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Crystallization-based optical resolution of 1,1′-binaphthalene-2,2′-dicarboxylic acid via 1-phenylethylamides: control by the molecular structure and dielectric property of solvent

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ABSTRACT

In the recrystallization of a diastereomeric mixture of amides (RS_a,S)-**1** formed from racemic 1,1′-binaphthalene-2,2′-dicarboxylic acid and (*S*)-1-phenylethylamine, either of the diastereomers crystallizes out as a diastereomerically pure form, depending on the solvent employed; sterically undemanding solvents, acetone, dichloromethane, and acetonitrile, afford crystals formulated as (S_a,S)-**1**·solvent with an exception of ethanol, which affords (R_a,S)-**1**·EtOH, while sterically bulkier solvents afford (R_a,S)-**1** including no solvent. The stereoselectivity can be rationalized by the crystal structures. A dielectrically controlled resolution (DCR) can also be carried out by using mixed solvents, which contain, for example, 25 vol % of acetone and varying ratios of hexane and 1-propanol in total 75 vol %; (S_a,S)-**1**·acetone is deposited as crystals from the solvents with a dielectric constant (ε) range $8.9 \leqslant \varepsilon \leqslant 10.2$, while (R_a,S)-**1** is deposited from the solvents with $14.8 \leqslant \varepsilon \leqslant 20.3$.

Recrystallization-based optical resolutions are important ways to obtain enantiopure compounds in both laboratories and industries because of the ease of operation and wide applicability.[1] Methods that are based on novel principles or those which greatly improve the efficiency of resolution, such as preferential enrichment[2] and Dutch resolution,[3] have been developed. The diastereomeric salt formation method is the one that resolves one enantiomer from its racemic mixture by crystallization after conversion into diastereomeric salts with a chiral resolving agent. It has been a common understanding in the resolution by this method that when one enantiomer of a target molecule crystallizes out with the (*S*)-enantiomer of a resolving agent as the less soluble diastereomeric salt, the antipode necessitates the (*R*)-enantiomer of the resolving agent to be deposited as crystals from a racemic mixture. During the course of the study on the development of an industrial process to resolve α-amino-ε-caprolactam (ACL),[4] however, one of us has found an interesting phenomenon that the enantiomer preferentially crystallized with *N*-tosyl-(*S*)-phenylalanine [(*S*)-TPA] varies depending on the dielectric property of the solvent employed; (*S*)-ACL is selected in solvents with ε values between 29 and 58, giving a diastereomeric salt formulated as (*S*)-ACL·(*S*)-TPA·H_2O with up to 100% de, while (*R*)-ACL is selected in solvents with lower (5–27) and higher ε ranges (62–78), giving that formulated as (*R*)-ACL·(*S*)-TPA with up to 69% de.[5] It is easily conceivable that the chiral molecules are associated in solution by forming a hydrogen-bond network. The DCR phenomenon has been interpreted as an outcome of structural change in the hydrogen-bond network depending on the dielectric property of solvent,[6,7] although further experiments have to be done to know how the chiral molecules are associated in solution and how the association affects crystal structures. The DCR phenomenon is not special for the ACL–TPA system but has

Table 1
Recrystallization of amides (RS_a,S)-**1** from various solvents

Entry	Solvent	ε	Yield (%)[a]	de (%)[b]	Absolute configuration[b]	Inclusion ratio[b] (**1**:solvent)
1	Toluene	2.4	5	100	R_a,*S*	—[c]
2	AcOEt	6.0	24	100	R_a,*S*	—[c]
3	CH_2Cl_2	8.9	27	100	S_a,*S*	1:0.87
4	2-PrOH	18.3	15	100	R_a,*S*	—[c]
5	1-PrOH	20.1	30	100	R_a,*S*	—[c]
6	Acetone	20.7	23	100	S_a,*S*	1:0.93
7	EtOH	24.3	34	100	R_a,*S*	1:0.98
8	MeCN	37.5	35	100	S_a,*S*	1:0.82

[a] Isolated yield.
[b] Determined by ^{1}H NMR analysis.
[c] No solvent inclusion was observed.

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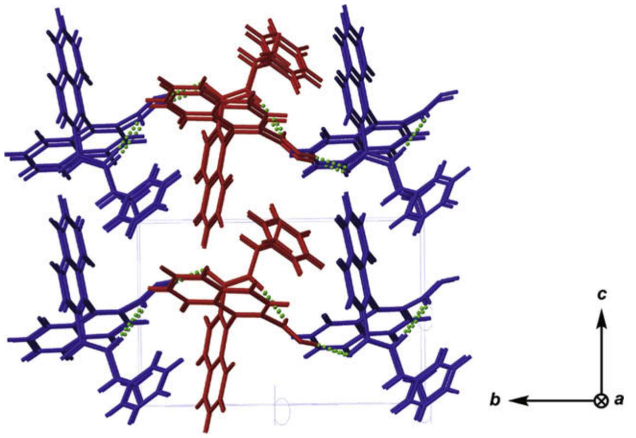
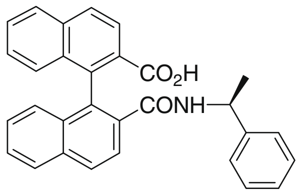


Figure 1. Crystal structure of (R_a,S)-**1**. Molecules are color-coded according to their orientations. Dotted lines indicate hydrogen bonds.

already been observed in five other resolutions via diastereomeric salt formation.[8,9] Moreover, we believe that the dielectric property of solvent can play a decisive role in a wide variety of chiral discrimination phenomena. As the first successful example of our efforts for exploring such a chiral recognition system, we report herein that the recrystallization of a diastereomeric mixture of amides (RS_a,S)-**1** formed from racemic 1,1′-binaphthalene-2,2′-dicarboxylic acid and (S)-1-phenylethylamine can be controlled by the molecular structure and dielectric property of the solvent employed.



(RS_a,S)-**1**

Previously, it was reported from our laboratory that one recrystallization of a diastereomeric mixture of amides (RS_a,S)-**1** from acetonitrile gave (S_a,S)-**1** in 43% yield, and the mother liquid, after concentration, was recrystallized twice from ethanol to give (R_a,S)-**1** in 40% yield; both of them were essentially diastereomerically pure.[10] This outstanding efficiency of the resolution for both the diastereomers prompted us to examine solvent effects on the stereoselectivity in this system. A 200 mg of 1:1 mixture of amides

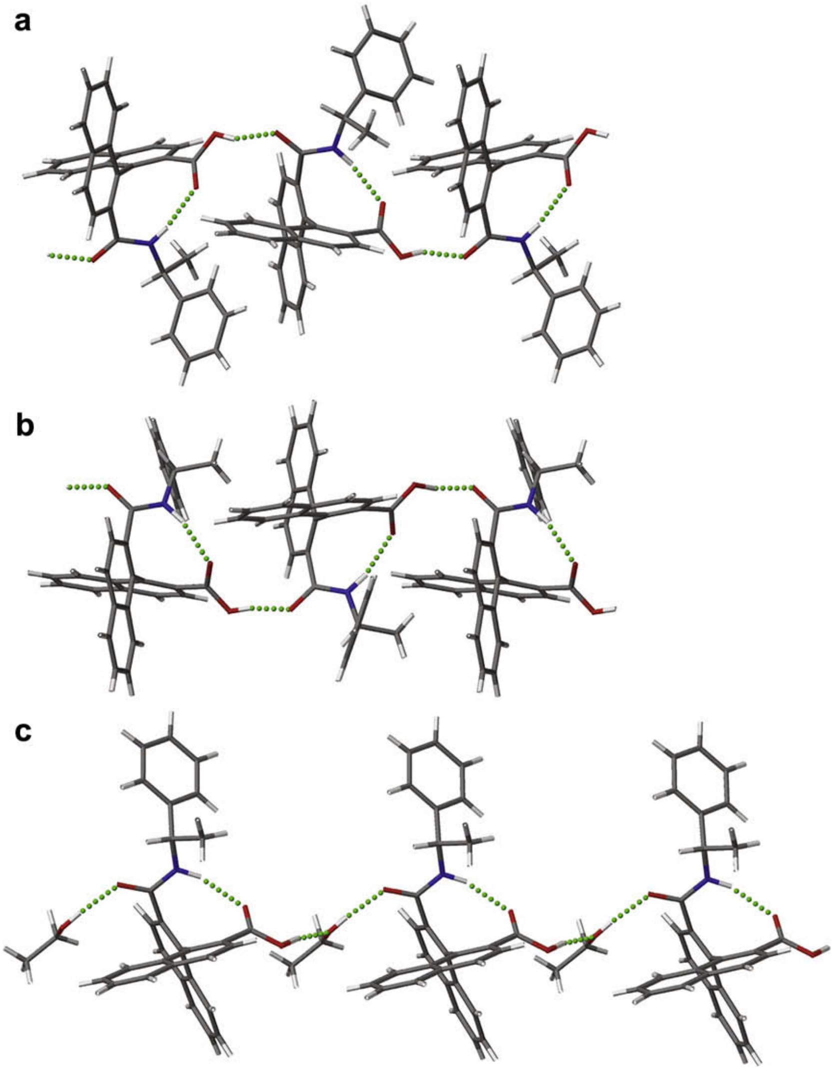


Figure 2. Hydrogen-bond network formed in the crystal. (a) (R_a,S)-**1**; (b) (S_a,S)-**1**·acetone; (c) (R_a,S)-**1**·EtOH.

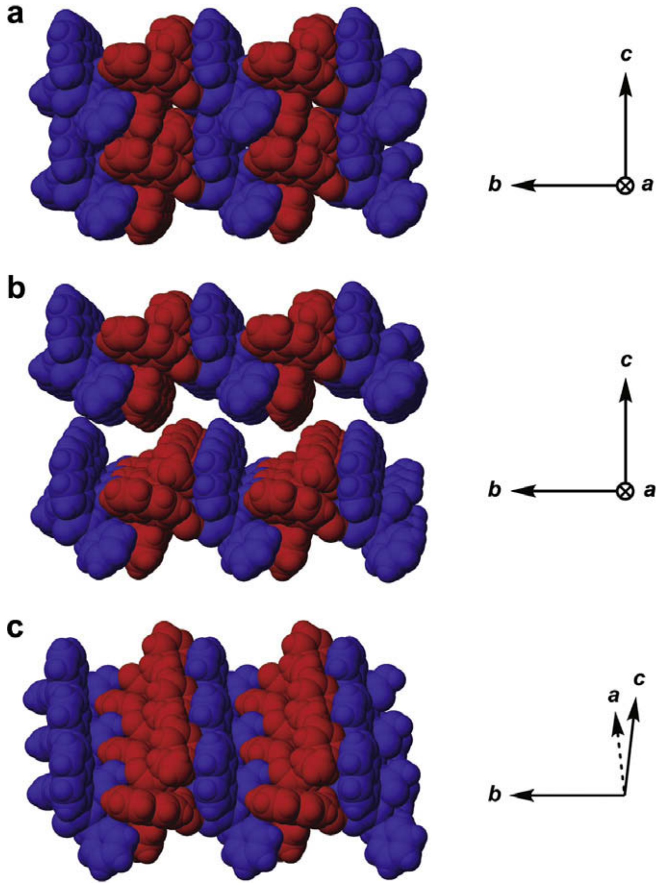


Figure 3. Crystal packing of (R_a,S)-**1**. (a) Cross-section parallel to the *b*–*c* plane; (b) layers separated along the *c*-axis; (c) surface of the separated layer.

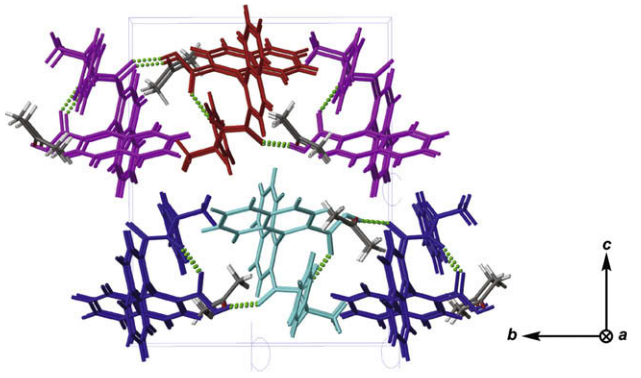


Figure 4. Crystal structure of (S_a,S)-**1**·acetone.

(RS_a,S)-**1**, prepared as reported previously,[10] was dissolved in a solvent at 50 °C by adding the solvent portionwise until it forms a nearly saturated solution, which was allowed to cool to room temperature and then kept overnight at 4 °C to induce recrystallization. Table 1 lists the results of the recrystallization from various solvents. Interestingly, under the conditions, either of the diastereomers crystallized out with complete selectivity from individual solvents employed, though the dependence on the dielectric property of solvent was not clear. The crystals of (S_a,S)-**1** included solvent molecules in a molar ratio of about 1:1 (**1**:solvent), while those of (R_a,S)-**1** did not, except for ethanol.

In order to clarify the reasons why the crystallized diastereomer varies depending on the solvents, X-ray crystallographic analyses were carried out.[11] Diastereomerically pure (R_a,S)-**1** was recrystallized from acetonitrile to give single crystals, including no solvent molecules. The crystal belongs to the $P2_1$ space group ($Z = 2$) (Fig. 1), in which a 2_1 helical structure is created along the *b*-axis by intramolecular hydrogen bonds between the carbamoyl NH and carboxy C=O groups (2.086 Å) and intermolecular hydrogen bonds between the carboxy OH and carbamoyl C=O groups (1.786 Å) (Fig. 2a). The helices are arranged parallel to each other along the *a*-axis to form a layer (Fig. 3c), which is laminated along the *c*-axis (Fig. 3a and b). Although the upper and bottom surfaces of each layer are uneven, every bumps and hollows engage with each other between two adjacent layers to form a tight packing structure ($\rho = 1.233$ g cm^{-3}).

On the other hand, single crystals formulated as (S_a,S)-**1**·acetone were obtained by slow diffusion of hexane vapor into an acetone solution of diastereomerically pure (S_a,S)-**1**. The crystal belongs to the $P2_12_12_1$ space group ($Z = 4$) (Fig. 4), in which a similar 2_1 helical structure to that observed for (R_a,S)-**1** is created along the *b*-axis (Fig. 2b); the bond lengths of the intra- and intermolecular hydrogen bonds are 1.989 and 1.658 Å, respectively. The helices are arranged parallel to each other along the *a*-axis to form a layer (Fig. 5c), which is laminated along the *c*-axis (Fig. 5a and b); every adjacent layers are turned 180° in the *a*–*b* plane. There are voids on the layer surface, which are filled with acetone molecules (Fig. 5c). The crystal density ($\rho = 1.222$ g cm^{-3}) is lower than that of (R_a,S)-**1** and should drop considerably ($\rho = 1.081$ g cm^{-3}), if there were no acetone molecules in the lattice. This suggests that the crystal structure cannot be kept without the aid of the solvent molecules. The crystals of (S_a,S)-**1** that include dichloromethane and acetonitrile molecules (Table 1) are expected to have similar packing

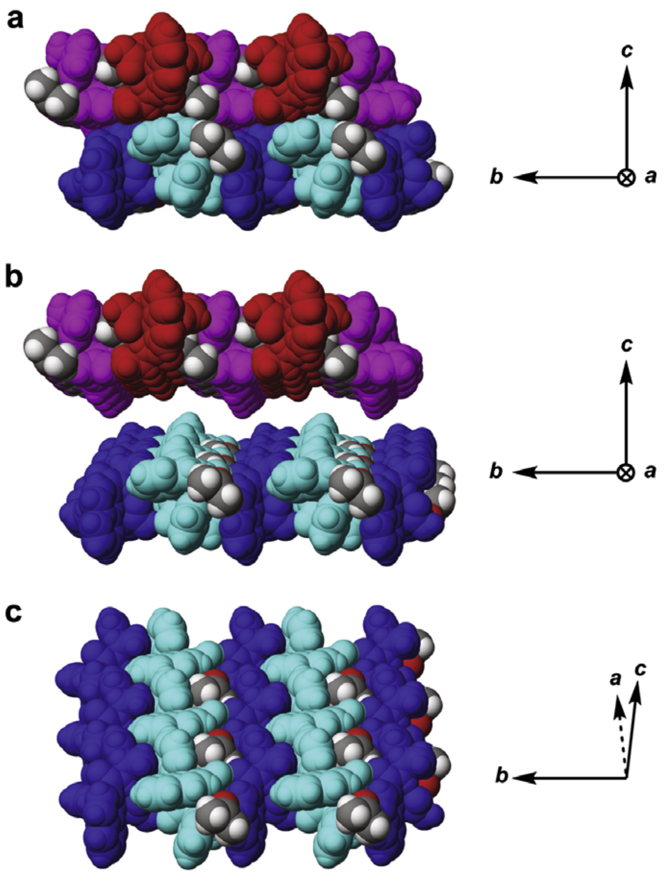


Figure 5. Crystal packing of (S_a,S)-**1**·acetone. (a) Cross-section parallel to the *b*–*c* plane; (b) layers separated along the *c*-axis; (c) surface of the separated layer.

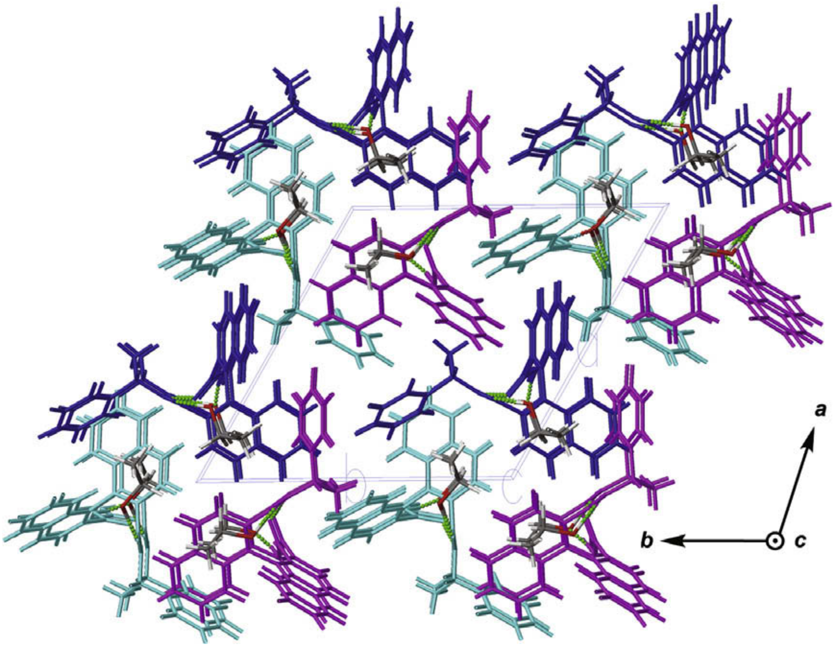


Figure 6. Crystal structure of (R_a,S)-**1**·EtOH.

structures to this, considering the fact that these molecules are similar to acetone in steric bulk.

In this connection, it is of interest to note that (S_a,S)-**1**·EtOH was not precipitated from ethanol. The X-ray analysis of (R_a,S)-**1**·EtOH prepared by recrystallization of diastereomerically pure (R_a,S)-**1** from ethanol revealed that the crystal structure is very different from the preceding ones, having $P3_2$ symmetry ($Z = 3$) (Fig. 6), in which a 3_2 helical structure is created along the c-axis by intra- and intermolecular hydrogen bonds (Fig. 2c). The intramolecular hydrogen bond is formed between the carbamoyl NH and carboxy C═O groups (2.143 Å) as observed in the above two crystal structures, while the intermolecular hydrogen bond between the carboxy OH and carbamoyl C═O groups is mediated by the hydroxy group of ethanol as C═O–OH···OH (ethanol)···O═C–NH, the bond lengths being 1.687 and 1.893 Å, respectively. The helices are packed tightly ($\rho = 1.259$ g cm^{-3}) as shown in Figure 7.

From these observations, we may conclude that (S_a,S)-**1**·solvent crystallizes out in preference to (R_a,S)-**1** from the solvents that have suitable molecular size for being incorporated into the crystal lattice formed by (S_a,S)-**1**. However, (R_a,S)-**1**·EtOH, having the exceptional packing structure, crystallizes out in preference to (S_a,S)-**1**·EtOH. From the other solvents, (R_a,S)-**1** crystallizes out in preference to (S_a,S)-**1**·solvent. In short, the ease of crystal formation falls in the order (R_a,S)-**1**·EtOH > (S_a,S)-**1**·solvent (solvent = acetone, CH_2Cl_2, or MeCN) > (R_a,S)-**1**.

As a solvent-dependent resolution system was in hand, we next tried to control the resolution by the dielectric property of solvent. The 18 solvents with different dielectric constants (Table 2) were prepared by mixing the corresponding components in the indicated volume ratios.[12] Each solvent mixture contains a constant vol % of acetone or dichloromethane that can be incorporated into the crystal lattice of (S_a,S)-**1**·solvent. The mixed solvents were nearly saturated with amides (RS_a,S)-**1** at 40–50 °C and kept at −2 °C for 2–3 days to induce recrystallization. Figure 8 shows the dependence of the diastereomeric excess of deposited amide **1** on the dielectric constant of solvent. In the recrystallization from the hexane–1-propanol-based solvents, the diastereomeric excess of deposited amide **1** drastically changed within a narrow ε range ($10.5 < \varepsilon < 14.8$), and diastereomerically pure (S_a,S)-**1**·solvent and (R_a,S)-**1** were deposited from the solvents with lower and higher ε ranges, respectively. This observation clearly indicates that the resolution can be controlled by the dielectric property of solvent. However, a comparison of the de change obtained from acetone–hexane–1-propanol with that from acetone–toluene–1-propanol revealed that the dielectric property of solvent does not solely determine the diastereoselectivity but it is also affected by the molecular structure of solvent. Sim-

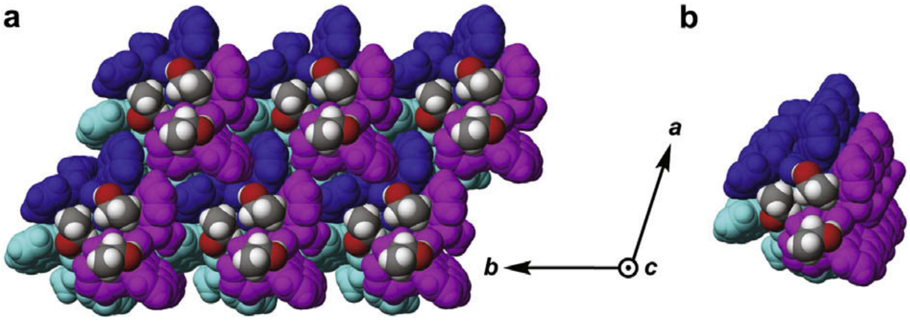


Figure 7. Crystal packing of (R_a,S)-**1**·EtOH. (a) Cross-section parallel to the a–b plane; (b) a 3_2 helix along the c-axis.

Table 2

Recrystallization oof amides (RS_a,S)-**1** from mixed solvents

Entry	Components and volume ratio of mixed solvent	ε	Yield (%)[a]	De (%)[b]	Absolute configuration[b]
	Acetone:hexane:1-PrOH				
1	25:63:12	8.9	23	100	S_a,S
2	25:55:20	10.2	21	100	S_a,S
3	25:43:32	12.5	14	32	R_a,S
4	25:30:45	14.8	4	100	R_a,S
5	25:19:56	16.8	9	100	R_a,S
6	25:7:68	18.9	10	100	R_a,S
7	25:0:75	20.3	4	100	R_a,S
8	25:0:75	20.3	10	100	R_a,S
	Acetone:toluene:1-PrOH				
9	25:75:0	7.0	6	92	S_a,S
10	25:63:12	9.2	7	100	R_a,S
11	25:50:25	11.4	3	100	R_a,S
12	25:50:25	11.4	9	100	R_a,S
13	25:20:55	16.7	9	100	R_a,S
14	25:12:63	18.0	4	100	R_a,S
15	25:12:63	18.0	4	100	R_a,S
16	25:0:75	20.3	10	100	R_a,S
	CH_2Cl_2:hexane:1-PrOH				
17	25:63:12	6.0	12	100	S_a,S
18	25:37:38	10.5	15	100	S_a,S
19	25:25:50	12.8	26	20	S_a,S
20	25:20:55	13.7	7	84	R_a,S
21	25:12:63	15.0	11	100	R_a,S
22	25:0:75	17.3	11	100	R_a,S

[a] Isolated yield.

[b] Determined by ^{1}H NMR analysis.

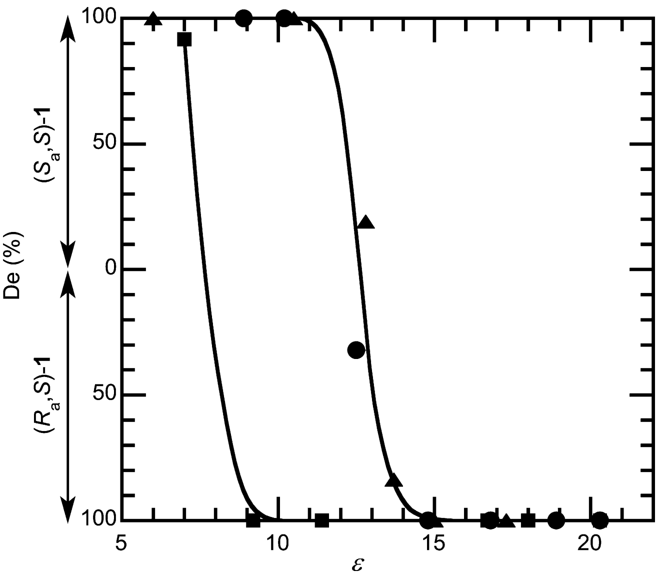


Figure 8. Dependence of the diastereomeric excess of deposited amide **1** on the dielectric constant of the solvent employed in the resolution; acetone–hexane–1-propanol (●), acetone–toluene–1-propanol (■), CH_2Cl_2–hexane–1-propanol (▲).

ilar observations have been reported for the resolution of diastereomeric salts.[9a,d,e]

The diastereomerically pure amides (S_a,S)- and (R_a,S)-**1** thus obtained can be converted into 1,1′-binaphthalene-2,2′-dicarboxylic acid without any appreciable loss of axial chirality by the treatment with thionyl chloride, followed by the alkaline hydrolysis of the resulting 2′-cyano-1,1′-binaphthalene-2-carboxylic acid.[10] Therefore, the solvent-controlled optical resolution of the diacid via 1-phenylethylamides has been achieved.

In conclusion, we have shown here that the recrystallization of a diastereomeric mixture of amides (RS_a,S)-**1** affords either of the diastereomers as diastereomerically pure crystals, depending on the solvent employed, and that the solvent dependence is attributed to the difference in crystal structure between the two diastereomers and to the steric and electronic properties of the solvent. In addition, we have succeeded in extending the DCR method to a covalent diastereomer-based resolution. We believe that detailed studies on this covalent diastereomer-based resolution, which is more simple than existing diastereomeric salt systems, afford deep insight into the chiral discrimination mechanisms that control the DCR phenomena.

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11. *Crystallographic data for* (R_a,S)-**1**: $C_{30}H_{23}NO_3$, fw = 445.49, T = 100(2) K, monoclinic, $P2_1$, a = 9.202(2) Å, b = 14.170(3) Å, c = 9.299(2) Å, β = 98.369(6)°, V = 1199.6(5) Å^3, Z = 2, ρ_{calcd} = 1.233 g cm^{-3}, 5145 independent reflections, 3951 reflections were observed ($I > 2\sigma(I)$), R_1 = 0.0577, wR_2 = 0.1276 (observed), R_1 = 0.0723, wR_2 = 0.1333 (all data). *Crystallographic data for* (S_a,S)-**1**·acetone: $C_{33}H_{29}NO_4$, fw = 505.37, T = 173(2) K, orthorhombic, $P2_12_12_1$, a = 11.325(2) Å, b = 13.892(2) Å, c = 17.405(3) Å, V = 2738.2(8) Å^3, Z = 4, ρ_{calcd} = 1.222 g cm^{-3}, 6381 independent reflections, 4054 reflections were observed ($I > 2\sigma(I)$), R_1 = 0.0485, wR_2 = 0.1071 (observed), R_1 = 0.0972, wR_2 = 0.1234 (all data). *Crystallographic data for* (R_a,S)-**1**·EtOH: $C_{32}H_{29}NO_4$, fw = 491.56, T = 100 (2) K, trigonal, $P3_2$, a = b = 14.8700(16) Å, c = 10.1538(16) Å, V = 1944.4(4) Å^3, Z = 3, ρ_{calcd} = 1.259 g cm^{-3}, 5603 independent reflections, 4312 reflections were observed ($I > 2\sigma(I)$), R_1 = 0.0430, wR_2 = 0.1028 (observed), R_1 = 0.0606, wR_2 = 0.1143 (all data). The details of the crystal data have been deposited with Cambridge Crystallographic Data Centre as supplementary publication Nos. CCDC 715192–715194.
12. The values of dielectric constants of mixed solvents were calculated as the weighted average of dielectric constants of components. See Ref. 9a.