Habit Modification of a Diastereomeric Salt with an Additive in Optical Resolution

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In the optical resolution of α-methylbenzylamine (**1**) with mandelic acid (**2**), the dimeric derivative of **1**, bis(α-methylbenzyl)amine (**4**), caused a habit modification of the diasteromeric salt, (*R*)-**1**·(*R*)-**2** (**3**). The habit modification was strongly influenced by the stereochemistry of **4**. Amine (*R,R*)-**4** changed the morphology of the crystal of the diastereomeric salt, even at a concentration of 0.007 mol% of **3**; the shape of the crystal became a hexagonal plate from a long hexagonal plate, whereas its stereoisomer ((*R,S*)-**4**) changed the morphology less than (*R,R*)-**4**, and (*S,S*)-**4** did not change at all. The habit modification of **3** by **4** is discussed on the basis of the crystal growth mechanism while considering the stereochemistry of **4**.

Optically active compounds are increasing in significance regarding pharmaceuticals, agrochemicals, and even advanced materials for electronics. Particularly, in pharmaceutical and agricultural fields, an undesired enantiomer is currently considered to be an impurity; it is very important to develop an effective method for obtaining a single enantiomer.

Optical resolution by crystallization via a diastereomeric salt is one of the fascinating methods to prepare single enantiomers from their racemates. Regarding the optical resolution, it is obviously necessary to improve the purity of less soluble diastereomeric salts in order to obtain the desired enantiomers with high optical purity.

On the other hand, solid–liquid separation in optical resolution by crystallization is a key step for the reproducibility of diastereomeric salt purity, and for operation efficiency at large scales, such as industrial production. In the case of a salt being thin plates, separation by a centrifuge, however, becomes very difficult, since the crystals become arranged perpendicularly to the centrifugal force, resulting in a considerable amount of contamination of the mother liquor. The optical purity of the obtained diastereomers therefore becomes lower than that expected from the actual diastereomeric composite. In such a case, it is desired to change the shape of crystals into more easily separable ones by some habit modification.

Lahav et al. have extensively studied the habit modification of amino acids by the coexistence of an additive,[1-3] and applied that habit modification to the determination of their absolute configurations.[4] They proposed a two-step mechanism involving "binding" and "inhibition" for this habit modification.[3]

Recently, we have found that the existence of an optically active additive results in a dramatic change of the crystal habit in the industrial resolution process of (*RS*)-α-methylbenzylamine (MBA, **1**) with optically active mandelic acid (MA, **2**). To our knowledge, habit modification with an optically active additive has not yet been reported, except for that of amino acids, reported by Lahav et al.[1-4]

We report here the habit modification of a less-soluble diastereomeric salt, (*R*)-**1**·(*R*)-**2** (**3**), by an optically active additive in the optical resolution of (*RS*)-**1** with (*R*)-**2** and the dependence of the stereochemistry of the additive. We discuss the mechanism of habit modification.

Results and Discussion

In the optical resolution of (*RS*)-**1** with (*R*)-**2** in water containing hydrochloric acid, less soluble diastereomeric salt (*R*)-**1**·(*R*)-**2** (**3**) crystallized in a form of long, thin hexagonal plates (Fig. 1a), which were difficult to separate from the solvent. In contrast, growth of the longest axis of the crystal was inhibited, when a dimeric derivative of optically active **1**, (*R,R*)-bis(α-methylbenzyl)amine (**4a**), coexisted in the resolution solution to give hexagonal plates (Fig. 1b) which could be easily separated from the solvent.

In order to elucidate the role of additive **4a** in habit modification, we also prepared stereoisomers of **4a**, (*R,S*)-isomer (**4b**) and (*S,S*)-isomer (**4c**), and compared their efficiency in habit modification. Additives were added as hydrochlorides into the resolution solution, due to their low solubilities. The results are summarized in Table 1, and the shapes of crystal **3** are shown in Fig. 1.

It is obvious that the shape of **3** dramatically changed from a long hexagonal plate into a hexagonal plate when **4a** (0.05 mol% of **3**) was added to the resolution solution, whereas **4b** and **4c** (0.05 mol%) did not affect habit modification. This phenomenon indicates that the stereochemistry of **4** strongly influences habit modifi-

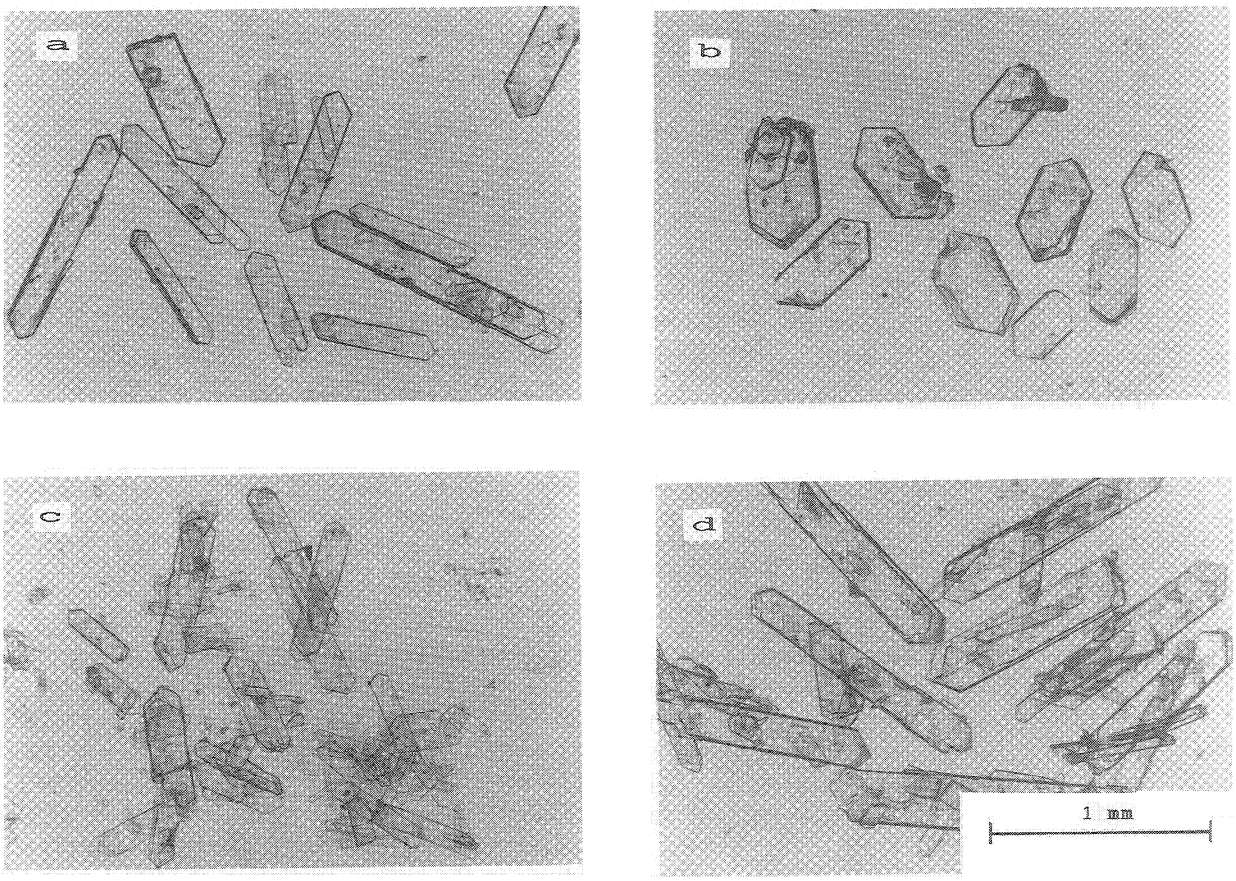

Fig. 1. Crystals grown a) in the absence of **4** and in the presence of b) **4a**, c) **4b**, and d) **4c**.

Table 1. Effective Additive for Morphological Change of Crystal **3**

Entry	Additive[a]	Concentration mol% of **3**	Coexistent salt	Morphological change[b]
1	**4a**·HCl	0.007	**1**·HCl	○
2	**4b**·HCl	0.29	**1**·HCl	○
3	**4c**·HCl	1.00	**1**·HCl	×
4	**4a**·HCl	1.00	None	×
5	**4b**·HCl	1.00	None	×
6	**4c**·HCl	1.00	None	×
7	**4a**·HCl	0.05	BA·HCl[c]	○
8	**4a**·HCl	0.05	EA·HCl[d]	○
9	**4a**·HCl	0.05	NH_4Cl	○
10	**4a**·HCl	0.05	NaCl	○
11	**4a**·HCl	0.05	$AcONH_4$	○
12	**5**·HCl[e]	2.41	**1**·HCl	×
13	**6**·HCl[f]	0.50	**1**·HCl	×

a) **4a**·HCl: (*R*,*R*)-bis(α-methylbenzyl)amine hydrochloride. **4b**·HCl: (*R*,*S*)-bis(α-methylbenzyl)amine hydrochloride. **4c**·HCl: (*S*,*S*)-bis(α-methylbenzyl)amine hydrochloride. b) ○ and × means the formation of affected hexagonal plates and unaffected long hexagonal plates, respectively. c) Benzylamine hydrochloride. d) Ethylamine hydrochloride. e) (*R*)-*N*-Benzyl-α-methylbenzylamine hydrochloride. f) Diethylamine hydrochloride.

cation.

In order to determine the effective concentration of **4**, we added **4** into the resolution solution until a morphological change was observed. Amine **4a** changed the morphology of **3**, even at a concentration of 0.007 mol%, to **3**; the shape of the crystal became a hexagonal plate, as shown in Fig. 1b (Table 1: Entry 1). In contrast, no morphological change could be observed until **4b** was added at a concentration of 0.29 mol% (about 40-fold concentration of **4a**); further, no change was observed upon adding **4c** up to 1 mol% (about 140-fold concentration of **4a**) (Table 1: Entries 2 and 3). These results indicate that **4a** is the most effective additive regarding habit modification among three stereoisomers

(**4a**—**c**).

Habit modification occurred only in practical optical resolution, whereas no morphological change was observed in the recrystallization of **3** from water (Table 1: Entries 4—6). The difference between both conditions is the existence of a soluble coexistent salt (**1**·HCl) (the former contained the coexistent salt, whereas the latter did not). In order to ascertain the necessity of a coexistent salt, about 10 mol% of an organic salt, such as benzylamine hydrochloride or ethylamine hydrochloride, or an inorganic salt such as ammonium chloride, sodium chloride, or ammonium acetate was added into a resolution solution of **3** containing 0.05 mol% of **4a**. In all cases, habit modification was observed, and the crystals of **3** were obtained as hexagonal plates, as shown in Fig. 1b (Table 1: Entries 7—11). Without **4a**, the morphology did not change, even in the presence of the coexistent salts. These facts suggest that these coexistent salts play a very important role in the inhibition of the crystal growth of **3** with **4a**. Although the function of the coexistent salts is not yet clear, the salts may increase the ionic strength in the solution and enhance inhibition, which would result from a strong adsorption of **4a** at one growing site of crystal **3**. In order to clarify the direction of inhibition for the crystal growth of **3**, we measured the interfacial angles appearing on the hexagonal plane of both uninhibited and inhibited crystal **3**, respectively. Two observed angles, α and β, averaged for 20 specimens of uninhibited crystals **3** (A in Fig. 2) coincided with those averaged for 20 specimens of inhibited crystals **3** (B in Fig. 2); they were 128 and 103°, respectively. Similar angles can be seen only on the *b*–*c* plane of crystal **3**, of which the crystal structure has been solved by Brianso,[5] as shown in Fig. 3 (129 and 101°, respectively). From these results, the inhibition of the crystal growth of **3** is concluded to occur in the direction of the *b*-axis, namely, at the {011} plane of the crystal.

In the crystal of **3**, there are O–H···O and N–H···O hydrogen bonds between two molecules (*R*)-**2** and between the molecules of (*R*)-**1** and (*R*)-**2** along the *b*- and *c*-axes, respectively; a helical column by hydrogen bonds, which makes the crystal rigid, is observed along the *b*-axis. Both molecules **1** and **2** individually form monolayers along the *b*-axis; these monolayers mutually repeat along the *c*-axis with hydrogen bonds to give a sandwich-like structure. In contrast, there is no hydrogen bond along the *a*-axis. Accordingly, the inhibition would result from stronger hydrogen bonding of the additive than (*R*)-**1** with (*R*)-**2**.

As shown in Table 1, habit modification strongly depends on the structure and/or stereochemistry of the additives. This dependence may be explained as follows: The hydrogen bonds between molecules **1** and **2** at the growing site of crystal **3** may unequivocally play an important role in the habit modification of **3**, since inhibition clearly occurs at the surface of the {011} plane (Fig. 3). Moreover, a chiral cavity formed by mandelic

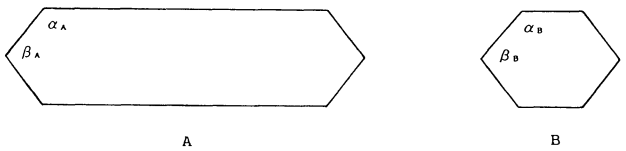

Fig. 2. Schematic crystal morphology of **3**. A) Unaffected without the additive and B) affected with the additive. $\alpha_A=\alpha_B=128°$. $\beta_A=\beta_B=103°$.

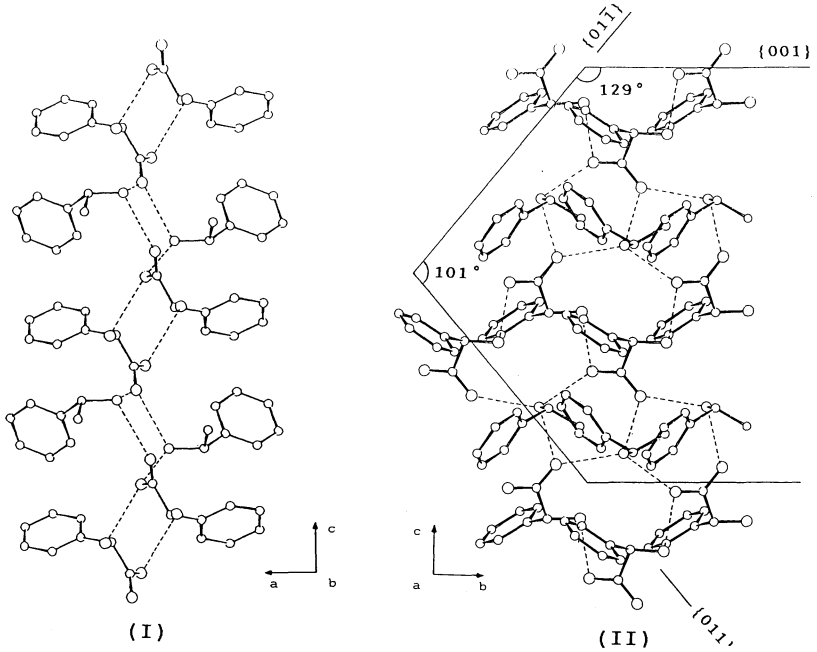

Fig. 3. Crystal structure viewed along the *b*- and *a*-axes.

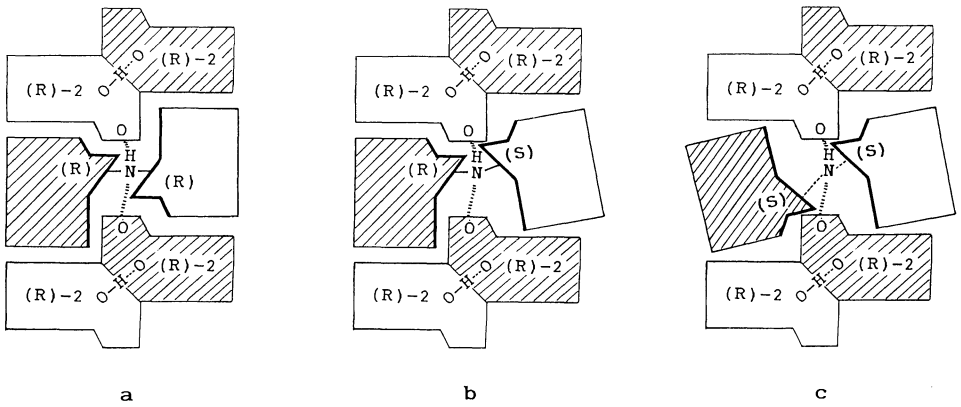

Fig. 4. Schematic interpretation of double chiral recognition.
a: **4a** (*R*,*R*), b: **4b** (*R*,*S*), c: **4c** (*S*,*S*).

acid monolayers would be favorable for the (*R*)-α-methylbenzylamine moiety, and would be unfavorable for the (*S*)-moiety, since only (*R*)-**1** is bound in the crystal during the optical resolution of (*RS*)-**1** with (*R*)-**2**. Therefore, the additives having an (*R*)-α-methylbenzylamine residue can strongly bind by the hydrogen bonds with (*R*)-**2** in the same way as the molecule of **1**; **4a** and **4b**, having an (*R*)-α-methylbenzylamine residue, affect habit modification, whereas **4c** and diethylamine (**6**), having no (*R*)-α-methylbenzylamine residue, do not at all. Thus, a distinct chiral recognition for an (*R*)-α-methylbenzylamine moiety at the surface of the {011} plane would be involved in habit modification. However, by considering single recognition, it cannot be explained how **4a** inhibits the crystal growth of **3** more effectively than **4b**, and that (*R*)-*N*-benzyl-α-methylbenzylamine (**5**) has no affect at all, even though these amines have an (*R*)-α-methylbenzylamine residue. The facts suggest that the morphological change of crystal **3** is controlled by "double" chiral recognition for the amines at the surface of the {011} plane. Namely, the cavity formed by two mandelic acid monolayers fits with and strictly recognizes an (*R*)-α-methylbenzylamine moiety of the additive (the first chial recognition), and then the neighboring cavity along the direction of the *a*-axis, which would also fit with an (*R*)-α-methylbenzyl moiety, recognizes the structure and/or the chirality of another *N*-substituent in the additive (the second chiral recognition). Subsequently, **4a**, having an (*R*)-α-methylbenzyl group as the second substituent, binds to the surface of the {011} plane stronger than **4b**, having an (*S*)-α-methylbenzyl group as the second substituent, and than **5** with an achiral benzyl group; the existence and direction (configuration) of a methyl group in the second substituent play a significant role in the strong binding of the additive at the {011} plane formed by mandelic acid monolayers. Double chiral recognition is schematically illustrated in Fig. 4. The additive strongly bound to the surface of the {011} plane disturbs the binding of (*R*)-**1**, resulting in an inhibition of crystal growth at the surface of the {011} plane.

Experimental

Materials. (*RS*)-, (*R*)- and (*S*)-**1** and (*R*)-**2** used in this experiment were purchased from Yamakawa Chemical Industry Co., Ltd.

Additives **4a** and **4c** were prepared as hydrochlorides according to the reported method.[6] Additive **4b** was obtained as a hydrochloride from filtrate in the preparation of **4c**, and purified by column chromatography.

4a·HCl((*R*,*R*)-isomer): Mp 265 °C; $[\alpha]_D^{26}$ +72.6° (*c* 3, EtOH); 99.9% diastereomeric exess (de); IR (KBr) 2950, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.99 (d, 6H), 3.83 (q, 2H), 7.2—7.8 (m, 10H)

4b·HCl((*R*,*S*)-isomer): Oil; 79.1% de; IR (Neat) 2960, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.33 (d, 6H), 3.77 (q, 2H), 7.23 (s, 10H)

4c·HCl((*S*,*S*)-isomer): Mp 266 °C; (Lit, >300 °C)[6]; $[\alpha]_D^{26}$ −72.5° (*c* 3, EtOH); 99.5% de; IR (KBr) 2950, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.93 (d, 6H), 3.82 (q, 2H), 7.2—7.8 (m, 10H)

Crystallization Conditions. Optical resolution of (*RS*)-**1** with (*R*)-**2** was performed by a method described in the literature.[7] Recrystallization experiments were carried out as follows. After dissolving 10.4 g of **3** in 89.6 g of water at 70 °C in the presence of a certain amount of **4a**—**c** (see Table 1), the solution was cooled to 50 °C and left standing for more than 30 min to crystallize without seeding. The crystals which appeared were collected by filtration at that temperature. Additives were added as hydrochlorides.

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