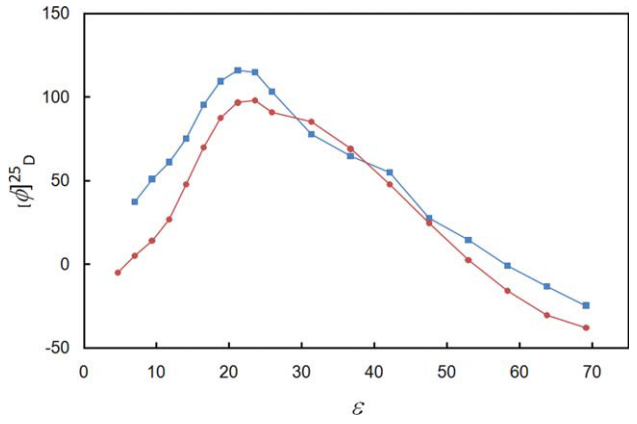

Fig. 6. Solvent dependence of molar rotation of the diastereomeric salts in MeOH/dioxane and MeOH/water: (*R*)-**1**·(*S*)-**2** (square), (*S*)-**1**·(*S*)-**2** (circle). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Comparison of the Dependence of Optical Rotation of Diastereomeric Salts for the Solvents

Previously, we have shown that a large difference of optical rotation values between two diastereomeric salts was often observed when dielectrically controlled resolution is applicable.[23,24] Optical rotation measurements reflect conformational change of the molecules in solution. To further investigate this solvent-dependent enantioseparation, we measured optical rotation values of (*S*)-**1**·(*S*)-**2** and (*R*)-**1**·(*S*)-**2** in MeOH/H_2O and MeOH/dioxane solvents with various mixed ratio (Fig. 6). It was revealed that little difference was observed between the two diasteremeric salts ($|[\phi]_{SS}-[\phi]_{RS}|$ = 0–36) in a whole range of the dielectric constants, though the solvent-dependent chirality inversion was observed by the addition of dioxane. This is probably because the chirality inversion is attributed to the inclusion of the solvent molecules in the crystalline state without any hydrogen bonds and therefore, solvents make little difference on the conformation of **1** and **2** in a solution state.

CONCLUSIONS

Control of the functionality of organic salt crystals by the included solvents is studied by other groups from the viewpoint of supramolecular chemistry.[29,30] In this study, we demonstrated that size and shape of the solvents are crucial factors to switch the selectivity of the enantioseparation of *rac*-**1** via the diastereomeric salt formation with (*S*)-**2**. The enantioselectivity of **1** dramatically changed from *S* to *R* with increasing the cyclohexane ratio of the crystallization solvents. The similar phenomena were commonly observed when solvents with a six-membered ring structure such as THP and cyclohexene were used. However, the chirality switch phenomenon was not observed when structurally similar resolving agents (*R*)-**3** and (*S*)-**4** were applied. Crystallographic analysis has revealed that THP was included in the salt (*R*)-**1**·(*S*)-**2** and stabilized it without any hydrogen bonds. It was shown from the comparison of the three salt crystals that the difference in the conformation of (*S*)-**2** plays an important role for their relative stability and enantioselectivity of **1**. Although the efficiency of enantioseparation of *rac*-**1** by (*S*)-**2** is not very high, the commonly observed chirality inversion phenomenon will help us to design more efficient separation systems controlled by crystallization solvents.

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